

## **Detailed Protocol**

**Title:** Low Intensity Focused Ultrasound Treatment for Drug-Resistant Epilepsy: An Efficacy Trial

**Version:** 3

**Version Date:** December 28, 2018

### **I. Background and Significance**

#### Epilepsy and Proposed Treatment

Epilepsy is one of the most common neurologic disorders, affecting 3.1 million Americans and 65 million people worldwide. Approximately 67% of patients with epilepsy achieve seizure control with antiepileptic drugs, leaving 33% of patients with persisting seizures despite medication. Ongoing seizures can be very debilitating, and are often associated with significant morbidity and even mortality. Many of these patients endure ongoing cognitive impairment related to persisting seizures and ongoing polypharmacy, which in turn has been associated with low quality of life. Because of the severity of the disease, there are high rates of seizure-related injuries (burns, falls), accidental deaths and an elevated suicide rate seen in this population. There also high rates (1:100) of sudden unexpected death in epilepsy (SUDEP) in this population. More people die from seizure-related injuries per year than from breast cancer.

Though the population affected by this disorder is large and the morbidity is high, epilepsy research remains largely underfunded. There are very few new treatments, pharmacologic or non-pharmacologic, coming down the pipeline to address this at-risk population. Despite this, the importance of reducing patients' seizure burden remains high. Ongoing seizures over the lifetime can result in progressive neurologic damage, along with the multitude of side effects antiepileptic polypharmacy carries. Reducing seizure burden can lessen the cognitive, behavioral, and psychosocial problems experienced by epilepsy patients, reducing their overall morbidity and mortality. It is clear that for many patients, antiepileptic medications will never stop their seizures [1]. Aside from epilepsy surgery, for which only a percentage of these patients are eligible, there

are few other options to help reduce seizure frequency in this population. Neurostimulatory devices such as Responsive Neurostimulation (Neuropace) and Vagal Nerve Stimulation (VNS) have been shown to be of some benefit, though these are limited to small, specific patient populations and responses vary. Noninvasive neurostimulation such as transcranial magnetic stimulation (TMS), though highly effective for some psychiatric illnesses, has produced disappointing outcomes in reducing seizures [2]. This is in large part due to the inability of TMS to reach deeper structures in the brain, such as the hippocampus in patients with epilepsy.

Thus, the large population of patients suffering from drug-resistant epilepsy with little or no treatment options warrants investigation using alternative forms of noninvasive neuromodulation for the treatment of epilepsy. Pulsed Low-Intensity Focused Ultrasound (PLIFUS) has been shown to safely modulate neuronal tissue, and is non-invasive and painless. Several human studies have shown the ability of PLIFUS to suppress somatosensory evoked potentials and induce functional magnetic resonance imaging (MRI) responses. To date, a reported 102 healthy subjects have been enrolled in these studies, and no adverse effects were reported from PLIFUS stimulation to the brain [3]–[9].

The most recent study using PLIFUS involved attempting to induce or suppress tactile sensation by transmitting FUS to somatosensory cortex regions [9]. Parameters were sonication frequency ( $f_0$ ) = 210 kHz, pulse period (PP) = 1 ms, pulse repetition frequency (PRF) = 500 Hz, sonication duration (SD) = 0.5 s, inter-stimulation interval (ISI) = 7 s, and 20 sonications per pulse train (dose) taking a total of 140 s. These pulse trains were transmitted to multiple locations at least 2 times in each location. Subjects underwent neurological and anatomical examination during FUS exposure, directly after treatments, and weeks after treatments for subject safety evaluation. No health issues or other irregular signs related to the FUS exposures were found in MRI, EEG, or Mini–Mental State Examination. Follow-up interviews conducted 2 months after FUS experiments revealed no discomforts or changes in the mental or physical status associated with the FUS exposure. Similar safety guidelines were used in other studies to suppress Somatosensory Evoked Potentials (SSEP) and activate brain regions identified by functional MRI with PLIFUS resulting in no health physical or mental health issues [3, 8].

Human and non-human primate studies have investigated the bioeffects of either repeated or long-term PLIFUS exposure. During a device evaluation study for delivering repeated PLIFUS through the temporal lobe in order to treat stroke, FUS exposure was transmitted for 2 hours at a maximum of  $I_{SPTA} = 0.72 \text{ W/cm}^2$  ( $f_0 = 2.0 \text{ MHz}$ , PRF = 8.3 kHz, and pulse duration [PD] = 5  $\mu\text{s}$ ) into 15 healthy volunteers. None experienced any adverse effects indicated by the neurological examinations during, immediately after the exposure, and at 24 hours, and no abnormality of the blood brain barrier was identified on post-MRI [10]. A non-human primate study examining the effects of long-term FUS for drug delivery through the BBB used  $f_0 = 1.0 \text{ MHz}$ , 2 sonications every 2 weeks for 4 months. The FUS device was implanted into the skull. None of the subjects experienced any adverse effects in regard to the FUS exposure and it was concluded from positron emission tomography images with fluorine-18–labeled fluorodeoxyglucose (FDG) that no changes in the cerebral metabolism of glucose were identified. No epileptiform signs or pathological central nerve conduction were observed in EEG and SSEP recordings either. Behavior in all animals remained normal and histological analysis showed no signs of tissue damage [11]. The device was later investigated in a clinical trial with 17 human subjects and resulted in no detectable adverse effects during neurological evaluation or MRI [12]. Another non-human primate study used a similar protocol but with a non-invasive FUS transducer ( $f_0 = 500 \text{ kHz}$ ) and multiple target locations were exposed to FUS for each treatment session. The study included on average 8 target locations with SD = 120 s, approximately 25 sonications per month, and for up to a 12-month course of treatment (long-term). Behavioral testing and MRI revealed no adverse effects in subjects due to FUS [13]. There are two current clinical trials in humans using PLIFUS, one to suppress seizure activity [14], another to stimulate thalamic regions in subjects with disorders of consciousness following acute severe brain injury [15]. In the latter, the device was reported to wake a subject who was in a coma from a brain injury for 19 days. FUS parameters were  $f_0 = 650 \text{ kHz}$ , PRF = 100 Hz, SD = 30 s, ISI = 30 s, and PP = 0.5 ms. A total of 10 sonications were administered in 3 different trials, with an approximate derated  $I_{SPTA} = 0.72 \text{ W/cm}^2$ .

### Transcranial Focused Ultrasound

The physics of FUS are similar to how clinical ultrasound-imaging probes work except the ultrasound energy is transmitted into a focal location (beam focus)

instead of spreading energy over an imaging region. FUS is a useful method for noninvasively delivering therapy to deep tissue targets since the spatial distribution of ultrasound energy over a sufficiently large area ensures that no therapeutic effect can occur except at the geometric focus of the transducer. Transcranial FUS has been studied for over 60 years [16]. Its safety and usefulness have since been largely assessed for many medical treatments. Transmission FUS frequencies below 800 kHz are typically chosen to avoid skull heating during transcranial applications. The absorption of ultrasound energy by the skull increases approximately linearly with transmission frequency. FUS is generally classified into two separate categories of high and low intensity. High-intensity FUS causes heating of tissue at the beam focus. The most recent clinical use of high-intensity FUS is noninvasive Thalamotomy for treating Essential Tremor [17]. A high intensity FUS beam is directed to the ventral intermediate nucleus of the thalamus, which causes the tissue at the beam focus to heat up resulting in localized tissue necrosis. Several other brain applications are currently under investigation using high-intensity levels. Real-time monitoring techniques have been developed to guide or monitor the safety of FUS procedures. Real-time MRI-thermometry values are used to display tissue temperature increase as the FUS intensity is increased at the beam focus. Acoustic Emission Detection (AED) is another intraoperative technique used to assure no tissue cavitation occurs during FUS transmission. Cavitation is the formation of bubbles within tissue in response to overbearing FUS intensities and can damage tissue in the FUS beam path. AED sensors are microphones programmed to listen for cavitation, which would instantly shutdown the FUS transmission if cavitation is identified.

In low-intensity FUS thermal rise and irreversible mechanical effects are negligible so thermometry and cavitation monitoring are not required. Low intensity FUS uses substantially lower intensity levels than high intensity FUS, so low as to not result in any ablative effect, tissue damage, permanent anatomical changes, and does not cause adverse effects as a result of treatment. Some recent examples of low-intensity FUS performed on humans are microbubble enhanced Blood Brain Barrier (BBB) disruption drug delivery and transcranial neuromodulation. The drug delivery method via BBB disruption uses the combination of IV injection of anti-cancer agent infused with microbubbles and positioning the beam focus over brain tumor sites to temporarily open the BBB to deliver drug into tumors. Clinical investigations are underway to evaluate this method in humans [18]. PLIFUS neuromodulation has been investigated in several human studies to successfully

show the temporary suppression or induction of auditory, visual, sensory, or motor functions by positioning the beam focus over specific portions of the cortex [19], [3], [4], [20]. FUS is pulsed during most low-intensity applications in order to distribute FUS energy exposure over time, avoiding overexposure the tissue target but still able to induce a physiological response. This allows the tissue to “rest” in between pulses, whereas in high-intensity FUS, the ultrasound is transmitted continuously at high intensities for long durations to maximize tissue exposure, causing an ablation.

Preclinical studies have demonstrated the ability of PLIFUS to suppress seizures in Kainic acid epilepsy models [21]. PLIFUS exposure can also temporarily expand extracellular and paravascular spaces in brain [22]. Thus, we hypothesize that PLIFUS stimulation will result in mechanical disruption of the target tissue (here, the epileptogenic focus), preserving the integrity of the tissue but rendering it unable (or less able) to mount seizure activity for a period of time.

In this study, we propose long-term, repeated PLIFUS stimulation of brain regions containing epileptic tissue, with the goal of decreasing seizure activity in subjects with drug-resistant temporal lobe epilepsy. We target temporal lobe epilepsy because it is the most common form of epilepsy; the temporal bone is also thinner than other areas of the skull, making the temporal window most amenable to sonification. The course of treatment will be 1 month in duration, spread over 2 sessions per week for 4 weeks of 45 minute PLIFUS treatment per session. Outcomes will be assessed by the reduction in seizure frequency and changes in electroencephalography (EEG).

## **II. Specific Aims:**

The aim of the proposed pilot study is to investigate patient tolerability and efficacy of moderate term, repeated exposure of PLIFUS in patients with drug-resistant temporal lobe epilepsy. We hypothesize that the treatments will be well-tolerated, subjects’ EEGs will show improvement (fewer and/or attenuated epileptiform discharges), and that subjects will experience a reduction in seizure frequency as a result of the treatment without adverse events.

## **III. Subject Selection:**

To be eligible for participation in this study, participants must be eighteen years or older with a diagnosis of drug-resistant temporal lobe epilepsy and meet the inclusion and criteria below. There are no exclusions based on race, ethnicity or gender. Study wide, the plan is to consent and enroll approximately ten (10) participants.

#### Inclusion Criteria:

- Subjects at least eighteen (18) years of age
- Subjects with drug-resistant temporal lobe epilepsy whose seizures involve altered awareness (ie failed at least two trials of antiepileptic drugs for seizures), as determined by one of the BWH epilepsy neurologists based on clinical seizure semiology and/or EEG findings.
- Subjects who experience at least 1-2 seizures per month on average, are aware of or have reliable caregivers who are aware of when seizures occur and can reliably log seizure frequency
- Subjects who have the cognitive ability to read and understand the consent form, describe any potential symptoms experienced during or after treatments.

#### Exclusion Criteria:

- Subjects with a cognitive or psychiatric disorder that limits the ability to give informed consent or are unable to cooperate with testing
- Subjects with dementia or other progressive degenerative disease, delirium or active psychosis
- Subjects with ferromagnetic materials in the head
- Subjects with severe cardiac disease, increased intracranial pressure, or a Transcutaneous Electrical Nerve Stimulation (TENS) unit
- Subjects who have primary generalized epilepsy or non-epileptic seizures
- Subjects who have experienced status epilepticus in the 3 months leading up to enrollment in the study
- Subjects (females) who are pregnant, or are of childbearing potential and not willing to use reliable birth control during the treatment period.
- Subjects who are unable to get a brain MRI for any reason (implanted metal in body, inability to lie still)
- Subjects with current brain tumors or an intracranial vascular lesion
- Subjects with severe, uncontrolled medical problems, such as diabetes mellitus, hypertension, pulmonary or airway disease, heart failure,

coronary artery disease, or any other condition that poses a risk for the subject during participation.

- Subjects with holes in the treatment area of the skull from trauma or prior surgery
- Subjects with pacemakers, medication pumps, and other implanted electronic hardware. If a subject has a working Vagal Nerve Stimulator in place, the device will be turned off prior to each treatment session and then turned back on after each session.

#### Source of subjects and recruitment methods:

Recruitment will primarily take place through BWH and MGH epilepsy clinics. Dr. Bubrick (PI) and her colleagues in the Division of Epilepsy at BWH will refer eligible patients to the study. The PI will discuss the trial in detail with the epilepsy division at MGH, and her research assistant will also screen epilepsy clinics at BWH and MGH for eligible subjects and alert the primary epileptologist (either Dr. Bubrick or one of her colleagues) when a patient is identified as eligible for the trial. If the patient meets eligibility criteria, the primary epileptologist will ask permission for the research team to approach him/her regarding the study. If interested in participating, Dr. Bubrick will meet with each subject to discuss all aspects of the trial and will obtain informed consent. Advertisements will also be posted at BWH, MGH, and online.

In the event that the potential subject is one of the PI's patients, the study team will ensure that patients do not feel obligated to participate in study by writing to the patient first and given the opportunity to make the first contact if he/she is interested, or a physician colleague (Co-I, Dr. Daniel Weisholtz) may initially explain the study or re-contact the potential subject after the Investigator has presented the study. We also plan to send the Consent Form home with any potential subjects to review it thoroughly and call back if they wish to participate or have any questions or concerns.

#### **IV. Subject Enrollment:**

Written informed consent will be obtained prior to study enrollment or administration of any measures or procedures. The consent process will be administered in person by the PI (Principle Investigator) or Dr. Weisholtz (who will

serve as CO-I (Co-Investigator) and back-up epilepsy attending if the PI is ever unavailable), both of whom have received research ethics training. The PI or Co-I will assess whether the potential participant understands the study procedures, and will ensure that all questions related to the study are answered. Potential subjects will be informed that participation is completely voluntary, that they may discontinue their participation at any time without penalty, and that declining to participate or discontinuing participation from the study will not in any way alter the clinical care they receive by their epilepsy physician. The PI will make the ultimate determination of whether a participant meets all the enrollment criteria and is appropriate to enter the study. Participants that do not meet the study criteria will be informed that based on the information collected, it has been determined they are not eligible for the current study.

## **V. Study Procedures:**

### Study Visits and Timeline

The study procedures include the following visits:

- 1) screening (1 hour)
- 2) updated MRI if previous MRI was completed 3 months prior to screening (2 hours)
- 3) treatment visits (8 sessions over 4 weeks with each lasting approximately 2 hours)
- 4) post treatment visit (1 hour)
- 5) phone follow-up (15 minutes)

### Detailed Subject Procedures:

#### Screening Visit

The subject will meet with the PI of the study, Dr. Ellen Bubrick, to determine if the subject qualifies for the study. If the subject is an appropriate candidate, the PI will review this consent form with the subject and review the details of the study and what exactly is involved including any potential risks and/or benefits. Any questions the subjects have regarding the trial will be answered to the best of her ability. If the subject decides to enroll in the study, the subject will need to sign this consent form before starting in the trial. Seizure frequency will also be confirmed upon review of the medical record including the month prior to



enrollment, and the subjects will log their seizure frequency using a daily seizure log diary form for one month prior to beginning the treatment.

We will collect de-identified clinical information regarding all subjects who participate in the study including basic demographics (age, sex) as well as information regarding each subjects' epilepsy (age of onset, duration of illness, medication history, laterality, mesial vs neocortical), tolerability of the trial, and any potential changes in seizure frequency or adverse effects.

### Pre-treatment MRI

Once the subject is enrolled in the study, the subject will be scheduled for a standard brain MRI scan at BWH if they have not had one in the last 3 months. An updated brain MRI will be obtained on each subject to exclude the possibility of any potential de novo lesions that may have developed since the subject's last clinical scan, and it will also be used to correlate with the neuronavigation software and to measure skull thickness in the treatment area. This will be reviewed by a BWH neuroradiologist, and an official clinical read will be placed into Epic, but the scan will be paid for by the study. If any new lesions or concerns are identified on that MRI scan, the PI will notify the patient's primary epileptologist to discuss with the patient.

The MRI scan (including MPRAGE T1 and also high resolution T2 sequences) will be performed on each subject with registration fiducials (PinPoint 128, Beekley Medical, Bristol, Connecticut) attached at multiple sites on the head (*e.g.*, across the forehead, face, and behind the ears). After obtaining the scan, the navigation system (Polaris Vicra, NDI, Waterloo, Ontario) will be used to register the fiducials with the MRI dataset (3D Slicer, Boston, Massachusetts). Four anatomical sites—inion, nasion, and pre-auricular points—will also be registered to the same MRI dataset using tracked probes. The registration data will be saved for the treatment sessions.

### Daily Seizure Log Diary and Questionnaires

The subject will be asked to keep track of their seizure events in the Daily Seizure Log Diary from the screening visit until 2 months after the last treatment session. The subject can complete the daily seizure activity on the subject's schedule outside of the hospital.

Each subject will be asked to complete a Beck Depression Inventory and a Quality of Life in Epilepsy (QOLIE-10) inventory at the beginning of the treatment period, and again one month after study completion.

### PLIFUS Treatment Sessions

The treatment period will include 8 treatment sessions total. These will occur 2 days per week for 4 weeks, each lasting approximately 1-2 hours, starting 1 month after seizure logging begins. The PI or the Co-I will be present at all treatment sessions.

EEG leads will be placed on the subject's scalp at the time of the first treatment session and at the last treatment session. Up to 22 EEG scalp electrodes will be positioned over the subject's scalp as well as a head-tracker band. Special conductive paste or sticky gel dots will be used to fasten the electrodes to the subject's scalp. The conductive paste and sticky gel dots are non-toxic, hypoallergenic, non-staining, and non-irritating for most patients. Connecting the electrodes may take up to 30 minutes. The subject will be seated in a comfortable therapy chair or adjustable bed where the subject will remain for approximately 1 hour for the duration of the therapy session. We are performing the first visit under EEG guidance to ensure no increased cortical irritability (i.e. epileptiform spiking) is seen after approximately 30 minutes of baseline EEG is obtained, and to identify any changes in interictal epileptiform spiking during the treatment. A repeat EEG will be obtained after completion of all treatments for comparison.

At the beginning of the treatment sessions, navigational trackers will be attached to the subject's head using an elastic headband. The tracked probe will be used to re-register the subject's head—via theinion, nasion, and pre-auricular points—to the subject's MRI dataset. The same MRI dataset will be registered to the ultrasound transducer using the navigation system, thus establishing registration between the subject's head, the MRI, and the ultrasound transducer. The navigational trackers will remain strapped to the subject's head during the treatment to maintain registration. Compounded errors (MRI-to-subject, subject-to-transducer), including inaccuracies in anatomical landmarking, leads to a spatial accuracy error estimation of 2 mm. Subject motion will be tracked at high temporal resolution during the treatment, so is not anticipated to contribute significantly to the error estimation.

The PLIFUS device will then be placed against the subject's scalp, just above the ear on the side the subject's doctor has determined the subject's seizures come from. The device uses a water filled membrane ("water bag") placed against the side of the subject's head to transmit PLIFUS stimulation to the subject's brain through the subject's skull. The contact area against the subject's temple is approximately the entire side of the subject's head (above the subject's lower eye line but not covering the subject ear). The membrane is slightly larger than a large earmuff pad. The device and its water bag membrane are held in place by an adjustable positioning bench. Ultrasound gel will be applied between the subject's skin and the membrane to ensure sufficient acoustic coupling (i.e. the gel prevents air bubbles from being trapped between the subject's scalp and the device, which blocks ultrasound waves). Ultrasound gel may be reapplied multiple times throughout the therapy session. The ultrasound gel is non-toxic, hypoallergenic, non-staining, and non-irritating to most patients.

On the opposite side of the subject's head (in the same region), a stabilizer pad made of soft material will be placed. The pad is about half the size of the water bag and will adjust to hold the subject's head steady against the water bag. The subject head will be positioned forward looking in a comfortable manner. Although the subject will be asked to keep the subject's head as still as possible during the PLIFUS stimulation, accidentally moving the subject's head will not disrupt the stimulation. The navigation system allows us to correct for any unintentional head movements. An EKG (or cardiac) lead may also be placed on the chest so we can monitor the subject's heart rate during the treatments.

Once the subject is comfortably connected to the PLIFUS device, we will begin the PLIFUS treatment session which will take approximately 50 minutes. The PLIFUS stimulation is activated when the operator presses a "Start Button" and he/she will tell the subject several seconds before he/she will push the button. One button push turns the PLIFUS stimulation "ON" for 2 minutes and 20 seconds. This time frame is called a "dose." The subject may receive up to 16 Doses during the 50 minute treatment. After each dose is delivered there will be a pause of at least 30 seconds until the operator pushes the On button again. The 30 second time period is used for the operator to steer the PLIFUS stimulation position to different parts of the subject's brain. It also gives the subject time to rest in between doses. After the last dose for that session is delivered, we will disconnect

the PLIFUS system from the subject’s head and remove any EEG or EKG electrodes that were placed.

At the end of each treatment session, the patient will be assessed for any potential symptoms including pain or discomfort by a member of the study team. An adverse effects form will be completed by the patient after each treatment session. Subjects will be encouraged to report any symptoms or discomfort experienced during treatment sessions or in between sessions, at which point the subject will be assessed by the PI or Co-I and a determination will be made as to whether it safe for treatment to be continued. Target areas for the Focused Ultrasound (FUS) will include the hippocampus and/or the anterior temporal lobe.

### Post Treatment Follow-ups

The subject will also have a post-treatment follow up visit with the study PI or the subject’s primary epilepsy neurologist approximately 1 month after the last treatment session. Subject will also be called by a study team member 3 months after treatment to check how the patient is doing generally and assess seizure frequency.

### **Study Schedule**

<b>Visit</b>	<b>Screening</b>	<b>Treatment 1</b>	<b>Treatment 2-7</b>	<b>Treatment 8</b>	<b>Post Treatment</b>	<b>Follow-up call</b>
<b>Timeline</b>	Day 0	Month 1	Month 1-3	Month 3	Month 5	Month 6
<b>Consent</b>	X					
<b>Review of Inclusion/Exclusion</b>	X					
<b>Demographics</b>	X					
<b>Review of Epilepsy History</b>	X					
<b>Neurological Exam</b>						
<b>BDI-II</b>		X	X	X	X	
<b>QOLIE-10</b>		X	X	X	X	
<b>Adverse Event</b>		X	X	X	X	
<b>Seizure Log</b>	X	X	X	X	X	
<b>EEG</b>		X		X		
<b>EKG</b>		X				

MRI	X					
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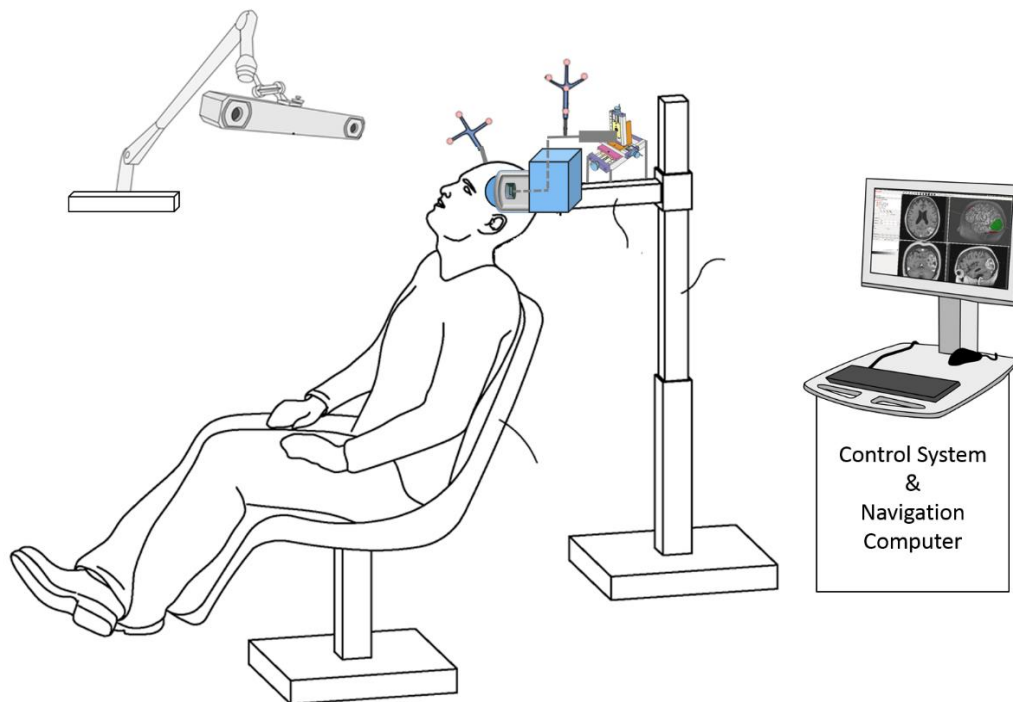
### Subject Compensation

Each subject will be compensated \$50 after 4 treatment sessions are completed, and then an additional \$150 at completion of the study for a total of \$200 if completed all study visits and assessments. Parking at BWH will also be compensated.

### Device Platform

The ultrasound transducer was designed, constructed, and characterized at the Focused Ultrasound Laboratory (FUS Lab) of the Brigham and Women's Hospital (Director, Nathan McDannold, PhD). It is composed of a spherically focused piezoceramic element (Piezo Kinetics, Bellfonte, Pennsylvania) mounted by room-temperature-vulcanizing silicone in an acrylic housing that maintains air backing under submersion in water at STP. Electrical coupling and passive matching circuitry were likewise designed and constructed within the electronic and machine shops of the FUS Lab's main research facility at 221 Longwood Avenue, EBRC 521, Boston, MA. The device is currently stored at the FUS Lab within a secured laboratory. When the study begins, the device will be stored in the EEG Lab, a clinical facility located within the BWH Hale Building for Transformative Medicine, 60 Fenwood Road, Boston, MA.

Detailed drawings, system calibration and maintenance procedures, and other comprehensive device specifications can be found in the Device Manual. The Device Manual is written to provide details of the custom device platform for the institutional review board Biomedical Engineering and Radiation Safety review process. We applied for and received an Investigational Device Exemption from the FDA Documentation supporting non-significant risk assessment is included in the IRB proposal packet.



The noninvasive device includes 5 subsystems including the FUS transducer, positioning system, water bag membrane, and water tank system, control system and safety monitoring interface, Neuronavigation system, and calibration equipment. All electronic hardware near or touching the patient are powered by isolation transformers. Device operation, calibration, and maintenance instructions are listed under the Device Manual.

### Stopping Rules for PLIFUS Treatment Sessions

The device operator will be in possession of a "STOP" button, which will be pressed immediately if he / she sense the subject are having any discomfort due to the stimulation. We do not expect this to occur, as no adverse events have been reported in prior studies as discussed above, but will proceed this way in an abundance of caution. The subject will be encouraged to let the study staff know if the subject feel any discomfort at any time, or want to stop the treatment for any reason. If this occurs, the operator will also push the "STOP" button immediately. The PI or Co-I who are BWH epilepsy neurologists will be present during the treatment session. If any symptoms are reported during the treatment session, the physician will evaluate the subject and assess if the subject need urgent medical care and whether it is safe to continue in the study.

An adverse event for this trial is defined as any neurologic or systemic symptom or sign that may occur during a treatment session, and persists even after sonication ends (when the “STOP” button is pressed or device is turned off).

In the unlikely event that a major clinical event occurs that in any way seemed to be associated with the treatment, enrollment will be stopped and no further treatments will be performed until a comprehensive safety evaluation of the device and procedures is completed. The study would only begin re-enrolling patients and continuing treatments once the safety issue had been identified and completely rectified. Any adverse events that may occur during the trial will be reported to our IRB and the FDA.

## **VI. Biostatistical Analysis:**

Specific data variables being collected for the study are patient demographics (including de-identified subject #, age, sex, duration of epilepsy and seizure history, number of antiepileptic medication trials, baseline EEG findings, seizure onset area), pre-determined target areas, FUS dosage parameters, skull thickness, EEG changes during or after treatment, patient tolerability, adverse events or reported symptoms during treatment, effect on seizure frequency via seizure logs. Study endpoints are patient tolerability, seizure frequency. We aim to evaluate only for any trends in seizure frequency, as our small number of only 10 subjects and the pilot nature of the trial does not provide the statistical power for more significant analyses.

## **VII. Risks and Discomforts:**

### Risks to subjects

All participants will be carefully screened prior to treatment for contraindications to PLIFUS (see exclusion criteria). Subjects may decline treatment at anytime, or take breaks as needed, or ask for the PLIFUS stimulation to be stopped at any time. PLIFUS will be administered by the PLIFUS operator with a physician present in the treatment room or in the building and immediately accessible by page. The PLIFUS operator will be a trained and qualified individual supervised by the PI to deliver, or assist in delivery of, PLIFUS. Training includes the knowledge of safety considerations and precautions associated with experimentally delivering PLIFUS stimulation to subjects.

The FUS platform that will deliver PLIFUS is adjustable in intensity, duration of stimulation, and steerable by neuronavigation software, which our group has extensive experience using in TMS and other transcranial stimulation modalities. The isotropic spatial accuracy of the optical tracking system (NDI Polaris Vicra) is 0.35 mm RMS (0.5-mm 95% confidence interval), as reported by the vendor's performance specifications assessment (<https://www.ndigital.com/medical/products/polaris-family/>). With our probe in place, the isotropic spatial accuracy was measured to be 0.93 mm (SD 0.74 mm) by comparative analysis of eight measured points in 3-dimensional space. A computer controlled mechanical positioning system (Velmex, Bloomfield, New York) was used as the gold standard (0.076-mm accuracy). When targeting the hippocampus (specifically, the anterior 2/3rds of the structure), we will be sonicating it perpendicularly across its anatomical axis. Even with the conservative assumption that the half-intensity focus must remain wholly within the hippocampus in cross-section, the tabulated average of 20 mm for the average adult human hippocampus diameter would require a targeting accuracy of approximately 7.6 mm. Our measured accuracy of 0.93 mm falls well within this requirement. The measured half-intensity beam widths of our transducer's ellipsoid focus are 4.8 mm (short axis) and 56.7 mm (long axis). Given the typical adult hippocampus cross-sectional diameter of 20 mm and our system's spatial accuracy of 0.93 mm, the 4.8 mm beam width ensures that no region outside the hippocampus lateral to the ultrasound propagation path will be affected. Due to the 56.7-mm beam length, the anatomical regions situated approximately 19.3 mm lateral and/or medial to the hippocampus could be affected. Anatomically, this would include the temporal lobe laterally, and medially the structures in the ambient cistern (alveus, fimbriae, cerebrospinal fluid, posterior cerebral artery, vein of Rosenthal and optic tract) and upper midbrain (tectum).

The proposed intensity levels are calibrated to only potentially yield functional neuromodulatory effects at the focus (*i.e.*, no measureable temperature rise or mechanical tissue destruction is anticipated). Beyond the focus, any induced effect would be vanishingly small and transient. Any leakage lateral to the hippocampus (ie temporal lobe) is unlikely to produce any adverse effects, that area is often resected along with the hippocampus in a temporal lobectomy surgery for epilepsy. Medially, the structures running through the ambient cistern, specifically the artery and vein noted above, are unlikely to be affected at proposed intensities. Involvement of the optic tract could potentially result in a



brief disruption in the corresponding visual field. A mild, transient visual or hearing disturbance could potentially also be experienced by sonicating the tectum. None of these are anticipated, however with the proposed intensities.

In addition, an extra layer of safety will be integrated into the device control system as a failsafe circuit so the maximum acoustic intensity output cannot exceed a set maximum safety threshold. Each subject will have an individual water bag membrane assigned to him/her throughout the course of treatment. Water bag membranes will be cleaned with alcohol before and after each treatment session. Subjects will be asked if they are sensitive to latex, and if they are, a non-latex water bag will be used.

To date, there are no standards specifically designed for the use of transcranial repeated, long-term PLIFUS exposure to humans. In our study, we will use the exact same PLIFUS parameters reported where PLIFUS was delivered to human subjects in single-session investigations in which no adverse effects resulted [3]. In this trial we will expand the safe single-session protocol into a multi-session course of treatment. We derive our “repeated, long-term” parameters by adapting what has been reported from existing PLIFUS studies in which repeated or long-term PLIFUS investigations on human or non-human primates were shown to be safe. These parameters include a 30 second rest time in-between PLIFUS dosages, similar to what has previously been used in repeated, long-term exposure of transcranial magnetic stimulation treatment trials for epilepsy [2] and other neurological disorders [23].

The maximum AI reported in past human studies was a derated  $I_{spta} = 3.5\text{--}4.4$  W/cm [9], which accounts for a transmission rate through the skull that varied from 20 - 25 % depending on skull thickness (4.7 to 7.8 mm at the entry position of the FUS beam). Transmissions occurred through the calvarium to target the cortex, whereas the FUS transmissions for temporal lobe target regions will occur through the less thick temporal bone. We make the  $AI_{loss}$  calculation as described earlier in the Device Power Settings and Limits section for scaling down the AI of the FUS transmission to account for the thinner temporal bone through which we will be transmitting FUS.

Although our treatment falls into the low-intensity FUS category, we will employ extensive safety monitoring of electrophysiology and FUS AI levels transmitted

during the FUS exposure. These include real-time EEG monitoring (during first treatment for each subject), and real-time cavitation detection via AED. We are adding these extra safety precautions since this is the first human study to combine long-term (8 sessions over 1 month) and repeated (45 minute sessions) FUS exposure to temporal lobe regions. None of the human studies reported use of real-time AED safety monitoring. This was because the FUS parameters used were not expected to produce cavitation or adverse effects. Every study reported adequate safety of the technique, but most of these studies were performed in healthy tissue and FUS exposure was not repeated over multiple sessions. Since our study will involve sonicating epileptogenic tissue and repeated long-term FUS exposure over multiple beam focus targets, we are including these extra layers of safety monitoring out of an abundance of caution.

FUS parameters in the proposed study will be  $F_0 = 548\text{kHz}$ ,  $PP = 1\text{ ms}$ ,  $PRF = 500\text{ Hz}$ ,  $SD = 0.5\text{ s}$ ,  $ISI = 7\text{ s}$ , and 20 sonications per dose taking a total of 140 s. We also define safety guidelines on the amount and timing of FUS doses delivered in a treatment session and for the course of treatment. Safety guidelines are as follows:

- 1) maximum dose count per session= 16
- 2) maximum doses per target location per session= 3
- 3) minimum rest period between each dose= 30 sec
- 4) maximum sessions per week= 2 .

AI during the 1<sup>st</sup> week of treatment will be set to 25 % of  $AI_{\text{max}}$  and be increased to 50, 75, and 100 % the 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> weeks of treatment, respectively. Even though no human studies have reported tissue cavitation occurring at these low-intensities levels during pulsed FUS transmission, we will perform a pre-treatment Acoustic Calibration Session (ACS) as an extra layer of safety. The session will 1) verify no cavitation occurs while delivering the 4 proposed AI levels at all FUS beam focus target chosen in each subject using a generic cavitation alarm algorithm and 2) obtain patient-specific baseline AED signals to calibrate real-time cavitation detection alarm algorithms for use during the remaining course of treatment. There will be 3 types of AED signals acquired and assessed from multiple locations around the head. 1) Global AED (gAED), which is the summed receiving signal of all the 8 AEDs sensors integrated into the 10-20 EEG grid. 2) Reflected AED (rAED) (2 cm diameter, 3 mm thick) oriented in a ring around the transmitting therapy transducer housing. 3) Far-field AED (fAED) is the receiving

signal of one piezoelectric disk (30 mm diameter, 3 mm thick) adjacent to the scalp opposite side of the water bag. The ASC includes steering the FUS transducer to all the FUS beam targets and ramping up the AI to each of the 4 intensity levels to obtain the AED baseline signals.

For example, an ACS will be performed in the following way where PLIFUS exposure is being applied to the entire left hippocampus. A FUS target T1 may be assigned to MRI coordinates (R2.0, A1.3, S5.3) corresponding to the most anterior region of the left hippocampus and T2 (Q1 = 650) is assigned 4 mm posterior at (R2, P0.7, S5.3) on the next portion of the left hippocampus. Once the FUS transducer is positioned for sonication delivery to T1, the transducer AI will be set to 25 % of  $AI_{max}$  and transmit a train of 5 sonications. A gAED, rAED, and fAED signal will be recorded for each sonication and then averaged for obtaining the patient-specific baseline AED signals. This will be repeated for 50, 75, and 100 % of  $AI_{max}$ . Next, the transducer will be manually steered for FUS exposure at T2 where the train of sonications is performed again. This procedure will be performed for all targets.

The transducer holder is largely constructed with aluminum and acrylic, so EM compatibility issues are not expected. The BWH Biomedical Engineering Department will perform a thorough and extensive assessment of electrical leakage and EM compatibility tests before we will be allowed to apply it to human subjects per Partners IRB stipulation. Interference is highly unlikely; (1) the equipment is shielded and the XDCC is submerged in deionized water, and (2) the respective operating frequencies are very far apart. In the unlikely event that electrical leakage or EM compatibility is noted to be an issue (*e.g.*, impacting patient safety or interfering with the navigation system), we will suspend the study to investigate and correct the conditions that led to the issue.

#### Methods for ensuring safety of subjects and escape criteria during study

The PI or Co-I will be present during all treatment sessions. Subjects will be encouraged to report if they feel any discomfort during a treatment, feel a seizure coming on or begin having a seizure while in the treatment room. If any symptoms are reported, the operator will immediately shut down the PLIFUS system. The PI or Co-I, both quite experienced in evaluation and treatment of

acute seizures, will perform a neurologic exam and evaluate the subject immediately. The PI or Co-I will assess if the subject requires any medical care, and whether it is safe to continue in the study. If a subject has one of his/her typical seizures during a treatment session, the treatment session will be aborted and the PI or Co-I will evaluate the subject. Further treatment sessions may continue as scheduled, as long as the subject has fully recovered from the seizure by the time the next treatment session is due. If a subject has a seizure that the seizure is worse (more intense or longer in duration) during a treatment session, the treatment session will be aborted and the PI or Co-I will evaluate the subject and determine if he/she requires urgent medical care or observation, in which case he/she will be taken to the BWH Emergency Department. It will later be determined by the PI whether it is safe for that subject to continue with future treatments or not. If a subject has a typical seizure while enrolled in the study, but not on a treatment day, he/she will be asked to log it in the seizure diary. If the seizure is worse than usual in any way, or if a subject's seizures are occurring more frequently while participating in the study, the PI will determine whether it is safe for that subject to continue with future treatments or not. Patients will be observed for up to an hour after the first treatment session to evaluate for any potential symptoms or issues.

In the unlikely event that a major clinical event occurs that in any way seemed to be associated with the treatment, enrollment will be stopped and no further treatments will be performed until a comprehensive safety evaluation of the device and procedures is completed. The study would only begin re-enrolling patients and continuing treatments once the safety issue had been identified and completely rectified. As always, any adverse events that may occur during the trial will be reported to our IRB and the FDA.

### Foreseeable Risks and Discomforts

Given the safety profile of FUS in both animal and human studies detailed above, we believe there are minimal risks to subjects from participating in this study. Most of those studies noted above were performed on normal brain tissue, though one was on patients with epilepsy. Other forms of neurostimulation/neuromodulation have also proven safe in patients with epilepsy including Transcranial Magnetic Stimulation (TMS), Responsive

Neurostimulation (RNS- Neuropace), Deep Brain Stimulation (DBS), and even Electroconvulsive Shock Therapy (ECT), which actually induces seizures to treat depression. All of these are significantly more invasive than FUS, except for TMS. They all have been used successfully to try to reduce seizures in humans, even ECT in the setting of refractory status epilepticus, with varying degrees of success. Both DBS and *high*-intensity focused ultrasound [17] have been shown to be safe and highly successful for treatment of tremor and other movement disorders. In fact the advent of neurostimulation/neuromodulation as treatment for epilepsy was modeled on the success seen in that of movement and other brain disorders—the idea of stimulating the tissue that is discharging abnormally as opposed to lesioning it. In all of these types of modalities, epileptic brains have tolerated this type of treatment quite well, it is the outcomes that have been disappointing. We believe PLIFUS has more potential for better outcomes in patients with epilepsy given its ability to stop seizures [21] in epilepsy models and modulate auditory, visual, sensory, or motor responses [20] with beam focus.

Specific risks related to the PLIFUS treatment are described below. Participants may be uncomfortable sitting or lying for an extended periods of time in the treatment chair during PLIFUS sessions. Study staff will monitor subjects during treatment sessions for any skin irritation and advise subjects to report any skin issues that may emerge in between sessions or in the month following the course of treatment. Conductive water-based or silicone based tacky dots will be used to place EEG scalp electrodes to the subject's head as is done in routine EEGs. The dots have similar material properties as EEG conductive electrode coupling gel and are expected to contain the same minimal risks as having the gel in contact with the scalp over long periods of time as is used clinically in continuous EEG monitoring in hospitalized patients. The water-based dots have passed biocompatibility and skin irritation testing under testing standard ISO 10993-1.

As PLIFUS has been used in previous human studies to elicit or suppress tactile sensory functions by simulating cortical targets, it is possible subjects could experience these temporary sensations as minor side effects during PLIFUS [5], [9]. The studies conducted reported some subjects having tingling sensations, feeling of weak electrical current flow, and numbness in their fingertips when the stimulation was turned on. Other types of sensations of heaviness, pressure, coolness, and brushing, were also reported, although the occurrences were not frequent and only felt when the stimulation was active and shortly after the

stimulation was turned off. But since the temporal lobe is the region being targeted with the FUS beam focus in our investigation, the reported sensations due to cortical stimulation is unlikely to occur. However, human studies where the FUS beam focus passed close to the labyrinth region reported slight auditory information being perceived by the subjects [24]. The FUS beam path used to target the areas such as the anterior temporal lobe in our investigations may pass close to the labyrinth region but the ultrasound energy of the “beam path” in the near field is significantly less than what is at the FUS beam focus target. Near field is the beam path area leading up to the beam focus from the transducer and the far field is the beam path area beyond the FUS beam focus. Another area shown to experience slight and temporary functional changes due to FUS stimulation is the visual system. A FUS beam focus was positioned to stimulate the optic tract in cats. Evoked potentials of the brain centers of the visual system were used as the indicator of functional changes. The FUS stimulation temporarily suppressed the evoked potentials for several seconds or up to a minute after the stimulation [25].

As noted above under PLIFUS Safety Summary, due to the 56.7-mm beam length, the anatomical regions situated approximately 19.3 mm lateral and/or medial to the hippocampus could be affected. Anatomically, this would include the temporal lobe laterally, and medially the structures in the ambient cistern (alveus, fimbriae, cerebrospinal fluid, posterior cerebral artery, vein of Rosenthal and optic tract) and upper midbrain (tectum). None of these are anticipated, however, with the proposed intensities. Given the effects on seizures without tissue damage in the preclinical studies cited in our proposal as well as those in normal humans who were sonicated in eloquent cortex without adverse effects, we hypothesize that PLIFUS stimulation will result in mechanical disruption of the target tissue (here, the epileptogenic focus), preserving the integrity of the tissue but rendering it unable (or less able) to mount seizure activity for a period of time. The highest AI level safely delivered to a human by PLIFUS was a derated  $I_{SPTA} = 4.4 \text{ W/cm}^2$  (average skull thickness of 1.9 mm) in order to stimulate the somatosensory cortex and no adverse effects were reported [9]. **This is approximately a 50% higher AI level ( $I_{SPTA} = 3 \text{ W/cm}^2$ ) than will be used in the proposed study.**

Participants will be asked to complete the above-mentioned questionnaires, which we estimate will require <1 hour total over the course of the study. Minimal risks associated with completing questionnaires are participant fatigue

and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning. If any concern for depression or suicidality emerges from the questionnaires, the PI will discuss this with the patient's primary epileptologist urgently so this can be addressed.

In the event that subject suffers any complications/adverse events as a direct cause of the treatments in this study, the study will pay for their medical care. If the events are unrelated to the treatments, subject's insurance will be billed.

### **VIII. Potential Benefits**

There is no guaranteed benefit for study subjects. It is possible that participants will notice a decrease in seizure frequency or improved mood [36]. Participating in this study may serve to improve future epilepsy treatment.

### **IX. Monitoring and Quality Assurance**

Research staff will all receive standard annual training in human subjects research, data security, HIPAA regulations, patient and data privacy, and good research practice. All personnel involved in this research will receive a copy of the approved protocol and the PI will ensure all study staff understand their role in the study and the functions that they must perform. The PI will also be responsible for monitoring the accuracy and completeness of the informed consent process and documentation and the data collection and entry. Participant confidentiality will be maintained by de-identifying personal information and following the applicable Good Clinical Practice guidelines for clinical research.

#### Data safety monitoring plan

Specific aspects of the data safety monitoring plan are: (1) Data sheets will be stored in a PI's locked files in a locked office; (2) Data will be entered in coded form; (3) Data will be stored in computer files protected from unauthorized access by passwords; (4) Information that might potentially allow an individual participant to be identified will not be allowed in any publications, or reports sent to individuals outside the study; and (5) All employees who are to handle data will be certified in Good Clinical Practice and Human Subjects Protection Training in confidentiality policies and procedures. Only information

relevant to the protocol will be recorded.

### Management of risks to confidentiality

Strict standards of confidentiality will be maintained. Precautions will be taken to prevent disclosure of information to unauthorized parties. All paper records, forms and data will be stored in secure files to which only members of the investigative team will have access. Computer records will be protected by standard measures that limit access of the data to designated trained research project personnel. Computers with identifiable subject data will be password protected and encrypted to ensure confidentiality and kept behind the Partners firewall.

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