Presubmission Meeting Request

for

Openwater LOFU Therapy System

March 07, 2022

Openwater
733 Front Street, Suite C1
San Francisco, CA 94111

Prepared by MDQR, LLC.

Table of Contents

List of Figures

List of Tables

1 Purpose

The purpose of the Pre-Submission Meeting requested by Openwater is to discuss the regulatory approach and clinical data for Openwater LOFU Therapy System. LOFU or "LOw intensity Focused Ultrasound" is intended for safe neurostimulation of the prefrontal cortex. Specifically, Openwater requests Agency feedback on the sufficiency of this approach to support a pre-market application and the proposed regulatory pathway for the device.

2 Background

Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) are FDA-cleared technologies that use either electromagnetic induction or direct electrical current, respectively, to accomplish noninvasive activation of targeted regions within the brain [20, 22]. TMS treatments employ a magnetic field generator positioned at specific areas on the surface of a patient's head in order to deliver focused magnetic fields to desired brain regions. These magnetic fields pass unimpeded through the skin and skull to induce directed electric currents in specific neurons of the targeted brain region. Exploiting the fact that neurons are electrochemical cells, this electric current is powerful enough to induce action potentials that result in neurotransmitter release. Repeated high-frequency excitation of the same brain region results in strengthening of synapses through a process known as long-term potentiation [25, 49], resulting in changes in functional connectivity [19]. Both tDCS and TMS have become important clinical tools in noninvasive brain stimulation [37].

Transcranial focused ultrasound stimulation (tFUS) is an emerging technique for non-invasive neurostimulation with improved spatial resolution and targeting compared to magnetic or electric non-invasive brain stimulation [13]. A number of studies have been performed using tFUS for non-invasive neurostimulation of targeted brain regions, including of the primary motor cortex and hippocampus [59], amygdala [17], and thalamus [12]. The first human transcranial application of focused ultrasound neuromodulation involved stimulation of the frontal cortex applied on 31 patients affected by chronic pain [23]. Subsequent use of the tFUS technique was described targeting the primary somatosensory cortex of healthy volunteers, in a within-patients, sham-controlled study [34]. There has been significantly increased interest in the clinical community on the applications of tFUS on neuromodulation, with a number of recent reviews published in order to summarize the state of the art on this topic [16, 17, 47, 60, 37].

In particular, systematic meta-analyses on tFUS safety across 33 studies performed in both humans and animals has demonstrated a favorable safety profile [49]. Clinical interest in the availability of tFUS as a clinical research tool is based in the fact that "tFUS offers several advantages over electromagnetic methods including high spatial resolution and the ability to reach deep brain targets." [53] Early results of measured clinical effects of tFUS in modulating mood and functional connectivity by targeting the right inferior frontal gyrus (rIFG), an area implicated in mood and emotional regulation, have shown promising signal [53]. Briefly, in a randomized, placebo-controlled, double-blind study, participants who received tFUS reported an overall increase in Global Affect, an aggregate score from the Visual Analog Mood Scales, consistent with a positive shift as also objectively measured via decrease in resting-state functional connectivity (FC) on functional magnetic resonance imaging (fMRI) within resting state networks related to emotion and mood regulation [53]. These results support tFUS as a safe and effective means of noninvasive transcranial brain stimulation that can be used to modulate mood and emotional regulation networks in the prefrontal cortex.

Openwater is developing the Openwater LOFU Therapy System, which is a low intensity transcranial focused ultrasound system intended to be used safely, in clinical research, for neurostimulation that targets the prefrontal cortex. This presubmission focuses on describing this device, proposing a regulatory approach to market this device, and obtaining FDA feedback to ensure alignment with Agency expectations for a future premarket submission. The efficacy of neurostimulation using LOFU or the subject device is not in scope of this presubmission.

3 Device Description

The Openwater LOFU Therapy System ("OLTS") is a low intensity focused ultrasound (LOFU) system intended for safe neurostimulation of the prefrontal cortex. One of the key uses of this system is to support clinical research and exploration of indications that can benefit from LOFU neurostimulation. Focused ultrasound (FUS) is a way of non-invasively delivering energy to specific points, or foci, in the form of an acoustic pressure wave. The acoustic waves can be focused to a particular location with a spatial resolution on the order of the wavelength of the driving frequency (approximately 3 mm at 0.5 MHz) [7]. The point of focus is achieved using an ultrasound array, where each element of the array is driven in a specific sequence to ensure that a focal spot can be formed through constructive interference of the ultrasound waves. The focal spot can be formed at depth within the tissue without affecting cells along the propagation path closer to the transducer [7]. In the case of LOFU used by OLTS, energy levels used for FUS are set to low intensity levels that do not cause thermal or mechanical damage to the target tissue and to any tissue between the device and the target (i.e., within diagnostic limits of MI < 1.9, and $I_{SPTA} < 720 mW/cm^2$).

The device operates in two steps and safety is incorporated into both steps:

1. *Treatment Planning*: in this step, the clinician uses the device user interface to provide the treatment volume to be stimulated as well as the desired stimulation parameters. The OLTS treatment planning software computes the optimal and safe patient specific simulation parameters and treatment plan. Treatment planning includes the computation of ultrasound mechanical index (MI) and cranial bone thermal index (TIC) to ensure that the ultrasound pressure and intensity levels are kept far below those that may cause tissue damage. The treatment plan also includes the sequencing parameters needed to drive each element in the OLTS's ultrasound array to achieve the foci needed to cover the treatment volume. The software limits the device's maximum peak-rarefactional pressure to be less than 1.5MPa for all driving frequencies offered by OLTS, which is well below the theoretical lower threshold for bubble nucleation or inertial cavitation of 3.9MPa [1]

   The treatment planning is discussed in detail in Section 3.3.1.

2. *Treatment Delivery*: in this step, the OLTS executes the treatment plan to deliver the neurostimulation. During the delivery, the OLTS monitors treatment safety control parameters such as ultrasound hardware output power, stimulation time, and surface temperature at the site of the ultrasound array to ensure safe operation.

3.1 OLTS Components

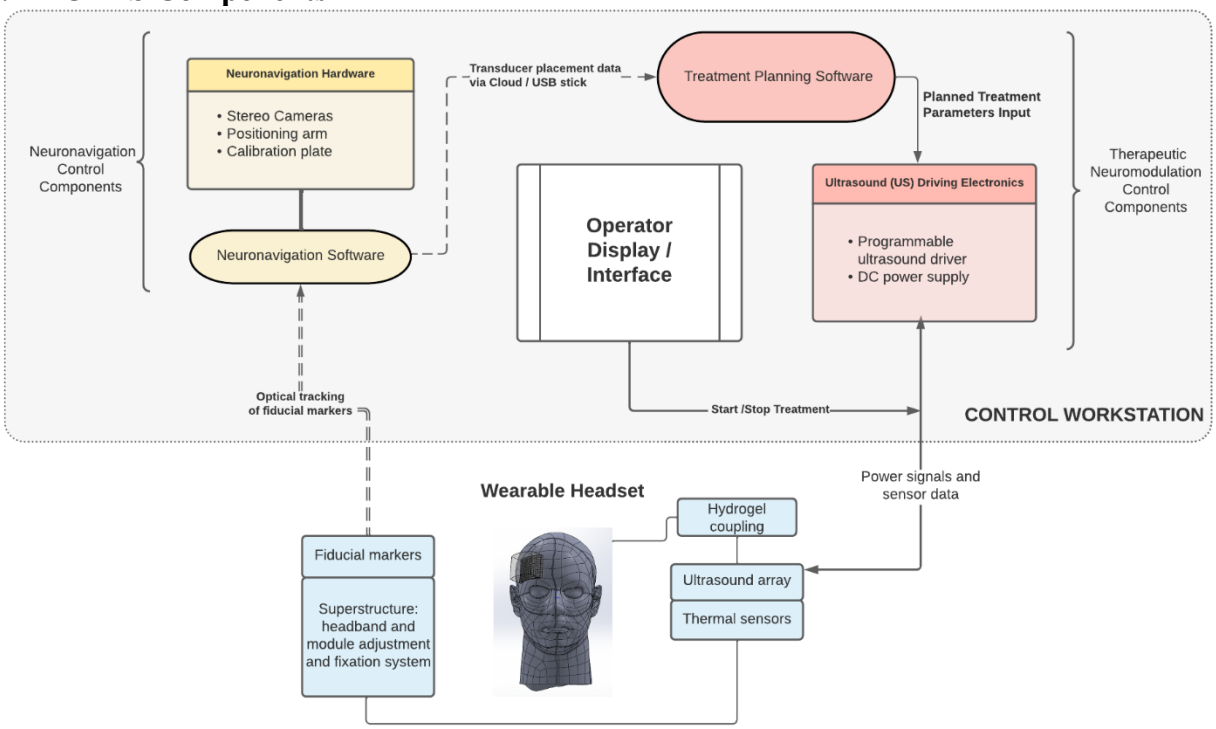

Figure 1: Components of the OLTS

OLTS consists of the following components (also shown in Figure 1 and Figure 2):

1. *Neuronavigation system*: a 3rd party neuronavigation system, which is an image-guided, optical positioning system that uses fiducial markers and custom software to co-register the patient's anatomical features and medical imaging (CT or MR). The neuronavigation system software is used to ensure precise positioning of the OLTS Headset relative to the treatment volume of interest.

   The neuronavigation system consists of a computer, optical (infrared) position sensor, subject tracker, transducer tracker, transducer calibration block, and a pointer tool. Using the patient's brain imaging (CT or MR), the operator will be able to choose anatomical landmarks (e.g. nasion, left and right ears, and the tip of the nose) in the images and co-register them with the subject's real-time position. Such co-registration is possible by indicating the selected landmarks by touching them with the pointer tool. In sequence, the transducer attached to its calibrated tracker will be overlaid on the brain scan images using the neuronavigation software.

   The OLTS treatment planning software can import the exact location of the OLTS Headset relative to the brain scan images and use this information to precisely target the treatment volume.

2. *Treatment planning software*: OLTS treatment planning software is a tool developed by Openwater to facilitate ultrasound neuromodulation at specific targets within the frontal cortex. This software is used to compute the overall stimulation parameters as well as the precise operating sequence of each ultrasound element in the OLTS Headset's ultrasound array. The software also computes the maximum pressure and intensity in the field along with the calculated MI and TIC associated with these values.

To create a treatment plan, the clinician defines the desired treatment volume below the OLTS Headset that will be stimulated as well as desired stimulation parameters for intensity, pulse duration, duty cycle, and total treatment duration (the software will adjust the pressure amplitude to keep within the defined safety limits). If imaging is available, using neuronavigation the clinician can identify this treatment volume precisely within the prefrontal cortex for neurostimulation.

Details of the treatment planning and its sequence of operation are provided Section 3.3.1.

3. *Ultrasound hardware*: Hardware consisting of driving electronics, power supply, and programmable logic controllers utilize a preprogrammed treatment plan to drive the OLTS Headset. The ultrasound driving hardware has an electrical connector to the OLTS Headset with a channel to each of the ultrasound array elements, through which the hardware can drive each element. Each channel is capable of delivering the desired electrical waveform and power to the individual ultrasound element for array operation. These signals are programmable such that the phase and amplitude of each signal can be individually controlled. The pulse length, pulse repetition frequency, and total time can all be adjusted in the software for each of the focal points. Once the treatment parameters are established, the entire treatment is programmed into the hardware for all of the focus locations. The only operator control on the ultrasound hardware is to start and stop the treatment that has been programmed into it from the control components.

Figure 2. OLTS Headset positioned over the left prefrontal cortex and includes the neuronavigation fixed fiducial marker attached to it

4. *OLTS Headset*: A non-invasive ultrasound head-worn device intended for stimulating neurological tissue in the prefrontal cortex as specified by the control components. OLTS's Headset consists of a head-mounted, steerable 2D ultrasound array that will be placed on the forehead of a subject by a superstructure and ensure adequate coupling to the subject's skin through a hydrogel pad. The 2D array consists of 128 ultrasound elements and has a surface area of approximately 21.5 cm^2.

The array is positioned in its proper treatment location either manually or through the assistance of the neuronavigation sub-system from the Control Components, which provides real-time feedback of the location through a fixed fiducial marker attached to it. The array has a curvature that will assist comfortable placement along the anatomical lines of the subject's forehead, and a hydrogel pad will be placed between its face and the subject skin, assuring

that the ultrasound can travel through an aqueous medium until it reaches the target tissue inside the brain.

The superstructure of the OLTS Headset consists of a headband around and above the subject's head, which allows for comfort and stable placement of the array throughout the entire planned treatment. The array and its superstructure comprising the headset will be connected to the ultrasound hardware through electronic cables that will wrap around the subject's head.

Based on the sequence and timing with which the ultrasound array in the OLTS Headset is driven, a focal spot can be formed through constructive interference of the incident acoustic waves. The three dimensional range over which this focus can be located is called the "steering range". This steering range is created not by moving the OLTS Headset but electronically by how the ultrasound array is driven. This type of electronic steering is also called beamforming. The steering range depends on the operating mode (Section 3.2)

5. *A standard off-the-shelf computer*: A computer used as the primary user interface for treatment planning. The same computer may also be used to manage the neuronavigation system.

3.2 Operating Modes

OLTS offers two modes of operation that ensure safe operation by bounding the stimulation parameters for ultrasound neuromodulation within diagnostic limits of MI < 1.9 and I_{SPTA} < 720mW/cm^2. The two modes are:

1. *Standard Operating Mode (SOM)*: This is the default mode of operation that uses patient specific maximization of stimulation parameters. The Standard Operating Mode allows for accurate and reproducible treatments.

   In SOM, treatment planning is conducted using a patient's head CT or MR image. A neuronavigation system will co-register this image with the patient's anatomy and location and orientation of the OLTS headset. Once the coregistration process is completed, the volume data that is generated by the neuronavigation system will be transferred to the OLTS treatment planning software (please refer to details Section 3.3.1). This software will assign focal targets to cover the treatment volume using the patient imaging data and all treatment parameter calculations will correct for aberrations specific to the patient anatomy and skull. Simulations of the ultrasound pressure field will be performed for each focal target to identify the amplitude of the driving signal necessary to achieve the desired pressure and intensity in the focus. All pressures and intensities will be kept within safe levels (i.e. MI<1.9, and I_{SPTA} < 720mW/cm^2). In addition to the pressure field simulation, thermal simulations will also be performed to ensure that the temperatures in the focal region will not exceed 2°C and the TIC in the skull is limited to safe limits. The SOM is discussed in more detail in Section 3.3.1.1 and in Appendix A.

2. *Restricted Operating Mode (ROM)*: The ROM is offered to allow treatment in situations when patient imaging is not available or possible. Like the SOM, the ROM also performs simulations of the ultrasound pressure field to deliver the treatment, but all computations are performed based on maximums as computed for water (with negligible attenuation)

instead of tissue and bone used in SOM. The user can choose to operate in Restricted Operating Mode with or without neuronavigation. Like the SOM above, OLTS treatment planning software is used to set up the ultrasound driving parameters, but the ROM offers restricted parameters, reduced steering ranges, no aberration correction, and no ability to increase the pressure amplitude of the delivery beyond the maximum determined in water. The ROM and these limits are described in more detail in Section 3.3.1 and in Appendix A.

OLTS is a LOFU system intended for neuromodulation using ultrasound. The use of imaging to perform treatment planning, i.e., the SOM, is the default and recommended mode of operation. However, there is significant ongoing research in the use of LOFU that does not use acoustic simulations of the patient specific anatomy [6, 29]. Such research uses different derating factors to estimate the focal pressures being applied to patients [20, 40]. In order to facilitate safe research of LOFU, Openwater is offering the ROM that performs all modeling and simulation of use within water so that the researchers have a consistent baseline to estimate the derated pressure of their choice.

3.3 Device Operation

The steps for using the device to treat a new subject (total duration estimated to be less than 30 minutes - not including acquisition of subject's head/brain medical image) are described in Figure 3 below.

1. *Acquire baseline neurological function*: A baseline measurement of patient's neurological function will be acquired before the treatment.
2. *Set operating mode*: Depending on the availability of patient imaging, the operator can choose to operate in Standard Operating Mode or Restricted Operating Mode.
3. *Set up OLTS Headset on patient*: If neuronavigation is being used, the operator ensures that the OLTS Headset is registered using fiducial markers and placed on the forehead in a position relative to the desired target in the prefrontal cortex. Alternatively, the operator will fit the device to a position on the forehead relative to the desired target in the prefrontal cortex.
4. *Create treatment plan*: The operator in partnership with the physician will define the desired treatment volume and stimulation parameters. The OLTS treatment planning software analyzes this input and create an appropriate and safe treatment plan specific for the patient. The software then loads this plan into the ultrasound driving hardware. Detailed description of treatment planning is provided in Section 3.3.1.
5. *Execute treatment protocol*: The operator will then execute the treatment protocol.
6. *Acquire neurological function*: Once treatment plan has been executed, the operator will acquire a post-treatment neurological assessment.

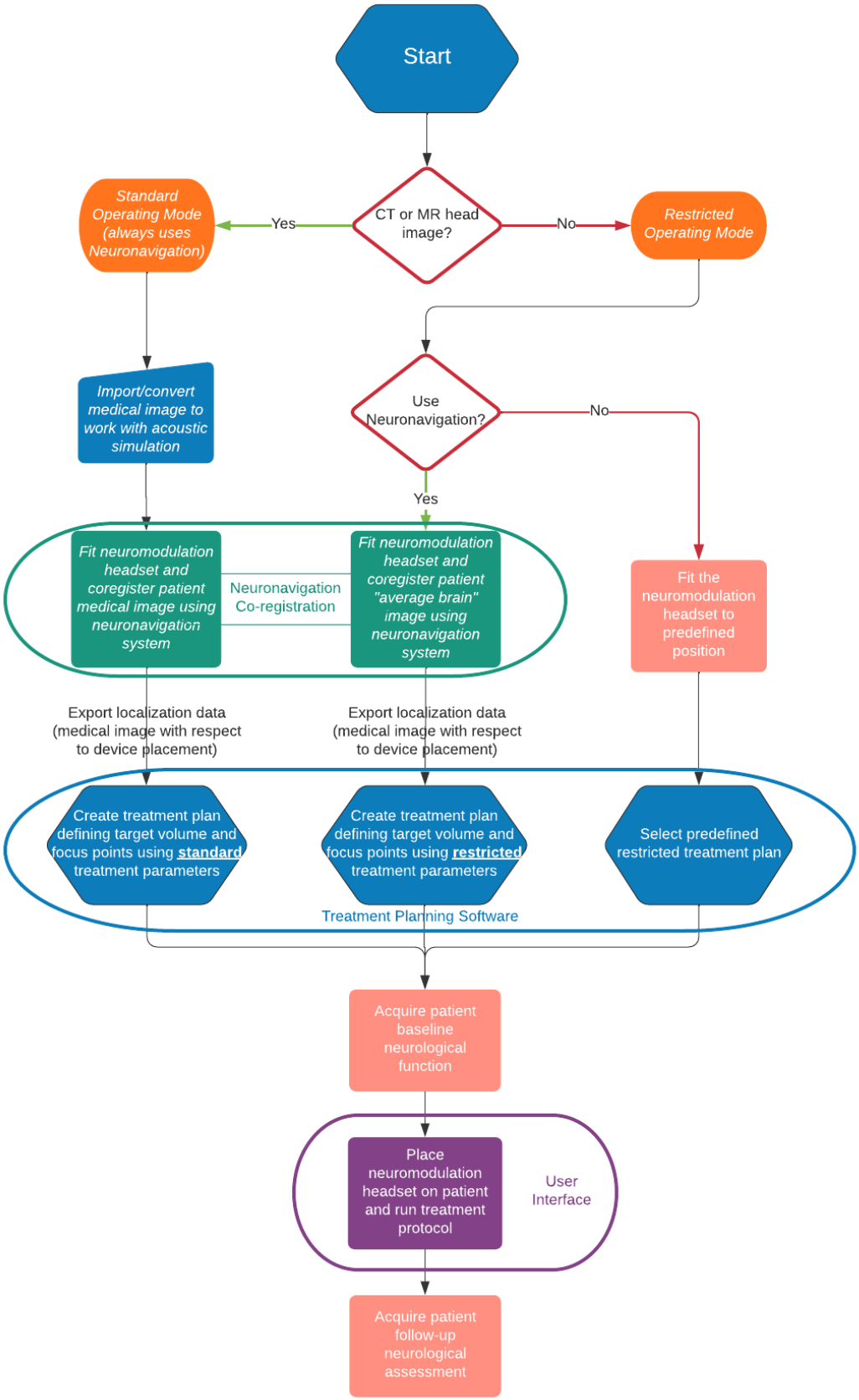

Figure 3: OLTS Use Workflow

3.3.1 Treatment Planning

OLTS treatment planning software is a tool developed by Openwater to facilitate ultrasound neuromodulation at specific targets within the frontal cortex. This software is used to compute the overall stimulation parameters as well as the precise operating sequence of each ultrasound element in the OLTS Headset's ultrasound array. The software also computes the maximum pressure and intensity in the field along with the calculated MI and TIC associated with these values. How these parameters and safety limits are computed depends on the type of operating mode, which is discussed further in Section 3.3.1.1 and Section 3.3.1.2 below.

The OLTS treatment planning software utilizes a popular open source acoustics simulation toolbox called k-Wave to perform the acoustic simulation of the pressure fields and thermal heating [37]. k-Wave was developed for time domain acoustic and ultrasound simulations in complex and tissue-realistic media. A detailed description of the treatment planning as well as the principles of its operation are provided in Appendix A.

Preliminary validations of the simulations through benchtop measurements using human skull bones and tissue mimicking phantoms is discussed in Appendix B. The treatment planning software validation methods to support a premarket submission are discussed Section 7.1. Specifically, measurements characterizing attenuation and aberration of the ultrasound beam by the skull will be performed in a water tank using a calibrated hydrophone to measure the acoustic pressure field. In addition, accuracy of the thermal rise estimations in the region of interest will be validated by thermocouple measurements in tissue mimicking phantoms and ex vivo animal brain tissue.

3.3.1.1 Planning in Standard Operating Mode (SOM)

In Standard Operating Mode (SOM), the device uses neuronavigation and patient imaging data. By utilizing neuronavigation with imaging, OLTS treatment planning software provides a visualization of the patient specific anatomy, which allows the clinician to precisely identify the treatment volume to target. Neuronavigation co-registration of the patient's anatomy, medical imaging, and the OLTS Headset is first performed and this information then imported into the planning software. The software transforms the medical image volumes into density, speed of sound, and attenuation maps, which will then be used as inputs to acoustic simulations (See Section A.1 in Appendix A for details).

Once the medical image with the relative device position is loaded into the software, the target stimulation volume can then be highlighted by the clinician. The software will then segment this highlighted region into multiple foci distributed throughout the volume such that the stimulation covers the entire region (Figure 5). Focal targets can be selected within a volume where the OLTS Headset's 2D ultrasound array can be steered. As noted earlier, the focus is achieved through delay-and-sum beamforming and the steering is electronically achieved. In other words, there is no physical movement of the OLTS Headset but the focus can be targeted by changing the sequence of activation of each element of the ultrasound array in the OLTS Headset.

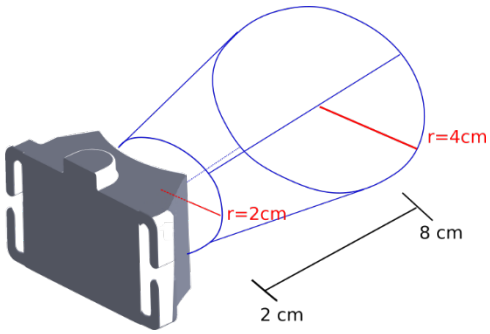

Figure 4: Steering volume available in Standard Operating Mode. Blue rings represent the radially steerable limits.

Treatment volume selection is made within the range where the ultrasound array can focus or steer. The steering range, developed based on a generalized brain model, allows the selection of the treatment volume that is ± 2cm in both lateral and vertical dimensions at 2 cm from the face of the array, and of ± 4 cm in both lateral and vertical directions at 8 cm from the face of the array (Figure 4). Based on the patient's anatomic features and imaging data, the OLTS treatment planning software will compute whether the foci can be achieved for the specific patient and ensures that focal pressures are no less than -6dB from the maximum achievable focal pressure. If the software determines that the foci cannot be achieved, then the user will need to move the Headset to a better position to adequately treat the volume and repeat the treatment planning.

Once the targets have been determined, time of flight calculations will be performed for each element of the ultrasound array to ensure proper beamforming. These calculations will correct for aberration through the skull. Following this correction, simulations of the ultrasound pressure field will be performed for each of the foci to identify the amplitude of the driving signal necessary to achieve the desired pressure and intensity in the focus. All pressures and intensities will be kept within safe levels in the stimulated tissue (i.e. MI<1.9, and $I_{SPTA} < 720 mW/cm^2$). In addition to the pressure field simulation, thermal simulations of ultrasound induced heating at every focus will be performed, to ensure that the treatment plan will not cause heating in excess of 2ºC in the tissue in the focus area. The simulations also evaluate the TIC to mitigate the risk of damage due to the heating in the skull.

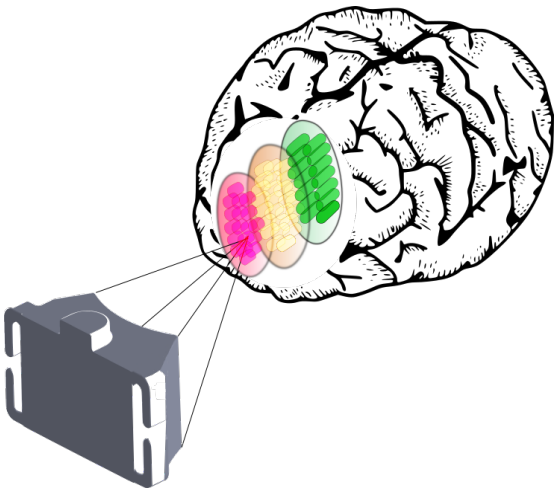

Figure 5: Covering the treatment volume with several foci

The following is a summary of steps the treatment planning software takes to compute the treatment parameters in SOM, and each step is discussed in greater detail in Appendix A:

1. Transform CT or MR images to density, speed of sound, and attenuation maps
2. Define the optimal foci within the treatment volume
3. Calculate the beamforming parameters
4. Model the acoustic field
5. Perform the thermal simulation to compute the thermal rise in stimulated brain tissue and TIC for the skull

3.3.1.2 Planning in Restricted Operating Mode (ROM)

The treatment planning sequence in ROM is quite similar to SOM, except that since there is no patient imaging available and all analysis is performed assuming that the medium is water with no skull to attenuate the acoustic intensity. As a result, the treatment parameters computed in ROM are quite conservative and the pressure intensities actually observed should be well below what is estimated during planning.

The treatment planning input starts with the clinician specifying the treatment volume within the steering range of the OLTS Headset allowed in the ROM. If neuronavigation is being used, a generalized brain model resized to the patient's head is shown to the clinician. This model is only an approximation but helps ease the identification of the treatment volume of interest. If neuronavigation is not used, the clinician specifies the treatment volume relative to the OLTS Headset by approximately locating the headset by sight. The device provides a generalized head/brain model for reference only to help locate the device for planning simulations.

Like the SOM, the steering range of the OLTS Headset will be limited locations where the focal pressures are no less than -6 dB from the maximum achievable focal pressure in water. Since there is no aberration correction in this operating mode, the axial limitations on the steering range in Restricted Operating Mode have been restricted to be between 3-7 cm, and the corresponding lateral steering will be kept to within 1.5 cm radially from the central focus position (Figure 6).

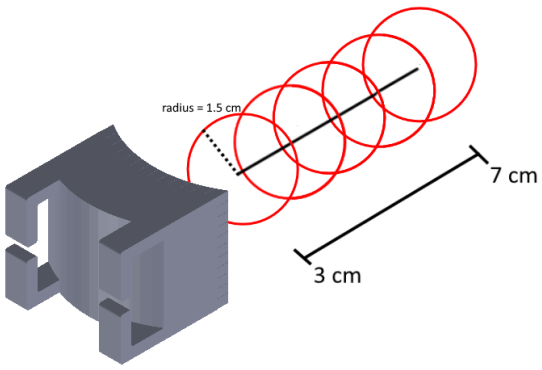

Figure 6: Steering range in Restricted Operating Mode. Red rings represent the radially steerable limits.

Like the SOM, the software will then segment the treatment volume into multiple foci distributed throughout the volume such that the stimulation covers the entire region (Figure 4). For these

focal positions, ultrasound pressures at the various focus points, as measured in the free field in water will be used to determine the maximum pressure to ensure that the mechanical index (MI) will not exceed 1.9. In addition to the pressure limitations of the ultrasound, like the SOM, there are also limitations in place for the intensity of ultrasound that is being applied, the maximum spatial-peak, temporal average intensity that will be utilizable is 720 mW/cm^2, and the treatment parameters are set up to limit to heating < 2ºC to ensure that there will be no adverse effects due to heating of the tissue. The simulations also evaluate the TIC to mitigate the risk of damage due to the heating in the skull.

Once the OLTS Headset has been located by the user on the patient's head (either with or without neuronavigation), the following is the summary of steps the treatment planning software takes to compute the treatment parameters in ROM, and each step is discussed in greater detail in Appendix A:

1. Define the optimal foci within the treatment volume
2. Calculate the beamforming parameters assuming that the medium is water instead of tissue and skull
3. Model the acoustic field
4. Perform the thermal simulation to compute the thermal rise in stimulated brain tissue and TIC for the skull

3.3.2 Treatment Parameters

The treatment planning software computes various treatment operating parameters including the characteristics defining the ultrasound acoustic wave, its duration, etc. A typical acoustic wave can be defined by two fundamental parameters:

- the peak pressure, defined as the amplitude of the wave, and
- the frequency, defined as number of cycles per second, which can be used to calculate the period, which is the length of time for a single complete oscillation.

In addition to these two parameters, the sonication duration is the total time of a single sonication treatment. During the sonication duration two paradigms of sonication can be used: continuous or pulsed, using protocols analogous to non-invasive brain stimulation with repetitive transcranial magnetic stimulation. [13, 14].

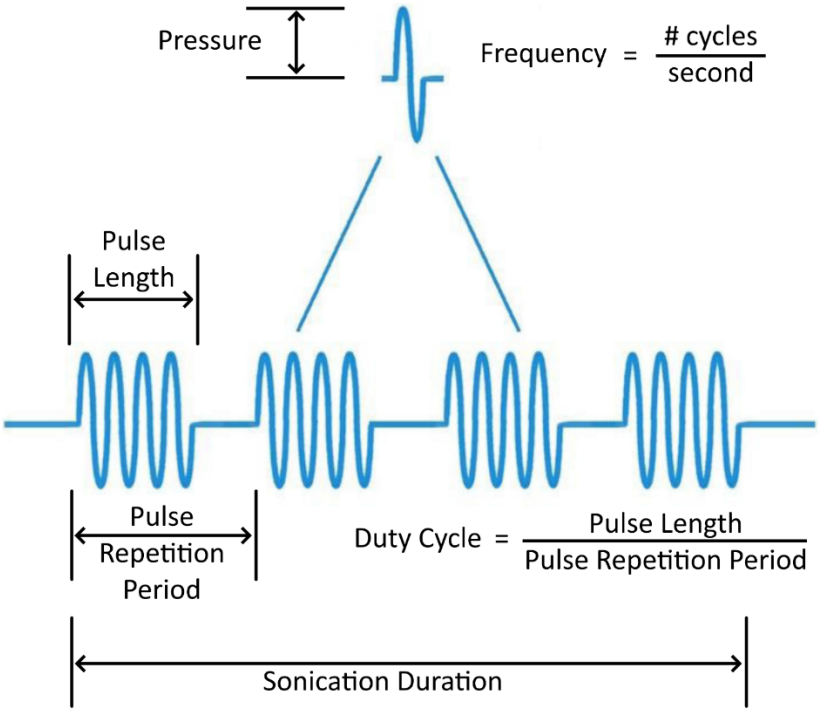

Figure 7: Treatment parameters, based on [62]

During the pulsed therapy, two additional parameters are important: the pulse length, which is the period of acoustic sonication from the starting point of oscillation to the ending point, before the pause; and the pulse repetition period, which is the period between the starting points of two consecutive pulses (sonications), or, in other terms, the sum of the pulse length and the pause between two consecutive sonications. This period is used to calculate the pulse repetition frequency. For the pulsed paradigm, the duty cycle is the fraction of the pulsed repetition period covered by the pulse length. For the continuous stimulation protocol, the sonication delivered during the stimulus duration period can be repeated, without pauses. All of these treatment parameters are illustrated in Figure 7.

For safety, indices that describe the thermal and mechanical effects of the sonication are defined and include parameters related to the acoustic pressure and duration of the stimulation, correspondingly. The two main mechanisms that can induce tissue damage are: local heating through ultrasound wave absorption by tissue and inertial cavitation. The latter is thought to be mediated by the expansion and violent collapse of gas bubbles caused by the rarefactional (peak negative) pressure exerted by the ultrasound wave.

The thermal index (TI) is the ratio of total acoustic power to the acoustic power required to raise tissue temperature by 1°C under certain assumptions. For modeling purposes, the treatment planning utilizes cranial bone thermal index (TIC), which is based on modeling the bone close to the surface and is a more appropriate factor to estimate given the low power levels of the device.

The non-thermal, mechanical bioeffect is described by the mechanical index (MI), which is directly proportional to the ultrasound beam's peak negative pressure and inversely proportional to the square root of the frequency of the beam. The intensity, spatial-peak pulse-average (I_{SPPA}) is the value of the pulse-average intensity at the point in the acoustic field where the pulse-

average intensity is a maximum or is a local maximum within a specified region. The intensity, spatial-peak temporal-average (I_{SPTA}) is the value of the temporal-average intensity at the point in the acoustic field where the temporal-average intensity is a maximum or is a local maximum within a specified region. The FDA guidance document for Marketing Clearance of Diagnostic Ultrasound Systems and Transducers define the safety threshold for diagnostic usage of ultrasound in Track 3 devices as $I_{SPPA} \leq 190$ W/cm^2, $I_{SPTA} \leq 720$ mW/cm^2, and a mechanical index ≤ 1.9 [15], for non-ophthalmic devices, which can be applied to neuromodulation for the purpose of noninvasive brain stimulation. These ultrasound parameter thresholds have also been shown to be safe with other transcranial doppler devices [4]. Additionally, both animal histological studies [28, 31] and human neuroimaging studies [32, 33] have confirmed that neuromodulation of brain circuits can be performed within the known safe threshold parameters without inducing tissue damage (Table 1).

Table 1: Examples of sonication parameters used within the known safe diagnostic thresholds of $I_{SPTA} \leq 720$ mW/cm^2 in low intensity transcranial ultrasound

Name of the US system and reference	Sonication Duration (s)	Pulse Width (ms)	Pulse Repetition Frequency (Hz)	Duty Cycle (%)
Neurotrek Sanguinetti et al, Frontiers (2020)	30	0.065	40	0.26
Neurotrek Sanguinetti et al, Frontiers (2020)	2	0.065	40	0.5
BX Pulsar - Brainsonix Stern et al. Brain Stimulation (2021)	0.5	2	250	50
BX Pulsar - Brainsonix Stern et al. Brain Stimulation (2021)	30	0.5	100	5

3.4 OLTS – Mechanism of Action

OLTS utilizes a 2D ultrasound array to deliver low intensity focused ultrasound (LOFU) precisely and safely to specific frontal lobe regions. Medical ultrasound technologies as diagnostic imaging tools and for therapeutic delivery have been used for many decades. Typically, diagnostic levels of ultrasound as defined by IEC 60601-2-37, are used in a pulse-echo mode for imaging, or quasi-continuous wave mode for doppler and blood flow interrogation. These diagnostic levels are considered safe for prolonged use and minimize any adverse events that could be caused by ultrasound. Therapeutic ultrasound, on the other hand, generally falls into the category of high intensity focused ultrasound (HIFU), where the desired effect is destruction of the cells or structures within the focus region. More recently, however, low-intensity ultrasound has been shown to induce biological effects including accelerated wound healing, angiogenesis, nerve growth and without inducing any thermal or mechanical damage to the targeted tissue [36, 48, 54]. Furthermore, it has been shown that lower frequencies are capable of inducing these more readily than higher frequencies [26], which is advantageous for transcranial applications since the amount of energy that is absorbed passing through the skull bones is also less at low frequencies [63].

3.4.1 Rationale for LOFU Neuromodulation

Focused ultrasound is a non-invasive, non-ionizing technique to deliver acoustic energy to biological tissue. This acoustic energy is capable of causing biological effects in tissue, and the effects are generally separated into two categories, thermal and mechanical, although both can play a role in the neuromodulatory effects. The thermal effects are associated with temperature rise from the attenuative tissue absorbing the mechanical energy, and mechanical effects where the wave motion itself can cause physical changes within the tissue. Even low levels of temperature rise, below tissue necrosis, could provide some neuromodulatory effects [8]. The mechanical effects, however, are more typically associated with LOFU due to the relatively low levels of heating [7, 62].

The mechanical interaction between these acoustic waves and neuronal membranes can modify the membrane gating kinetics through action on mechanosensitive voltage-gated ion channels and neurotransmitter receptors to induce neural action potentials [60, 44, 45].

In a preclinical study of ex vivo mouse brains and hippocampal slice cultures, low-intensity, low-frequency ultrasound has demonstrated the ability to activate voltage-gated sodium and calcium channels, change membrane permeability, and result in subsequent neuronal action potential induction [60]. The bilayer sonophore model of ultrasound neuromodulation explains how the mechanical ultrasound pressure wave causes periodic expansions and contractions of the membrane. Increase in membrane permeability changes the instantaneous membrane capacitance leading to a current that activates voltage-dependent sodium and potassium channels [51, 30].

The neuronal bilayer sonophore model combines the biomechanical and bioelectrical properties of the cell membrane to predict the stimulation parameter needed to reach a successful motor cortex stimulation. The model explains the reason for higher efficacy of long ultrasound stimulation pulses and how the action potential can be elicited by the ultrasound stimulus with a good overlap with the experimental results obtained using stimulation of the mouse motor cortex [59, 51, 30, 27].

Regardless of the precise mechanism, or more likely combination of mechanisms, there have been many successful studies showing that LOFU (within the same parameter space defined here) is capable of effecting improved sensory discrimination, attenuated amplitude of somatosensory evoked potential (SEP), phase modulation on EEG, elicited tactile sensations, suppressed SEP, EEG peaks, phosphene Perception, fMRI BOLD activation, and recovery from severe brain injury after sonication [18].

3.5 OLTS User Interface

The OLTS has two different user interfaces (UI). The operator additionally will interact with third party neuronavigation software. The two device user interfaces include:

1. *Treatment planning UI*. The first custom user interface is in the form of the treatment planning software. As shown in the workflow chart (Figure 3), there are three different ways that the device can operate, the Standard Operating Mode, Restricted Operating Mode with neuronavigation, and Restricted Operating Mode without neuronavigation.

If neuronavigation is being used, the first step is to register the OLTS Headset using the neuronavigation UI. The registration uses the patient specific imaging for the Standard Operating Mode, and a generalized brain model in Restricted Operating Mode.

In Standard Operating Mode the operator will go through the steps outlined in the Section 3.3.1, "Treatment Planning", where patient specific anatomy is used and the focal the operator will be allowed to choose both the focal target volume and the desired acoustic intensity (spatial-peak, temporal-average), as long as the intensity is at or below 720mW/cm^2.

In Restricted Operating Mode with neuronavigation, the user follows steps similar to the Standard Operating Mode with the restriction that the maximum I_{SPTA} of 720mW/cm^2 being the intensity that would be measured in water. Steering options will be provided to specified regions in the generalized brain model, but no aberration correction will be offered.

In Restricted Operating Mode without neuronavigation, the user is offered steering options relative to the OLTS Headset and a maximum I_{SPTA} of 720mW/cm^2 being the intensity measured in water. No aberration correction will be offered.

2. *Ultrasound Driving Hardware UI*. This is the device operator interface and is quite limited in its control. The operator loads the desired treatment protocol that was created by the treatment planning software. The operator is then able to start and stop the treatment. The operator is shown the treatment operating mode (Standard or Restricted), desired focal intensity, and duration (with a countdown timer for operation). In addition, the operator is shown risk mitigation measures such as the temperature being measured at the probe surface, and time since last treatment. The ultrasound driving hardware will stop executing the treatment plan if any of the following occur:
    a. the OLTS Headset surface temperature exceeds specified limits,
    b. if the software requested an output power higher than safe limits (software risk mitigation), or
    c. if the device was last used within a designated amount of time (to mitigate any cumulative thermal effects).

3.6 Device Risks and Mitigations

Table 2 provides a summary of a preliminary hazard analysis to identify key risks of OLTS as well as proposed mitigation measures.

Table 2: OLTS Risks and Mitigations

Risk	Mitigation
Thermal or mechanical injury from focused ultrasound exposure causing damage to target and/or non-target tissue. Harms include: • Heating/burns to skin on forehead • Heating to skull and/or brain tissue	1. Limit power output: Utilize ultrasound power levels that are known to be safe 2. Treatment planning: Model of the effects of treatment in planning phase to ensure safe operation 3. System testing:

Table 2: OLTS Risks and Mitigations

Risk	**Mitigation**
• Mechanical damage to skin or brain tissue	a. Bench performance testing of ultrasound components (see Section Performance Testing for details), b. Phantom and ex vivo testing and validation of simulations for intensity levels and thermal heating c. Software verification and validation – with experimental measurements 4. Labeling: Instructions for use, describing safe operation of device 5. Training: Training videos for operators to learn safe operation of device prior to first use
Improper placement (wrong treatment area causing unwanted cognitive changes). Harms include: • Generalized neurological deficit • Focused neurological deficit • Seizure • Headache (severe, moderate, mild)	1. Real-time tracking of OLTS Headset using neuronavigation system 2. Treatment planning: Identification of target locations and foci needed for safe delivery of low intensity transcranial focused ultrasound. 3. Labeling: Instructions for use, describing safe operation of device 4. Training: Training videos for operators to learn safe operation of device prior to first use
Adverse Tissue Reaction leading to inflammation	Biocompatible design supported by biocompatibility risk assessment for contacting intact skin and associated testing, as applicable.
Electrical shock/Electromagnetic interference	Compliance to IEC 60601-1, 60601-1-2. Labeling.

4 Indications for Use/Intended Use

Openwater proposes an initial Indications for Use statement as follows:

> *Openwater LOFU Therapy System is intended to provide transcranial low intensity focused ultrasound (LOFU) for neuromodulation of the prefrontal cortex in adult patients (over 18 years of age) for clinical research use. The device is intended for use by a qualified healthcare professional. The prospective clinical value of LOFU neuromodulation has not been demonstrated.*

Proposed intended use for the device: Neuromodulation of brain tissue using LOFU.

5 Regulatory History

There have been no previous submissions or discussions with FDA for this device.

6 Regulatory Pathway

Openwater conducted a search for appropriate product codes to define the regulatory pathway for OLTS. The search for product codes utilized the following considerations:

- Intended use: Stimulation of brain tissue using transcranial focused ultrasound
- Technology: Low intensity transcranial focused ultrasound (i.e., under standard transcranial diagnostic ultrasound power limits)

Based on the intended use, the following product codes for neurostimulation were reviewed:

- OBP, Transcranial Magnetic Stimulator, Class II
- OKP, Transcranial Magnetic Stimulator For The Treatment Of Migraine Headache, Class II
- QCI, Transcranial Magnetic Stimulation System For Obsessive-Compulsive Disorder, Class II
- QMD, Transcranial Magnetic Stimulation System For Smoking Cessation, Class II

While all these product codes may have equivalent intended use, they utilize fundamentally different technology, i.e., transcranial magnetic stimulation to achieve their intended use. The difference in technology would raise different questions of safety or effectiveness and thus would not be appropriate product codes to apply to the subject device.

The following product codes based on the subject device's technology were reviewed:

- ITX, Transducer, Ultrasonic, Diagnostic, Class II
- IYN, System, Imaging, Pulsed Doppler, Ultrasonic, Class II
- IYO, System, Imaging, Pulsed Echo, Ultrasonic, Class II
- IMG, Stimulator, Ultrasound And Muscle, For Use In Applying Therapeutic Deep Heat, Class II
- OHV, Focused Ultrasound For Tissue Heat Or Mechanical Cellular Disruption, Class II
- PLP, High Intensity Ultrasound System For Prostate Tissue Ablation, Class II
- NRZ, Ablation System, High Intensity Focused Ultrasound (Hifu), MR-Guided, Class III
- POH, MR-Guided Focused Ultrasound System, Class III

No product code was found that applied low intensity focused ultrasound transcranially. Though equivalent power levels to the subject device applied transcranially are present in devices in ITX, IYN, and IYO product codes, there are no devices within these product codes that utilize focused ultrasound for neuromodulation. There are other devices that use focused ultrasound but apply at higher intensity levels to ablate tissue and thus not appropriate for the subject device's intended use or mechanism of action.

Based on Openwater's search, no appropriate product codes nor comparable devices were found that are used to administer low intensity focused ultrasound transcranially for neurostimulation.

To establish an appropriate review pathway, Openwater analyzed the risks of the device (see Table 2) and concluded that the device may be regulated as Class II device through a de novo review based on the similarity of the subject device to several other Class II devices, including:

- Transcranial doppler devices that utilize similar power levels of MI < 1.9 and $I_{SPTA} \leq 720$ mW/cm^2, such as K170859, Dolphin/IQ,
- Devices with similar intended use as the subject device such as K203735, Brainsway Deep TMS System, and K210201, Deep Transcranial Magnetic Stimulation System, and

- Devices at higher power levels than the subject device, such as some high intensity focused ultrasound (HIFU) (e.g., K212150, Exablate Prostate System, and K202286, Tulsa-Pro System).

Given the considerable history of regulating transcranial ultrasound and the history of regulating transcranial magnetic stimulation devices for neuromodulation, Openwater believes that by applying similar risk mitigation principles, general and special controls would provide reasonable assurance that the OLTS would be safe and effective for its intended use. Note that the proposed device is intended for research use only and specific indications would require additional regulatory pathway analysis.

Based on this assessment, Openwater proposes to utilize the following special controls as part of its future de novo premarket submission:

1) Non-clinical performance data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   a) Characterization of acoustic pressure and power output at clinically relevant levels;
   b) Measurement of targeting accuracy and reproducibility of low intensity transcranial ultrasound output;
   c) Ultrasound-induced heating verification testing at target and non-target tissues;
   d) Electrical safety testing; and
   e) Electromagnetic compatibility testing.
2) Software verification, validation, and hazard analysis must be performed.
3) The elements of the device that make surface contact with the patient must be demonstrated to be biocompatible.
4) Training must be provided so that upon completion of the training program, the physician can:
   a) Use all safety features of the device; and
   b) Accurately target the low intensity ultrasound energy within the desired region of the brain.
5) Labeling must include a section that describes the device controls for safe and effective operation of the low intensity focused ultrasound output

7 Performance Testing

Based on the analysis of design and principles of operation, Openwater is proposing a set of bench tests in this section that focus on ensuring that the device is safe for its intended use. Efficacy of treatment protocols utilizing the OLTS are not in scope of this submission as no claims of efficacy are being made in the device's indications for use. OLTS is intended for research use only.

7.1 Bench performance testing

The following is a summary of proposed bench performance tests with a reference to the section where details are provided:

- Verify that the array output power and focus position precisely correspond to the planned ones in the free field in water (7.1.1, 7.1.2) and transcranially, i.e., subjected to the aberrative and attenuative effects of the skull (7.1.5)
- Verify that the array cannot generate an MI or TI beyond specified limits (7.1.3, 7.1.4)
- Verify that the treatment planning and simulations align with the surface and tissue measurements at the surface of and at the focus inside of an ex vivo head model (7.1.6)

Appendix B discusses the experimental data collected by Openwater so far to simulate and test prototype devices.

7.1.1 Ultrasound array output characterization for steering and calibration

Test: Acoustic field measurements in a water tank: Scanning a hydrophone in 3D to map the acoustic field of the transducer array while focused to various target locations. This will provide a means of validating the acoustic simulations used during treatment planning and allow for calibration of the device in terms of driving signal amplitude to acoustic pressure output.

Justification: To demonstrate that the OLTS meets all design specification and performance requirements. Testing will accurately characterize the acoustic beam profile and establish that the acoustic energy is delivered and concentrated in the desired target location.

Related Standards:

- IEC standard 62359 Edition 2.1 2017-09 Ultrasonics - Field characterization - Test methods for the determination of thermal and mechanical indices related to medical diagnostic ultrasonic fields
- IEC standard 60601-2-37 Edition 2.1 2015 Medical electrical equipment - Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment

7.1.2 Ultrasound array power measurements

Test: Acoustic and electrical power measurements: Using an electrical power meter, measure the delivered electric power to the transducer and using an acoustic radiation force balance, measure the acoustic power being emitted from the transducer.

Justification: The acoustic power measurements will be conducted to demonstrate that the radiated acoustic power is repeatable and that there is low variability among transducers. This will also be used to determine electro-acoustic efficiency and estimate the potential heat buildup in the transducer and corresponding heat rise in the skin.

Related Standards:

- IEC standard 62555 Edition 1.0 2013-11 Ultrasonics -- Power measurement -- High intensity therapeutic ultrasound (HITU) transducers and systems
- IEC standard 61161 Edition 3.0 2013-01 Ultrasonics -- Power measurement -- Radiation force balances and performance requirements

7.1.3 Verification that device cannot cause inertial cavitation

Test: Show that no inertial cavitation is occurring using transducer array and passive cavitation detector with ex vivo animal brain tissue (pig or cow) and ex vivo human skull. Focus the array in a tissue mimicking phantom and have one or more transducers (Passive cavitation detectors - PCDs) focused in the same location as the treatment array. A protocol for measuring increased wide band noise will be used as it is indicative of inertial cavitation. This verification will be performed at the lowest, middle, and highest operating frequency.

Justification: Inertial cavitation would have a destructive effect on tissue, even if it is transient; this test will be used to confirm that inertial cavitation does not occur up to the highest in situ pressure level (corresponding to a MI of 1.9, i.e. 1.5 MPa at the highest operating frequency) and that the device stays well below the theoretical threshold for bubble nucleation or inertial cavitation of 3.9MPa [1].

Related Standards:

- IEC standard 60601-2-37 Edition 2.1 2015 Medical electrical equipment - Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment
- IEC standard 60601-2-62 Edition 1.0 2013-07 Medical electrical equipment - Part 2-62: Particular requirements for the basic safety and essential performance of high intensity therapeutic ultrasound (HITU) equipment

7.1.4 Thermal testing

Test: Ultrasound transmission through human skull into tissue mimicking phantom or ex vivo brain tissue. Ultrasound device is acoustically coupled to the skull with thermocouples in the vicinity of the acoustic focus and on the surface of the skull to verify temperature rise matches what is predicted. Additionally, there will be thermocouples on the device face to monitor its temperature.

Justification: There are many associated risks with having the temperature exceed a certain threshold for a certain amount of time. Typically, a formula for cumulative equivalent minutes is used when thermal necrosis is desired. However, in this case the intent is to prevent thermal effects associated with temperature rises of greater than 2ºC in the target tissue. The goal is to ensure that the device does not elevate or cause any thermal damage to the tissue proximal or adjacent to the target tissue.

Related Standards:

- IEC standard 60601-2-37 Edition 2.1 2015 Medical electrical equipment - Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment

- IEC standard 60601-2-62 Edition 1.0 2013-07 Medical electrical equipment - Part 2-62: Particular requirements for the basic safety and essential performance of high intensity therapeutic ultrasound (HITU) equipment

7.1.5 Ultrasound array output calibration for focusing and focus steering in water (Restricted Operating Mode)

Test: Perform acoustic simulations of field being propagated in Restricted Operating Mode. Compare to acoustic field measurements will be taken in a water tank. A hydrophone will be attached to a 3D positioning system in a water tank and will be used to map the acoustic field of the ultrasound array while it is electronically focused (without any aberration correction) to various target locations in water.

Justification: To demonstrate that the focused ultrasound system meets all design specification and performance requirements. Testing will accurately characterize the acoustic beam profile and establish that the acoustic energy is delivered and concentrated in the desired target location. This will also provide information to determine an upper limit to the voltage being applied to the transducer such that one can ensure no adverse thermal or mechanical events.

Related Standards:

- IEC standard 62359 Edition 2.1 2017-09 Ultrasonics - Field characterization - Test methods for the determination of thermal and mechanical indices related to medical diagnostic ultrasonic fields
- IEC standard 60601-2-37 Edition 2.1 2015 Medical electrical equipment - Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment
- IEC standard 60601-2-62 Edition 1.0 2013-07 Medical electrical equipment - Part 2-62: Particular requirements for the basic safety and essential performance of high intensity therapeutic ultrasound (HITU) equipment

7.1.6 Verification of treatment planning using CT scan of ex vivo skull (Standard Operating Mode)

Test: Perform acoustic simulations of field being propagated through ex vivo skull and determine appropriate surface pressures and phase delays to obtain desired pressure in the focuses. These acoustic surface pressures will be translated into driving voltage based upon previous calibration. Following simulation, experimental validation by using the ultrasound device to transmit with the simulation determined parameters through the same ex vivo skull, and measuring the resulting acoustic field using a hydrophone in a water tank. Multiple foci simulated and experimentally validated will be targeted to ensure accurate targeting is achieved.

Justification: These tests will be critical for validation of the steering and pressure calibrations of the probe to ensure that the desired levels of acoustic dose are delivered.

Related Standards:

- IEC standard 62359 Edition 2.1 2017-09 Ultrasonics - Field characterization - Test methods for the determination of thermal and mechanical indices related to medical diagnostic ultrasonic fields

- IEC standard 60601-2-37 Edition 2.1 2015 Medical electrical equipment - Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment
- IEC standard 60601-2-62 Edition 1.0 2013-07 Medical electrical equipment - Part 2-62: Particular requirements for the basic safety and essential performance of high intensity therapeutic ultrasound (HITU) equipment

7.2 Biocompatibility

A biocompatibility risk assessment of all patient-contacting surfaces per ISO 10993-1 will be conducted and appropriate testing to address the risk will be conducted. Given that the device makes contact with intact skin for 30 minutes or less, the testing would likely involve an assessment of cytotoxicity, sensitization, and irritation.

7.3 Cleaning

Given that the OLTS Headset is intended to contact intact skin on the head and makes no contact with mucous membranes or blood, the device will not require high level disinfection or sterilization. The device instructions for use will provide methods to clean the OLTS Headset. Validation that the device can be cleaned will be conducted including an assessment that afterwards, the device continues to perform as intended.

7.4 EMC and Safety

Electrical safety and electromagnetic compatibility testing per IEC 60601-1 and 60601-1-2 will be conducted.

7.5 Software

Product software will be assessed per FDA Guidance, “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices”, dated May 2005, and cybersecurity assessments based on FDA Guidance FDA Guidance, “Guidance for the Content of Premarket Submissions for Management of Cybersecurity in Medical Devices”, dated October 2018 and FDA Guidance, “Postmarket Management of Cybersecurity in Medical Devices”, dated October 2018. Documentation as required by the guidance will be developed and software verification and validation will be conducted to demonstrate that the Openwater Headset software satisfies its software requirements. Based on the guidance noted above, Openwater assessed the level of concern in the tables below and concluded that the device has a “Moderate” level of concern. This is consistent with the level of concern Openwater noted in several transcranial diagnostic ultrasound devices as well as transcranial magnetic stimulation devices.

Table 3: FDA Guidance Table 1: Major Level of Concern

Question	Response	Notes
1. Does the Software Device qualify as Blood Establishment Computer Software?	No	OLTS does not qualify as Blood Establishment Computer Software.
2. Is the Software Device intended to be used in combination with a drug or biologic?	No	OLTS is not intended to be used in combination with a drug or biologic.

Table 3: FDA Guidance Table 1: Major Level of Concern

Question	Response	Notes
3. Is the Software Device an accessory to a medical device that has a Major Level of Concern?	No	OLTS is not an accessory to another medical device.
4. Prior to mitigation of hazards, could a failure of the Software Device result in death or serious injury, either to a patient or to a user of the device?	No	OLTS is intended to deliver ultrasound at limits known to be safe and is limited within the hardware. The failure of the device could not directly lead to death or serious injury per risk analysis and risk mitigation.
a. Does the Software Device control a life supporting or life sustaining function?	No	OLTS is not intended to control a life supporting or sustaining function.
b. Does the Software Device control the delivery of potentially harmful energy that could result in death or serious injury, such as radiation treatment systems, defibrillators, and ablation generators?	No	OLTS is intended control delivery of a ultrasound energy, but the energy output is limited in hardware to limits known to be safe. As a result, a failure in the device software cannot result in the delivery of potentially harmful energy that could result in death or serious injury.
c. Does the Software Device control the delivery of treatment or therapy such that an error or malfunction could result in death or serious injury?	No	While OLTS software controls the treatment planning, the delivery of treatment is controlled in hardware which includes limitations to ensure safe operation.
d. Does the Software Device provide diagnostic information that directly drives a decision regarding treatment or therapy, such that if misapplied it could result in serious injury or death?	No	OLTS does not provide any diagnostic information.
e. Does the Software Device provide vital signs monitoring and alarms for potentially life-threatening situations in which medical intervention is necessary?	No	OLTS does not provide vital signs monitoring or alarms.

Conclusion: Openwater Headset is <u>not</u> a Major Level of Concern software.

Table 4: FDA Guidance Table 2: Moderate Level of Concern

Question	Response	Notes
1. Is the Software Device an accessory to a medical device that has a Moderate Level of Concern?	No	OLTS is not a component of other medical devices.
2. Prior to mitigation of hazards, could a failure of the Software Device result in Minor Injury, either to a patient or to a user of the device?	Yes	Prior to mitigation of hazards, failure of the software in OLTS could cause minor injury.

Table 4: FDA Guidance Table 2: Moderate Level of Concern

Question	Response	Notes
3. Could a malfunction of, or a latent design flaw in, the Software Device lead to an erroneous diagnosis or a delay in delivery of appropriate medical care that would likely lead to Minor Injury?	Yes	OLTS is intended to provide neurostimulation. A software malfunction or latent design flaw could result in delay in delivery of appropriate medical care that would likely lead to Minor Injury.

Conclusion: OLTS is a Moderate Level of Concern software.

7.6 Human Factors

Openwater proposes to conduct human factors evaluation per FDA Guidance, "Applying Human Factors and Usability Engineering to Medical Devices", dated, February 2016 as part of its evaluation of OLTS.

7.7 Clinical Testing

Since the device includes no efficacy claims, no clinical performance testing is being proposed.

8 Specific Questions and Issues for Discussion

Openwater is in the development phase of the Openwater LOFU Therapy System (OLTS) and is seeking early Agency feedback on its regulatory approach to ensure the device is appropriately characterized for a future premarket device submission. Openwater requests Agency feedback on the following topics:

Regulatory Strategy Questions

1) Does FDA agree that the proposed regulatory pathway is appropriate for OLTS? Specifically,
    a. Does the FDA agree that based on the regulatory strategy provided and the device's risk profile, the subject device may be classified as a Class II device?
    b. Does the FDA agree that based on the regulatory strategy provided that a de novo pathway would be appropriate?
2) Does the Agency have any comments on the proposed special controls for the subject device discussed in Section 6?

Future Device Strategy Question

3) When the OLTS device has successfully has been granted a de novo by the FDA, Openwater intends to market the device for neuromodulation clinical research without requiring an IDE. When such clinical research can establish efficacy for specific claims (e.g., treatment of mood disorders), Openwater would approach the Agency for a premarket submission for these efficacy claims.

    For efficacy claims similar to TMS devices that are regulated as Class II devices, could Openwater use the OLTS de novo as a predicate to expand the indications for use in a 510(k) premarket submission or would the efficacy claims require a de novo premarket submission? Does the FDA have any comments on the regulatory approach for future LOFU-based neuromodulation efficacy submissions using the OLTS device?

Performance Testing Questions

4) Does the FDA have any comments on the proposed testing plans to assess device performance, as described in Section 7, for a future device submission?
    a. Does the FDA have any comments on the proposed bench testing plan for the OLTS? Are there any specific considerations that Openwater should additionally include in its test plans?
    b. Based on the regulatory strategy provided, does FDA agree, based on the discussion provided, that animal performance testing data is not needed to support a future device submission?
    c. Based on the regulatory strategy provided, does FDA agree, based on the discussion provided, that clinical performance testing data is not needed to support a future device submission?
    d. Does FDA agree that the OLTS software is a "Moderate" level of concern and that the level of documentation that will be included in an upcoming marketing submission is consistent with FDA's recommendations provided in FDA's guidance entitled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" as part of the premarket device submission?

Other considerations

5) Does the FDA have any other concerns or topics they would like Openwater to consider for OLTS premarket device submission?

9 Mechanism of Feedback

In addition to written feedback, Openwater is requesting an in-person 1-hour long teleconference meeting to discuss the questions listed in Section 8.

Materials needed during meeting:

- Conference bridge to share information and slides

Suggested FDA Staff who should attend the meeting:

- Lead Reviewer
- Assistant Director for the reviewing branch
- Additionally, Openwater would appreciate if any one of the following could comment on the presubmission feedback, or attend the meeting:
    - Subha Maruvada, Ph.D.
    - Keith Wear, Ph.D.,
    - Gregory Clement, Ph.D.

Proposed dates:

Openwater proposed the following dates for the meeting. Per FDA guidelines, these dates are proposed 60-75 dates from the submission date.

- Any business day between May 09, 2022, to May 20, 2022, between 11am – 5pm EST

Openwater Attendees:

The following Openwater personnel and its consultants will attend this meeting:

Name	**Title**
Maurizio Vecchione	President, Openwater
Achal Singh Achrol, MD	Chief Medical Officer, Openwater
Soren Konecky, Ph.D.	Chief Technology Officer, Openwater
Chris Bawiec, Ph.D.	Principal Ultrasonic Engineer, Openwater
Tatianna Khokhlova, Ph.D.	Research Associate Professor, Medicine, University of Washington Ultrasound Consultant to Openwater
Casey Trubo	Director of Program Management, Openwater
Prabhu Raghavan	Regulatory Consultant to Openwater

10 Works Cited

1. AIUM. Statement on Biological Effects of Ultrasound in Vivo. https://www.aium.org/officialStatements/82. Last accessed February 21, 2022.
2. AIUM. Official Statement Recommended Maximum Scanning Times for Displayed Thermal Index (TI) Values. https://www.aium.org/officialStatements/65. Last accessed February 21, 2022
3. Abbott, J. G. (1999). Rationale and derivation of MI and TI—a review. Ultrasound in medicine & biology, 25(3), 431-441
4. Alexandrov AV, Mikulik R, Ribo M, Sharma VK, Lao AY, Tsivgoulis G, Sugg RM, Barreto A, Sierzenski P, Malkoff MD, Grotta JC. A pilot randomized clinical safety study of sonothrombolysis augmentation with ultrasound-activated perflutren-lipid microspheres for acute ischemic stroke. Stroke. 2008 May;39(5):1464-9. doi: 10.1161/STROKEAHA.107.505727. Epub 2008 Mar 20. PMID: 18356546; PMCID: PMC2707058.
5. Aubry JF, Tanter M, Pernot M, Thomas JL, Fink M. Experimental demonstration of noninvasive transskull adaptive focusing based on prior computed tomography scans. J Acoust Soc Am. 2003 Jan;113(1):84-93. doi: 10.1121/1.1529663. PMID: 12558249.
6. Badran, B. W., Caulfield, K., Stomberg-Firestein, S., Summers, P., Dowdle, L. T., Savoca, M., ... & George, M. S. (2020). Sonication of the Anterior Thalamus with MRI-Guided Low Intensity Focused Ultrasound Pulsation (LIFUP) Changes Pain Thresholds in Healthy Adults: A Double-Blind, Concurrent LIFUP/MRI Study. medRxiv.
7. Blackmore, J., Shrivastava, S., Sallet, J., Butler, C. R., & Cleveland, R. O. (2019). Ultrasound neuromodulation: a review of results, mechanisms and safety. Ultrasound in medicine & biology, 45(7), 1509-1536.
8. Constans C, Mateo P, Tanter M, Aubry JF. Potential impact of thermal effects during ultrasonic neurostimulation: retrospective numerical estimation of temperature elevation in seven rodent setups. Phys Med Biol. 2018 Jan 9;63(2):025003. doi: 10.1088/1361-6560/aaa15c. PMID: 29235453.
9. Cox BT, Laufer JG, Kostli KP, Beard PC. Experimental validation of photoacoustic k-space propagation models. InPhotons Plus Ultrasound: Imaging and Sensing 2004 Jul 12 (Vol. 5320, pp. 238-248). International Society for Optics and Photonics.
10. Culjat MO, Goldenberg D, Tewari P, Singh RS. A review of tissue substitutes for ultrasound imaging. Ultrasound in medicine & biology. 2010 Jun 1;36(6):861-73.
11. Darrow DP. Focused ultrasound for neuromodulation. Neurotherapeutics. (2019) 16:88–99
12. Dallapiazza RF, Timbie KF, Holmberg S, Gatesman J, Lopes MB, Price RJ, et al. Non-invasive neuromodulation and thalamic mapping with low-intensity focused ultrasound. J Neurosurg.(2018) 128:875–84
13. di Biase L, Falato E, Di Lazzaro V. Transcranial Focused Ultrasound (tFUS) and Transcranial Unfocused Ultrasound (tUS) Neuromodulation: From Theoretical Principles to Stimulation Practices. Front Neurol 2019;10:549
14. Di Lazzaro V, Rothwell JC. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. J Physiol. (2014) 592:4115–28.
15. FDA Marketing Clearance of Diagnostic Ultrasound Systems and Transducers. Draft Guidance for Industry and Food and Drug Administration Staff (2017). Available online at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM578118

16. Fini M, Tyler WJ. Transcranial focused ultrasound: a new tool for non-invasive neuromodulation. Int Rev Psychiatry. (2017) 29:168–77
17. Folloni D, Verhagen L, Mars RB, Fouragnan E, Constans C, Aubry J-F, et al. . Manipulation of subcortical and deep cortical activity in the primate brain using transcranial focused ultrasound stimulation. Neuron. (2019) 101:1109–16.e1105
18. Fomenko A, Neudorfer C, Dallapiazza RF, Kalia SK, Lozano AM. Low-intensity ultrasound neuromodulation: an overview of mechanisms and emerging human applications. Brain Stim. (2018) 11:1209–17
19. Fox MD, Buckner RL, White MP, et al: Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry 2012; 72:595–603].
20. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol. 2006 Apr;117(4):845-50
21. Gangnam Severance Hospital. "Efficacy of Clinical Application of Transcranial Low Intensity Focused Ultrasonic Stimulation for Patients With Major Deperessive Disorder - Exploratory Clinical Trial. NCT04405791. Retrieved from https://clinicaltrials.gov/ct2/show/NCT04405791. Last accessed February 28, 2022
22. Hallett M: Transcranial magnetic stimulation and the human brain. Nature 2000; 406:147–150][Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol. 2006 Apr;117(4):845-50
23. Hameroff S, Trakas M, Duffield C, Annabi E, Gerace MB, Boyle P, et al. Transcranial ultrasound (TUS) effects on mental states: a pilot study. Brain Stimul. (2013) 6:409–15
24. Harris GR, Church CC, Dalecki D, Ziskin MC, Bagley JE. Comparison of thermal safety practice guidelines for diagnostic ultrasound exposures. Ultrasound Med Biol 2016; 42:345-357
25. Huerta PT, Volpe BT: Transcranial magnetic stimulation, synaptic plasticity, and network oscillations. J Neuroeng Rehabil 2009]
26. Iacono MI, Neufeld E, Akinnagbe E, Bower K, Wolf J, Vogiatzis Oikonomidis I, Sharma D, Lloyd B, Wilm BJ, Wyss M, Pruessmann KP. MIDA: a multimodal imaging-based detailed anatomical model of the human head and neck. PloS one. 2015 Apr 22;10(4):e0124126.
27. King RL, Brown JR, Newsome WT, Pauly KB. Effective parameters for ultrasound-induced in vivo neurostimulation. Ultrasound Med Biol. (2013) 39:312–31
28. Kim H, Chiu A, Lee SD, Fischer K, Yoo S-S. Focused ultrasound-mediated non-invasive brain stimulation: examination of sonication parameters. Brain Stimul. (2014) 7:748–56.
29. Korb, A. S., Shellock, F. G., Cohen, M. S., & Bystritsky, A. (2014). Low-intensity focused ultrasound pulsation device used during magnetic resonance imaging: Evaluation of magnetic resonance imaging-related heating at 3 Tesla/128 MHz. Neuromodulation: Technology at the Neural Interface, 17(3), 236-241.
30. Krasovitski B, Frenkel V, Shoham S, Kimmel E. Intramembrane cavitation as a unifying mechanism for ultrasound-induced bioeffects. Proc Natl Acad Sci. (2011)
31. Lee W, Lee SD, Park MY, Foley L, Purcell-Estabrook E, Kim H, et al. Image-guided focused ultrasound-mediated regional brain stimulation in sheep. Ultrasound Med Biol. (2016) 42:459–70.
32. Lee W, Kim HC, Jung Y, Chung YA, Song IU, Lee JH, et al. . Transcranial focused ultrasound stimulation of human primary visual cortex. Sci Rep. (2016) 6:34026

33. Lee W, Kim H, Jung Y, Song IU, Chung YA, Yoo SS. Image-guided transcranial focused ultrasound stimulates human primary somatosensory cortex. Sci Rep. (2015) 5:8743
34. Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, et al. . Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. Nat Neurosci. (2014) 17:322–9
35. Ling, Y. T., Martin, E., & Treeby, B. E. (2015, October). A discrete source model for simulating bowl-shaped focused ultrasound transducers on regular grids: Design and experimental validation. In 2015 IEEE International Ultrasonics Symposium (IUS) (pp. 1-4). IEEE.
36. Liu X, Hu Y, Wu L, Li S. Effects of collimated and focused low-intensity pulsed ultrasound stimulation on the mandible repair in rabbits. Ann Transl Med. 2020 Feb;8(4):98. doi: 10.21037/atm.2019.12.89. PMID: 32175391; PMCID: PMC7049032.
37. Lucena MFG, Teixeira PEP, Bonin Pinto C, Fregni F. Top 100 cited noninvasive neuromodulation clinical trials. Expert Rev Med Devices. 2019 Jun;16(6):451-466
38. T. Douglas Mast , "Empirical relationships between acoustic parameters in human soft tissues", Acoustics Research Letters Online 1, 37-42 (2000) https://doi.org/10.1121/1.1336896
39. McDannold, N., Vykhodtseva, N., Jolesz, F. A., & Hynynen, K. (2004). MRI investigation of the threshold for thermally induced blood–brain barrier disruption and brain tissue damage in the rabbit brain. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine, 51(5), 913-923
40. Medical University of South Carolina. Low Intensity Focused Ultrasound Pulses (LIFUP) to Modulate Pain. NCT04339972. https://clinicaltrials.gov/ct2/show/NCT04339972. Last accessed February 28, 2022
41. Menikou G, Damianou C. Acoustic and thermal characterization of agar based phantoms used for evaluating focused ultrasound exposures. J Ther Ultrasound 2017;5:14
42. Miller GW, Eames M, Snell J, Aubry JF. Ultrashort echo-time MRI versus CT for skull aberration correction in MR-guided transcranial focused ultrasound: In vitro comparison on human calvaria. Med Phys. 2015 May;42(5):2223-33. doi: 10.1118/1.4916656. PMID: 25979016.
43. Miller, M. W., Nyborg, W. L., Dewey, W. C., Edwards, M. J., Abramowicz, J. S., & Brayman, A. A. (2002). Hyperthermic teratogenicity, thermal dose and diagnostic ultrasound during pregnancy: implications of new standards on tissue heating. International journal of hyperthermia, 18(5), 361-384
44. Morris CE, Juranka PF. Lipid stress at play: mechanosensitivity of voltage-gated channels. In: Current Topics in Membranes. Elsevier (2007a) p. 297–338
45. Morris CE, Juranka PF. Nav channel mechanosensitivity: activation and inactivation accelerate reversibly with stretch. Biophys J. (2007b) 93:822–33
46. Mueller JK, Ai L, Bansal P, Legon W. Numerical evaluation of the skull for human neuromodulation with transcranial focused ultrasound. J Neural Eng. 2017 Dec;14(6):066012. doi: 10.1088/1741-2552/aa843e. PMID: 28777075.
47. Munoz F, Aurup C, Konofagou EE, Ferrera VP. Modulation of brain function and behavior by focused ultrasound. Curr Behav Neurosci Rep. (2018) 5:153–64.
48. Ogata T, Ito K, Shindo T, Hatanaka K, Eguchi K, Kurosawa R, et al. (2017) Low-intensity pulsed ultrasound enhances angiogenesis and ameliorates contractile dysfunction of pressureoverloaded heart in mice. PLoS ONE 12(9): e0185555. https://doi.org/10.1371/journal. pone.0185555

49. Ogiue-Ikeda M, Kawato S, Ueno S: The effect of repetitive transcranial magnetic stimulation on long-term potentiation in rat hippocampus depends on stimulus intensity. Brain Res 2003; 993:222–226
50. Pasquinelli et al "Safety of transcranial focused ultrasound stimulation: A systematic review of the state of knowledge from both human and animal studies" Brain Stimulation 2019
51. Plaksin M, Shoham S, Kimmel E. Intramembrane cavitation as a predictive bio-piezoelectric mechanism for ultrasonic brain stimulation. Phys Rev. X. (2014) 4:011004
52. Robertson JL, Cox BT, Jaros J, Treeby BE. Accurate simulation of transcranial ultrasound propagation for ultrasonic neuromodulation and stimulation. The Journal of the Acoustical Society of America. 2017 Mar 13;141(3):1726-38.
53. Sanguinetti JL, Hameroff S, Smith EE, et al. Transcranial Focused Ultrasound to the Right Prefrontal Cortex Improves Mood and Alters Functional Connectivity in Humans. Front Hum Neurosci. 2020;14:52.
54. Sato M, Motoyoshi M, Shinoda M, Iwata K, Shimizu N. Low-intensity pulsed ultrasound accelerates nerve regeneration following inferior alveolar nerve transection in rats. Eur J Oral Sci. 2016 Jun;124(3):246-50. doi: 10.1111/eos.12271. Epub 2016 Apr 5.
55. Singh RS. A review of tissue substitutes for ultrasound imaging. Ultrasound in medicine & biology. 2010 Jun 1;36(6):861-73.
56. Uwe Schneider et al. The calibration of CT Hounsfield units for radiotherapy treatment planning. 1996 Phys. Med. Biol. 41 111
57. Treeby BE, Cox BT. k-Wave: MATLAB toolbox for the simulation and reconstruction of photoacoustic wave fields. J Biomed Opt. 2010 Mar-Apr;15(2):021314. doi: 10.1117/1.3360308. PMID: 20459236.
58. Treeby BE, Cox BT. K-Wave User Manual. http://www.k-wave.org/manual/k-wave_user_manual_1.1.pdf. retrieved March 1, 2022
59. Tufail Y, Matyushov A, Baldwin N, Tauchmann ML, Georges J, Yoshihiro A, et al. . Transcranial pulsed ultrasound stimulates intact brain circuits. Neuron. (2010) 66:681–94], amygdala [Folloni D, Verhagen L, Mars RB, Fouragnan E, Constans C, Aubry J-F, et al. . Manipulation of subcortical and deep cortical activity in the primate brain using transcranial focused ultrasound stimulation. Neuron. (2019) 101:1109–16.e1105
60. Tyler WJ, Lani SW, Hwang GM. Ultrasonic modulation of neural circuit activity. Curr Opinion Neurobiol. (2018) 50:222–31.
61. Tyler WJ, Tufail Y, Finsterwald M, Tauchmann ML, Olson EJ, Majestic C. Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound. PLoS ONE. (2008) 3:e3511.
62. Wang, S., Meng, W., Ren, Z., Li, B., Zhu, T., Chen, H., ... & Jiang, H. (2020). Ultrasonic Neuromodulation and Sonogenetics: A New Era for Neural Modulation. Frontiers in Physiology, 11, 787.
63. White PJ, Clement GT, Hynynen K. Local frequency dependence in transcranial ultrasound transmission. Phys Med Biol. 2006 May 7;51(9):2293-305. doi: 10.1088/0031-9155/51/9/013. Epub 2006 Apr 19. PMID: 16625043; PMCID: PMC1560343.
64. Advisory Group on Non-ionising Radiation. 2010 Health effects of exposure to ultrasound and infrasound. UK:Health Protection Agency pg 88

Appendix A Treatment planning

A detailed description of the treatment planning as well as the principles of its operation are discussed below.

A.1 Transformation of imaging data to density, speed of sound, and attenuation maps

The first step in treatment planning within the Standard Operating Mode (SOM) is to transform the imaging data for use in treatment planning. Note that this step is skipped in Restricted Operating Mode (ROM) which will model the simulations for use to be driven within water.

If CT data is provided, the following steps will be used:

1. Read CT images and generate a corresponding volume of Hounsfield units
2. Convert Hounsfield units to acoustic properties using empirical relationships per Mueller et. al. [46].

$$\psi = 1 - \frac{H}{1000} \quad (1)$$

$$c_{skull} = c_{water}\psi + c_{bone}(1 - \psi) \quad (2)$$

$$\rho_{skull} = \rho_{water}\psi + \rho_{bone}(1 - \psi) \quad (3)$$

$$\alpha_{skull} = \alpha_{min} + (\alpha_{max} - \alpha_{min})\psi^{0.5} \quad (4)$$

where H represents Hounsfield units, ψ is porosity, c_{skull} is speed of sound in the skull, c_{water} is the speed of sound in water, c_{bone} is the speed of sound in bone, ρ_{skull} is the density of skull, and α_{skull} is the attenuation in the skull. Acoustic parameter values are given in the table below.

Table 5: Simulation material parameters [46, 10]

Speed of sound (m/s)	Density (kg/m^3)	Attenuation (dB/cm)
c_{water} = 1500	ρ_{water} = 1000	α_{water} = 0
c_{bone} = 2900	ρ_{bone} = 2100	α_{bone_min} = 0.2, α_{bone_max} = 8
c_{brain} = 1560	ρ_{brain} = 1040	α_{brain} = 0.6

If MR data is provided, the following steps will be used:

1. Read MR data and segment out bone, air and soft tissue [42].
2. Assign speed of sound, density and attenuation values provided in the Table 5 to each segmented class.

A.2 Define the optimal foci locations within the treatment volume

Once the treatment volume is defined, the number of focal distance planes that will be treated as well as the number of foci per plane will be defined, which will correlate to the focal volume dimensions for each focal distance. The focal volume size will be defined as a -6dB pressure drop from maximum based on simulation. In order to accurately assess the size of the foci, benchtop

hydrophone measurements in water will be compared to simulations for all of the steerable foci locations. Openwater's custom algorithm will allow for the entire treatment volume to be treated with the desired dose.

In order to help visualization of the different sized foci in the different distance planes, the following figure was created from simulation of the headset ultrasound array. The figure illustrates the shapes of the focal area within -6dB level for different focusing depths.

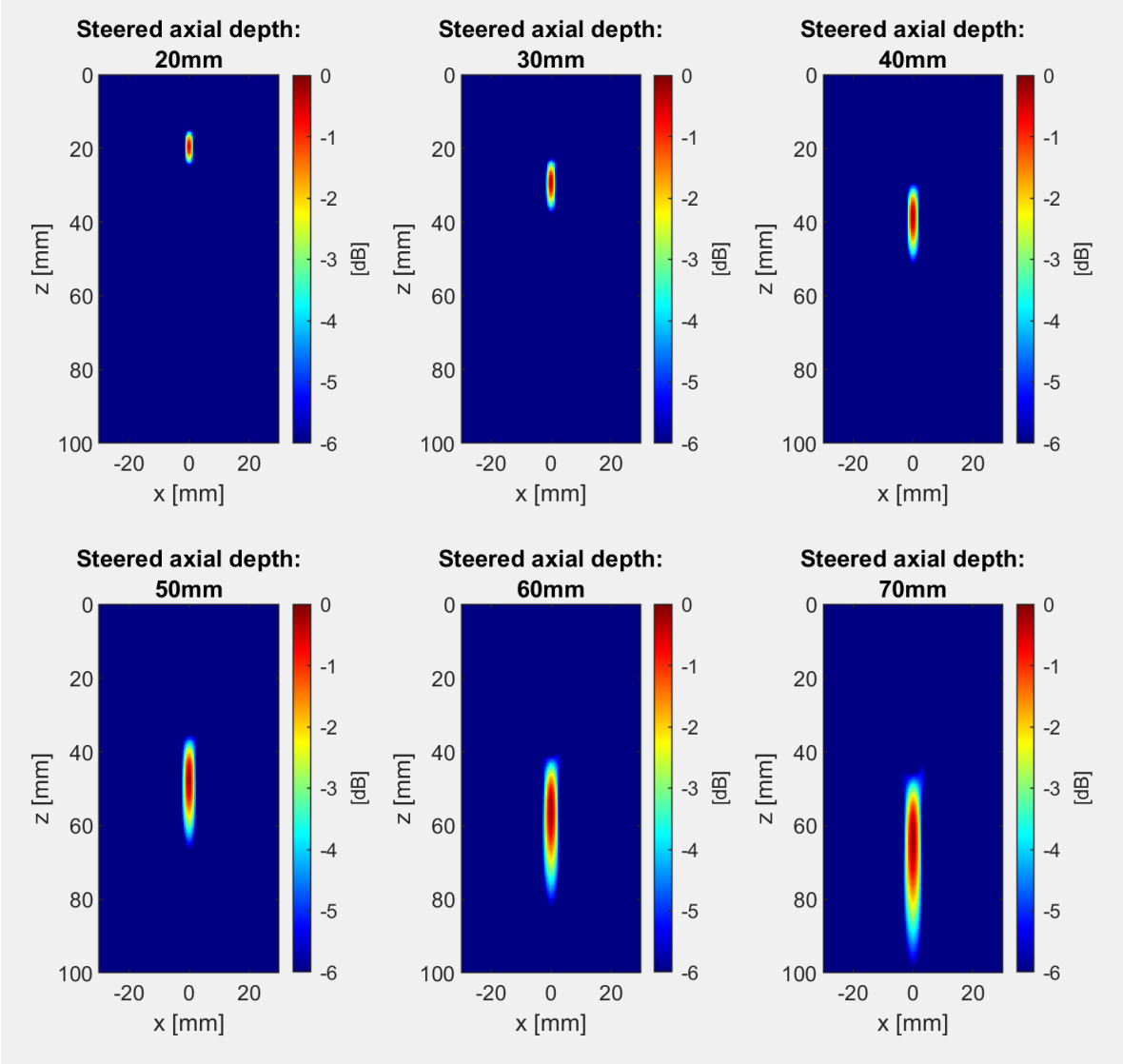

Figure 8: Cross sectional pressure amplitude plots of the ultrasound array firing at different focal depths. Focal beamwidth varies between 3-6.5mm and the beam length varies between 10-53mm.

A.3 Calculating array element delays for beamforming

Once the optimal focus positions have been identified, beamforming will be used to calculate the appropriate phases of all the device's elements. In Restricted Operating Mode (ROM), a constant speed of sound value of water is used with the beamforming algorithm, however, this can lead to

inaccuracies in the focus location due to strong aberration caused by the skull. Therefore, it is recommended to use the device in SOM, where the time delays are calculated for each element accurately, using the speed-of-sound map (that is generated from CT/MR scan) for both skull and brain tissue (Table 5). This enables the time of flight to be computed between each element and focus location. Time delays for each element will then be assigned accordingly.

A.4 Acoustic field modelling

Once the simulation volumes have been calculated, the treatment volume has been determined, the foci have been selected, and the phase delays have been calculated (beamforming), acoustic field simulations will be performed using the tool, k-Wave. k-Wave is an open source software to simulate propagation of acoustic waves in time domain. k-Wave is capable of simulating both linear and nonlinear wave propagation, with arbitrarily defined heterogeneous medium and power law acoustic absorption.

The acoustic field simulations use the following inputs:

- parameters defining the geometry of the simulation,
- acoustic tissue properties such as speed of sound, density and attenuation,
- properties of the transducer, driving function, surface acoustic pressure, and
- desired measurement location of the simulated quantities.

k-Wave has been extensively used in acoustic field modeling and its accuracy is validated by comparison with experimental measurements [35]. With k-Wave, both pressure and particle velocity field can be calculated at all times and all points on the computational domain. The output can then be used to calculate the relevant parameters (pressure, intensity (spatial-peak, temporal-average, and spatial-peak, pulse-average), mechanical index (MI), Thermal Index (TI), temperature rise, and secondary forces such as radiation and streaming). k-Wave has also been used extensively by many researchers validating its use for transcranial acoustic simulations [9, 52].

A.5 Calculation of key ultrasound parameters to ensure acoustic levels are within limits

The standard and restricted operating modes use the same limits, with the key differentiation being that the values are calculated for patient specific models that include attenuation for the SOM and in water for the ROM.

For all focal positions, the maximum ultrasound pressure will be set to ensure that the mechanical index (MI) will not exceed 1.9. The MI metric is used to ensure that no cavitational damage will occur in tissue.

$$MI = \frac{P^{-}_{peak}}{\sqrt{freq}}$$

Where, P^{-}_{peak} is peak negative (rarefactional) pressure in MPa, and $freq$ is the center frequency in MHz. Although these concepts were developed for short ultrasound imaging pulses, it is used here to facilitate comparison. At a common LOFU driving frequency of 400kHz, this limits the

device's maximum peak-rarefactional pressure to 1.2 MPa. No derating is done to this pressure calculation as it does not significantly affect the maximum pressure, and it provides an extra margin of safety in the calculation. It should also be noted that a peak-negative pressure at this amplitude is unlikely to cause cavitation since it is well below the theoretical threshold for bubble nucleation or inertial cavitation of 3.9MPa [1].

In addition to the pressure limitations of the ultrasound, there are also limitations in place for the intensity of ultrasound that is being applied. Regardless of the operating mode, the maximum spatial-peak, temporal average intensity that will be utilizable will be 720 mW/cm^2. This spatial-peak, temporal-average (SPTA) intensity level I_{SPTA} is calculated based upon the peak pressure combined with the total ultrasound on-time per second of the applied ultrasound.

$$I_{spta} = (dutycycle) * P_{peak}^2/(2\rho c) \text{ where,}$$
P_{peak} is the peak-pressure,
ρ is the density, and
c is speed of sound.

As an example, at a 5% duty-cycle or 50ms on-time per second the maximum peak pressure allowable in the focus is approximately 700kPa. At a 50% duty-cycle, or a 500ms on-time per second the maximum allowable peak pressure is approximately 220kPa.

A.6 Thermal Simulation in Standard Operating Mode

The same stimulation parameters that will be used for the acoustic field simulation and resulting quantities will be used as inputs into the treatment planning's numerical model. The model will contain the location of the wearable headset with relation to the acoustic volume that is created with the relevant ultrasound parameters from the medical image data. This 3D volume will then be used to simulate the acoustic propagation of the waves and allow for the determination of the acoustic intensity throughout the entire volume. This intensity data will then be used to calculate the temperature rise of the skull and brain tissues with an emphasis on the stimulated treatment region of the brain. This will allow selection of treatment parameters that will not result in unwanted thermal damage or effects. This will be done for operation of the device in all of the modes of operation.

The output of the thermal simulation will be to verify that the stimulation parameters will not cause any damaging thermal effects in the brain.

In addition to the simulation functions for modelling of acoustic wave propagation, k-Wave also includes functions for the time domain simulation of heat diffusion and perfusion in heterogeneous media. These simulations use four input parameters:

- parameters defining the computational grid,
- the thermal properties of the medium,
- the properties and locations of any thermal sources (instantaneous pressure/intensity), and
- locations of the sensor points used to record the evolution of the temperature field over time. [58]

k-Wave solves Pennes' bioheat equation, so there are two sets of medium properties that can be defined. The first set is related to the diffusion of heat (conduction to other parts of the medium), and the second set is related to perfusion (the removal of heat by blood circulating in the tissue).

k-Wave is being used in the acoustic community for the thermal heating prediction such as neurostimulation, LOFU, and HIFU applications.

A.7 Thermal Simulation for Restricted Operating Mode

In contrast to the SOM, ROM does all of the acoustic simulations with the properties of water. This does not allow the calculation of the thermal heating in the entire acoustic space because a key input to the heating is the attenuation which is neglected in water simulations. To account for this difference ROM places a limitation on the treatment duration that will be allowed. This will ensure that there will be no adverse effects due to heating of the tissue. Since heat-related bio-effects are known not to occur until exposures of 1.5°C - 2.5°C over baseline temperature for at least 1 hour, OLTS will limit heating to 2°C and a maximum possible total treatment time of 1 hour [38, 64].

In addition, since there have been no significant adverse biological effects observed due to temperature increases less than or equal to 2°C [1] for exposure under 250 minutes according to the following empirical relationship, which is far longer than the expected treatment time of less than 30 minutes.

$$t = 10^{[B*(A-\Delta T)]}$$

where,
ΔT = 2°C,
A = 6°C, and
B = 0.6°C

The equation that is used in ROM which governs the rate at which tissue temperature changes over time due to the absorption of ultrasound is:

$$\frac{dT}{dt} = \frac{\alpha I_{spta}}{\rho C}$$

where, α is the attenuation coefficient, I_{spta} is the spatial-peak, temporal-average intensity, ρ is the density, and C is the heat capacity of tissue. This equation overestimates the heating that will occur, as it does not take into account heat diffusion or blood perfusion which would draw much of the heat away from the targeted region.

As described previously the maximum spatial-peak, temporal-average intensity will be limited to 720mW/cm^2, and using this value as an input into the thermal rise equation, it can be shown that for tissue attenuation of 0.6 dB/cm/MHz [55], density of 1.05 g/ml, and a heat capacity of 4.18 J/g/°C, the temperature in the focus will be increased by approximately 0.0045 °C/sec or 0.27 °C/minute. Therefore, when operating in ROM at the maximal set intensity of 720mW/cm^2, all treatments will be limited to a maximum of 7 minutes and 20 seconds of continuous on time, in order to keep the temperature from raising more than 2°C in total. However, if a longer treatment is desired, at this intensity level, multiple treatments may occur in the same session with a wait time between treatments to allow for heat dissipation.

Calculating thermal dose
The concept of thermal dose (TD) was introduced to quantify the heating energy brought to tissues and evaluate the risk of associated thermal damage. It takes into account the temperature

rise, and the time of sonication: 1 CEM is a unit representing a thermal dose equivalent to one minute at 43°C. Typically, a 240 CEM thermal dose corresponds to a total necrosis of any type of tissue and 17.5 CEM is the threshold for a 50% probability of brain damage and 10 CEM was shown to have no brain damage [39]. Therefore, OLTS will ensure that the device CEM will be below 10.

During the simulation, the thermal dose delivered to the tissue is automatically calculated in units of cumulative equivalent minutes (CEM). This is calculated using the formula

$$TD = \int R^{43-T} dt$$

where dt is the time step and the parameter R is 0.5 if the temperature T is above 43 degrees Celsius, and 0.25 if it is below [8]. Thermal dose is provided as reference information to the user during treatment planning.

A.8 Calculation of Thermal Index for cranial applications (TIC)

The Thermal Index (TI) is used as a metric for knowing the approximate temperature rise, and potential for thermal biological effects. It is a dimensionless ratio of attenuated acoustic power at a specified point to the attenuated acoustic power required to raise the temperature at that point by 1°C in tissue [3]. There are special use cases associated with this metric for diagnostic ultrasound where it is important to show the user what the TI is so that the over scan time can be kept to a minimum. This is associated with the ALARA principle of using As Low As Reasonably Achievable levels of ultrasound to minimize the potential for adverse events. In the special case where one is transmitting ultrasound through the bone an equation is used for determining the TIC (cranial-bone thermal index). The method for deriving this calculation can be found in a paper from Abbott et al. [3]. The actual equation that will be used to calculate this quantity comes from IEC standard IEC 62359, "Ultrasonics – Field characterization – Test methods for the determination of thermal and mechanical indices related to medical diagnostic ultrasonic fields". For the subject device, the scanned TIC is more relevant and the scanning times will be under the recommended guidelines set forth by the AIUM (shown in Table 6).

$$TIC_{SC} = \frac{P/D_{eq}}{C_{TIC}}$$

where,

C_{TIC} = 40 mW/cm^2,

P = output power (as measured by radiation force balance or calculated from hydrophone scans),

$$D_{eq} = \sqrt{\frac{4}{\pi}A}$$

A = output beam area (-12dB of maximum in plane of the front face of the transducer).

Table 6: Recommended maximum scanning time and TI ranges for adult transcranial, general abdominal, peripheral vascular, neonatal (except head and spine), and other scanning examinations (except the eye) [2, 24]

TI Range	Max Scanning Time (minutes)
6.0 < TI	Not recommended

5.0 < TI <= 6.0	<0.25 (15 s)
4.0 < TI <= 5.0	<1
3.0 < TI <= 4.0	<4
2.5 < TI <= 3.0	<15
2.0 < TI <= 2.5	<60
1.5 < TI <= 2.0	<120
TI <= 1.5	No time limit

A.9 Electronic Driving Parameters

In order to produce acoustic output from the ultrasound transducer array and steer the acoustic pressure to the desired locations, it is necessary to deliver an electrical driving signal to each of the transducer elements in the array. Each element is delivered an alternating electrical signal that enables the transducer element to vibrate at a specific frequency and amplitude, for a certain duration. The voltage amplitude of the electrical signal has a linear relation to the pressure measured in the acoustic field of the transducer. Through hydrophone measurements, the voltage to pressure relationship will be established such that the simulation's surface acoustic pressure amplitude parameter can be directly translated into the desired voltage amplitude for the array element.

Another electronic driving parameter that will be considered based upon the simulation is apodization of the elements. With the subject device's ultrasound driving hardware it is possible to assign specific amplitudes to different elements in the array, such that the device can create foci with the desired size while minimizing any sidelobes or acoustic energy outside of the focus. Different apodization techniques such as multiplying the driving signals with a windowing function, may be employed. These include applying different voltage waveforms to certain elements depending on their contribution strength to the desired focus. For example, if the desired focus is located outside of a specific element's directivity main lobe, it's apodization would be zero as it cannot contribute to the focus.

In addition to frequency and variable amplitudes other parameters will also be taken directly from the simulation. These include pulse length, pulse repetition frequency, and total time. For these variables it is a matter of on/off time and they can be controlled using simple gating techniques.

Appendix B Testing and Simulation of the OLTS Prototypes

The following sections provide a brief overview of simulations and testing performed by Openwater using prototypes. This testing informed the developed of the bench test proposals noted in Section 7.1.

B.1 Aberration and attenuation simulation and experimental validation

Using a single element focused transducer, experimental data was collected using a calibrated hydrophone in a water tank to measure the acoustic field generated by a 5 cycle pulse in 3 dimensions. Axial 1D scans along the acoustic axis and 2D lateral scans in the focal region were performed with the hydrophone to measure the pressure waveforms at these locations. Simulations were then performed with the same transducer geometry and water medium and matched to the experimental measurements.

Once the water-only experimental measurements were taken and the simulations were validated (showing the amplitude and shape of the acoustic fields matched), a human skull fragment was mounted in the path of the transducer (between the face of the transducer and the focus of the acoustic field) (Figure 9). Axial 1D scans along the acoustic axis and 2D lateral scans in the focal region were then performed to measure the pressure waveforms at these locations. Then 3D scans with the hydrophone were performed in the vicinity of the focus to identify both the highest amplitude and the aberrated shape of the focus.

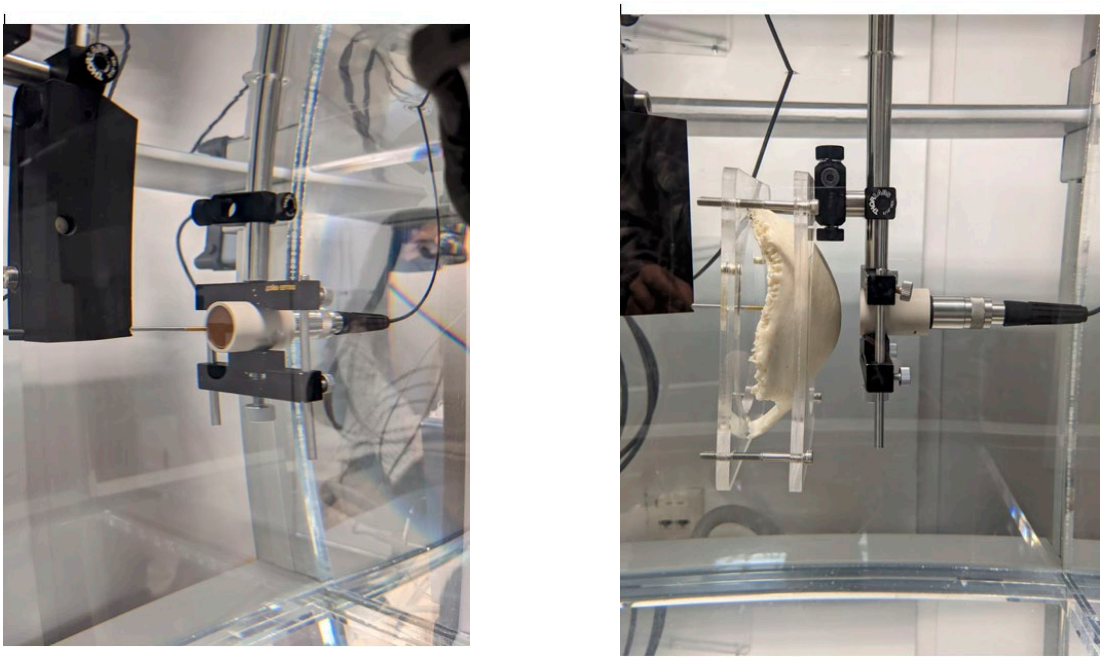

Figure 9: Acoustic measurement setup, fixed position transducer with a calibrated hydrophone on a 3D positioning arm. Left) picture of transducer in water tank with needle hydrophone taking pressure recordings. Right) Experimental setup with skull fragment between the face of the transducer and the hydrophone.

Using a high resolution CT scan of the skull fragment, an acoustic property volume of the skull fragment was generated (density, speed of sound, attenuation). This was then loaded into the acoustic simulation to precisely model the experiment conditions and the simulation is performed. The amplitude and shape of the resulting focal volume was then compared with those derived from the hydrophone measurements. Figure 10 shows the results of the comparison. The

modeling has some uncertainties due to errors within the hydrophone measurements as well as the errors caused by the mismatch between the modeled tissue properties and the actual tissue properties but an accuracy of modeling pressures within 10% should provide sufficient characterization to assist the clinician in treatment planning, while maintaining safe operating limits.

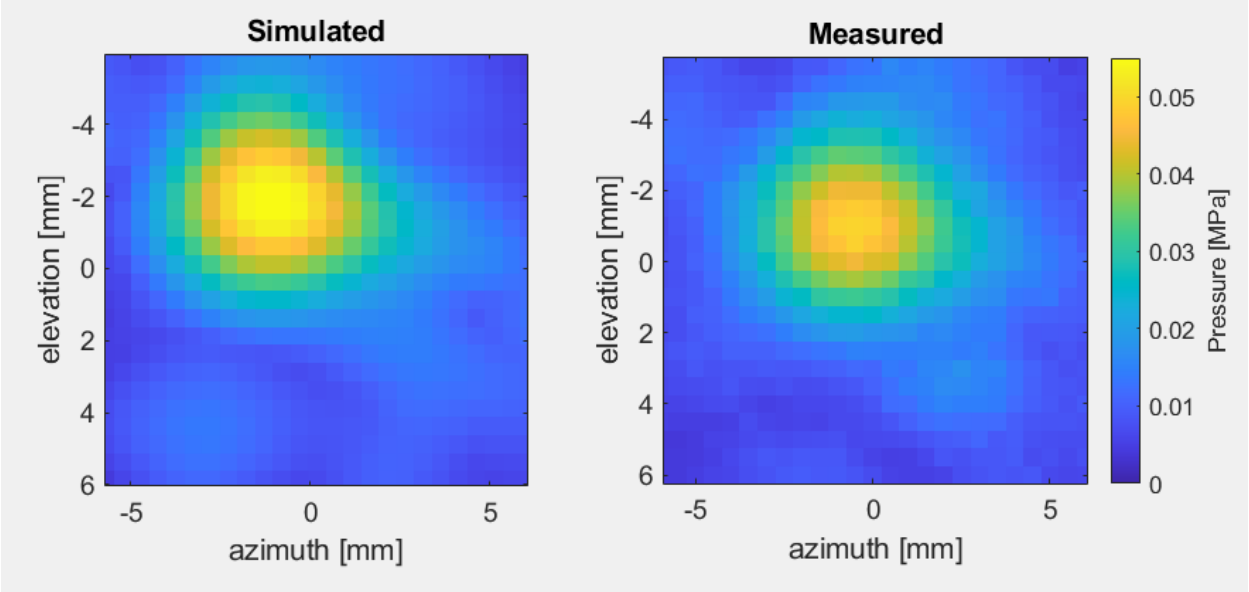

Figure 10: Left) Simulated lateral pressure map at focus of the transducer through the skull fragment. Peak pressure value is 0.56 MPa at position [-0.8,-1.6]. Right) Measured lateral pressure map at focus of the transducer through the same skull fragment. Peak pressure value is 0.49 MPa at position [-0.5, -1].

B.2 Tissue mimicking material heating measurements and simulation validation

A tissue mimicking material (TMM) was fabricated that had acoustic properties similar to those of soft tissue. The TMM was an agar-based phantom with added evaporated milk and silica dioxide for scattering and attenuation properties [41]. The speed of sound and attenuation were measured experimentally to ensure that they matched the predicted values using multiple, different thickness phantoms. Other acoustic properties used in the simulation were taken from literature. As with the attenuation and aberration experiments, the transducer being used was characterized in water via hydrophone measurements such that the simulation could accurately match the pressures obtained in the focal region in water. Phantom material (TMM) properties:

- Attenuation: 0.5 dB/cm/MHz
- Density: 1050 kg/m3
- Speed of sound: 1540 m/s
- Thermal conductivity: 0.55
- Specific heat: 4100

Simulations were performed based upon the experimental setup with continuous wave ultrasound being applied and the acoustic focus being located directly in the center of the TMM. The expected temperature rise inside of the phantom was calculated based upon a specific sonication duration (e.g. 10 or 20 seconds).

Experimental validation of this temperature rise was performed using fabricated TMM with an embedded type K beaded wire (0.4mm diameter bead) at the center. The TMM was placed in the water tank with the transducer in a custom fixture that allowed for the center of the phantom to be placed directly in the focus of the transducer. Continuous wave electrical signals were then applied to the ultrasound transducer for the desired amount of time for comparison with simulation.

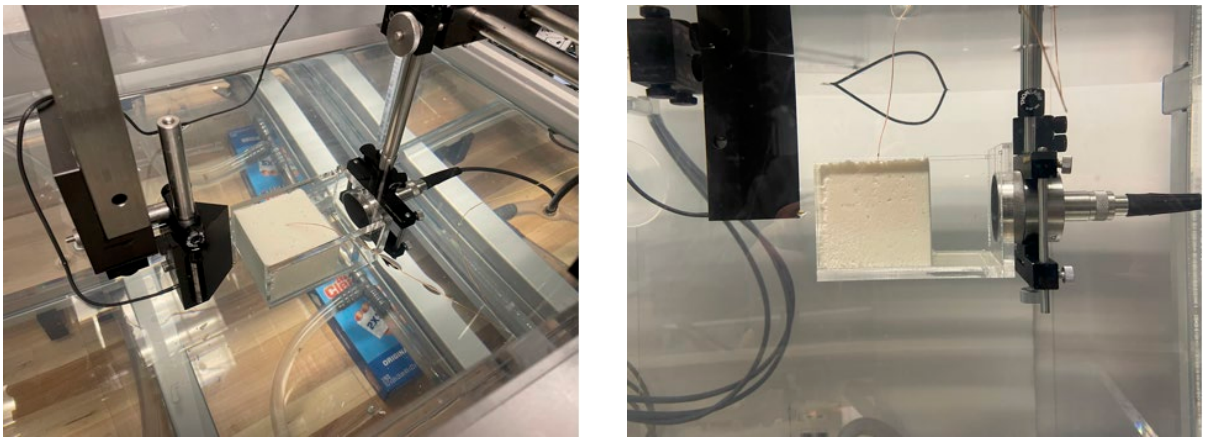

Figure 11**: Photographs of the thermal measurement setup. The transducer and the tissue mimicking material (TMM) were coaxially aligned in a custom laser cut fixture such that the center of the acoustic focus was at the center of the TMM. A thermocouple was embedded into the TMM such that the sensing element was also located at the center of the phantom (center of the focus).**

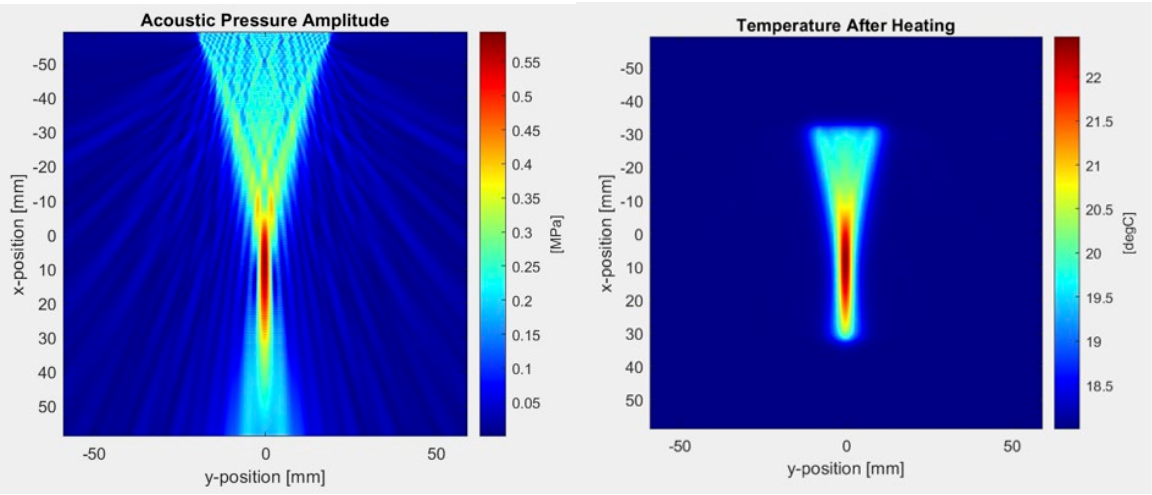

Figure 12: Acoustic pressure and thermal simulations Left) Maximum of acoustic pressure field used for calculating the thermal effects in the phantom. Right) Temperature map at the end of 30sec, obtained from simulating the temperature increase from continuous wave ultrasound (~3.5-4 deg is 30 seconds).

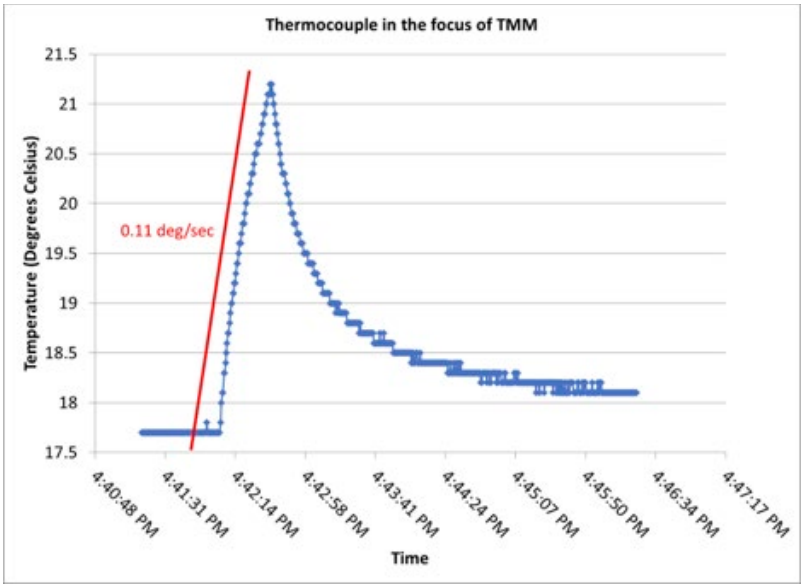

Figure 13: Thermal Measurement: This is a plot from the thermocouple embedded in the TMM phantom located at the center of the focus of the ultrasound transducer. The plot (in blue) starts before the ultrasound is turned on and once it is the temperature begins to rise. The red line represents an approximation of the slope. At the peak, the ultrasound is turned off. In approximately 30 seconds, there was a 3.5 deg temperature rise.

B.3 Simulations of the arrays steering capabilities

The OLTS is meant to deliver focused ultrasound energy to different regions of the frontal cortex in the human brain. Therefore, simulations were performed of the ultrasound array in water to determine the steering range capabilities of the array (see Section 3.2 for details on steering capabilities). Anything less than half of the maximum level at the nominal focus was determined to be out of the steering range. These ranges could be expanded on a patient to patient basis, since simulation will be run for all focal regions and it might be possible to achieve adequate amounts of treatment energy outside of the currently specified range.

Using the MIDA model [26], specific focal targets were simulated using the planning software to demonstrate the capability of steering the ultrasound focus to those locations.

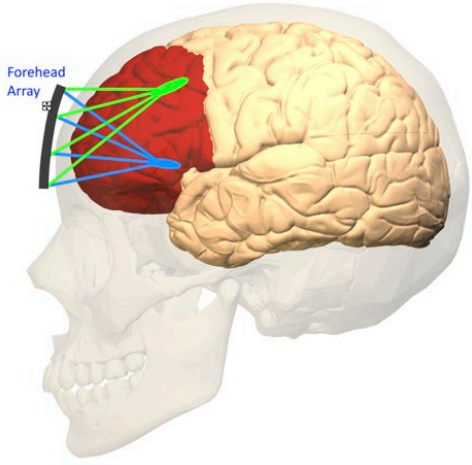

Figure 14: Schematic representation of the OLTS focusing to different locations in the brain through the forehead.

B.4 Thermal Simulation of the OLTS through the skull targeting the prefrontal cortex with two sets of parameters

The simulation was conducted using two sets of parameters that has been used in neuromodulation clinical research [see Table 1, BX Pulsar - Brainsonix] to calculate the pressure levels and temperature rise after the sonication (Figure 15, Figure 16). Thermal simulation is done using k-Wave. For both parameter sets, the observed temperature rise is less than 1 degree Celsius after one minute of sonication in the skull and less than 0.1 degree Celsius in the brain.

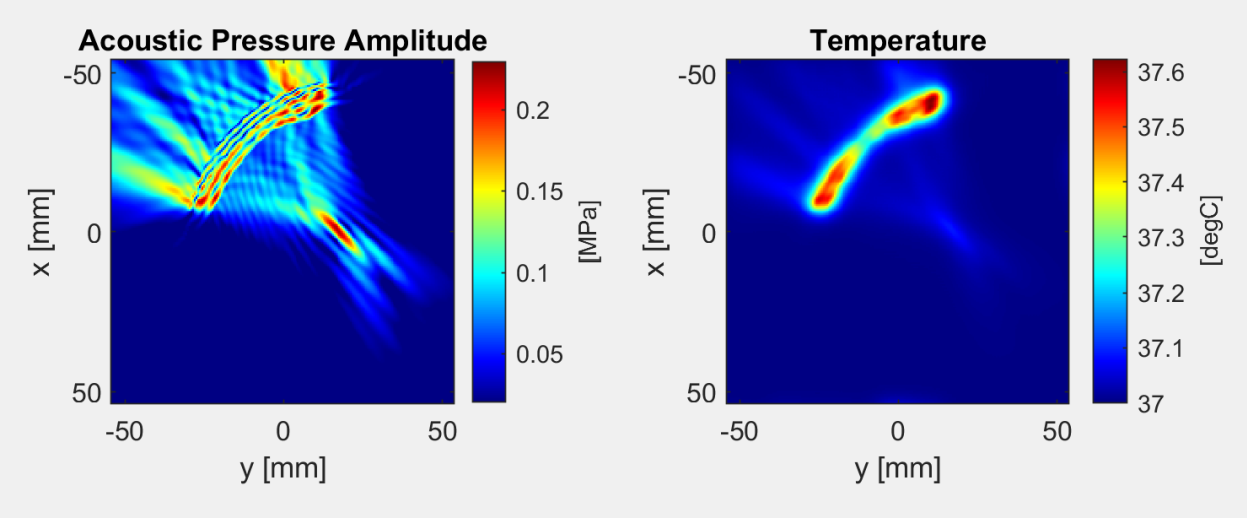

Figure 15: Thermal heating simulation 1: Thermal simulation of array through the skull with the following sonication parameters: pulse width = 2ms, repetition frequency = 250 Hz, duty cycle = 50%, sonication duration = 1 minute, depth of focus = 5cm, peak pressure at focus = 220kPa. Left) Acoustic pressure amplitude. Right) Temperature after one minute of sonication, beginning temperature was 37degC.

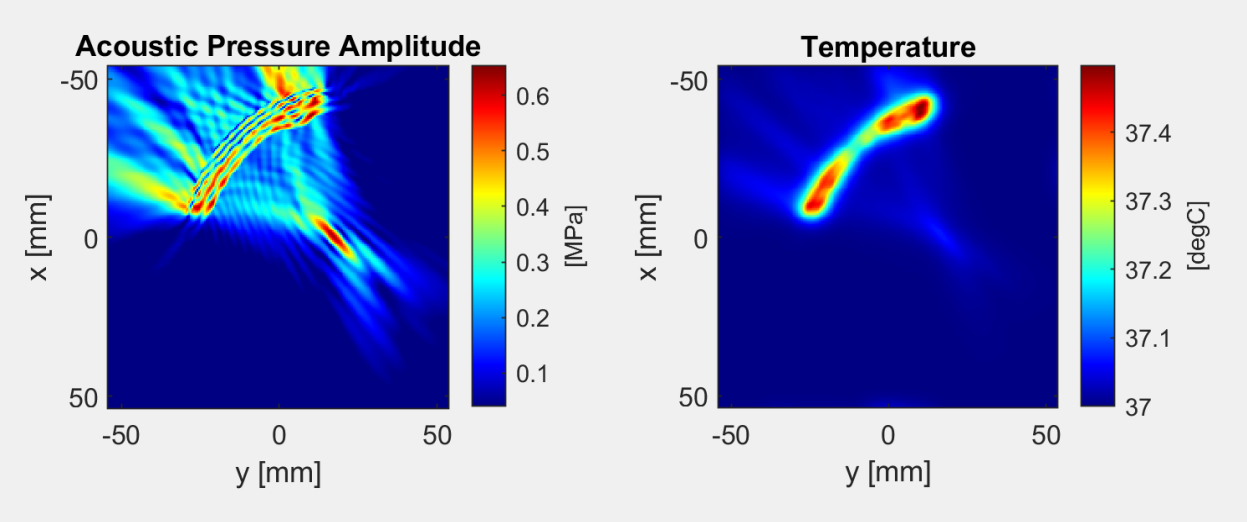

Figure 16: Thermal heating simulation 2: Thermal simulation of array through the skull with the following sonication parameters: pulse width = 0.5ms, repetition frequency = 100 Hz, duty cycle = 5%, sonication duration = 1 minute, depth of focus = 5cm, peak pressure at focus = 700kPa. Left) Acoustic pressure amplitude. Right) Temperature after one minute of sonication, beginning temperature was 37degC.