Participant Name: _____ Date: _____

Title of Study: Low Intensity Focused Ultrasound: A New Paradigm for Depression & Anxiety

Principal Investigator: Noah S. Philip, MD VA Facility: Providence 650

Study Group: Participants with Depression

KEY SUMMARY INFORMATION ABOUT THIS STUDY

You are being invited to take part in a research study that is being funded by the National Institute of Mental Health and Focused Ultrasound Foundation. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive. Taking part in this study is completely voluntary.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

This study is about using ultrasound to change brain activity. By doing this study, we hope to learn if we can change brain activity in areas that are connected to depression and anxiety symptoms using ultrasound. Your participation in this research will last about 6 weeks. See ***Table 1*** for overview.

The purpose of this research is to gather information on the safety and feasibility of the Brainsonix Pulsar 1002 low intensity focused ultrasound (LIFU) device when used to target an area of the brain involved in depression and anxiety. This is an investigational device and is not cleared by the US Food and Drug Administration (FDA) as a treatment device. The use of this device in this study is overseen by the FDA.

TABLE 1. Study Overview

	Pre-Intervention		**Intervention (Low-Intensity Focused Ultrasound (LIFU)) Phase**					
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Purpose	**Screening**	**Baseline**	**LIFU Session 1 (LIFU 1)**	**24-HR post LIFU 1**	**1-week post LIFU 1**	**LIFU Session 2 (LIFU 2)**	**24-HR post LIFU 2**	**1-week post LIFU 2**
Activities	•Informed consent •Information Session •Questionnaires/ Assessments •Interviews with trained research staff •Physical Examination •Questions about mental health •Pregnancy/ drug test, if applicable	•CT scan •MRI •Short mental tasks • Self-reported symptoms scales •Clinician administered assessments and interviews •Questions about mental health	•Pregnancy test, if applicable •MRIs with task •LIFU Stimulation •Questionnaire/ Assessments •Physical Examination •Questions about mental health	•MRI •Short mental tasks •Questionnaires/ Assessments •Questions about mental health		•Pregnancy test, if applicable •MRIs with task •LIFU Stimulation •Questionnaire/ Assessments •Physical Examination •Questions about mental health	•MRI •Short mental tasks •Questionnaires/ Assessments •Questions about mental health	
Compensation	$0*	Up to $150**^	Up to $150**	Up to $150**	Up to $150**	Up to $150**	Up to $150**	Up to $150**
Duration (maximum)	3 hours	4 hours	4 hours	4 hours	4 hours	4 hours	4 hours	4 hours

Computerized Topography Scan (CT Scan), Magnetic Resonance Imaging (MRI), Low Intensity Focused Ultrasound (LIFU)

*If ineligible at Visit 1 after consent, participants will receive $50.

** Participants will receive $100 for MRI procedures, plus $50 for all other procedures/ measures.

^ If ineligible at Visit 2 prior to MRI, participants will receive $50. Participants will receive $150 if found ineligible at the end of Visit 2.

The study will involve eight study visits. Participants may be asked to attend up to six additional follow-up visits if indicated. As part of these study visits you will be asked to complete questionnaires/ assessments and medical examinations. At one visit, you will be asked to undergo a Computerized Topography (CT) scan. Seven of the standard eight study visits will include magnetic resonance imaging (MRI) scans. The MRI scans are pictures of your brain and brain activity. You will be asked to do certain tasks while in the scanner. In two MRI sessions, you will receive ultrasound energy while in the scanner to see how the ultrasound changes your brain activity. You will receive stimulation to 2 different areas of the brain (area A at 1st LIFU session and area B at 2nd LIFU session, or vice versa). You will also be examined by medical doctors before and after the ultrasound stimulation.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You will not receive direct benefits for participating in this research study. *For a complete description of benefits, refer to the 'Detailed Information about the Study' section.*

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

The ultrasound device puts energy into your brain. The energy used in this study is like what is used by doctors to look at blood flow in the body. Not all the effects of ultrasound use to change brain activity are known. Since this is the first use of the LIFU device in a patient population, the FDA has deemed this project to be a significant risk device study. There are also risks associated with getting MRI and CT scans, but these can be safely managed by taking appropriate precautions. *For a complete description of risks, refer to the 'Detailed Information about the Study' section.*

This is not a treatment study. You may choose not to participate and continue with any care you already receive.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer. All NIMH studies are required to provide participants with an option to have their collected data shared with the research community through the NIMH Data Archive (NDA). You will still be allowed to participate in this study even if you decline to have your data shared with NDA. *For a complete description of Optional participation in the NDA, please refer to the 'Detailed Information about the Study' section.*

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Noah Philip, MD of the Providence VA Medical Center. If you have questions, suggestions, or concerns regarding this study or

you want to withdraw from the study his/her contact information is 401-273-7100 ext. 16200. You may contact a study team member at: 401-273-7100 ext. 16437.

DETAILED INFORMATION ABOUT THE STUDY

WHAT IS THE PURPOSE OF THIS STUDY?

By conducting this research project, we hope to learn if we can use ultrasound energy to change brain activity when used to target an area of the brain involved in depression and anxiety. Ultrasound devices put sound waves higher than you can hear into the body. They are most often used to look at parts of the body underneath the skin. Recently, researchers have found that this same energy can be used to change brain activity in animals. Other studies have safely used ultrasound energy in some parts of the brain in humans. This is not a treatment study. This study hopes to show that using ultrasound to change brain activity in humans is safe and can change mood.

This study will use the Brainsonix Pulsar 1002 low intensity focused ultrasound device. Our goal is to gather information on whether this device is safe to use (safety) and whether it can be used the way we plan (feasibility). This device has not been cleared by the FDA for changing brain activity. The use of this device in this study is overseen by the FDA.

HOW LONG WILL I BE IN THE STUDY?

We aim to have 50 people participate in this study. This research study is expected to take approximately 4 years. Your individual participation in the project will take 1.5 months. Over the course of approximately 6 weeks, you will have 8 visits at the Providence VA Medical Center.

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

If you choose to participate in the study, you will come to the Providence VA Medical Center for 8 study visits. Please reference ***Table 1. Study Overview*** for more information regarding study involvement. Each study visit is detailed below. Research staff will assist in scheduling study visits. If you choose to participate, the first study visit can be on the same day as you sign the consent form.

Visit 1: The first study visit will help the research team know that this study is appropriate for you.

- Research staff will ask you questions related to your mental health, specifically about symptoms of depression and anxiety
- You will be asked to complete a few short mental tasks, such as drawing figures and remembering words

  - These tasks will be administered by a member of the research team
- A medical doctor on the research team will do a physical examination to test your nervous system, called a neurological exam
- You will also be asked to complete questionnaires that ask questions about symptoms related to posttraumatic stress, depression, and anxiety
- You may be asked to complete a pregnancy test or breathalyzer/urine toxicology test
- The main purpose of this visit is to determine eligibility for further study participation
- Total time for visit 1 is about 3 hours

Visit 2: The second study visit will include multiple types of brain scans. It may be on the same day as visit 1. Study procures may occur over the course of two days if needed.

- You will receive a computed tomography scan (CT, sometimes called a CAT scan)
  - The CT scan uses X-rays to look at your brain and your skull
  - You will be asked to lie on a bed and hold still in the CT scanner
  - The CT scan may become part of your medical record
  - The CT scan will take about 15 minutes
- You will receive MRI scans at this visit
  - The MRI scanner uses magnets to take pictures of your brain and its activity
  - You will be asked to lie on a bed and hold still in the MRI scanner
  - Some of the pictures from the MRI scans may become part of your medical record
  - The MRI scans will take about 1.5 hours
- You will also be asked to complete a series of tasks, such as drawing lines or remembering words
  - Research staff will instruct you in each of these tasks before you do them
- Research staff will ask you about symptoms of depression and anxiety, as well as other questions related to your mental health
- You will also be asked to complete questionnaires that ask questions related to posttraumatic stress, depression, and anxiety symptoms
- This visit will help us verify that it is safe for you to continue in the study and receive ultrasound stimulation
  - It is possible that you may not be eligible for further participation based on information collected at this visit.
- Total time for visit 2 is about 4 hours

Visit 3: The third study visit will include brain scans and the first ultrasound stimulation.

- You may be asked to complete a pregnancy test
- You will receive MRI scans at this visit
  - The MRI scanner uses magnets to take pictures of your brain and its activity
  - You will be asked to lie on a bed and hold still in the MRI scanner

  - Some of the pictures from the MRI scans may become part of your medical record
  - The MRI scans will take about 2 hours
  - During part of the MRI scanning session, you will be asked to complete a task
    - You will be asked to press buttons in response to images you will see on a screen
    - The task will include images of faces, numbers, or shapes
    - You will be able to practice these tasks before you go into the MRI scanner
  - You will receive ultrasound stimulation at this visit
    - The ultrasound device will be strapped to your head before you go into the MRI scanner
    - You may be moved in and out of the MRI scanner several times at the beginning of the session to adjust the position of the ultrasound device
    - The ultrasound stimulation will last 10 minutes
  - You will receive the ultrasound energy to 1 of 2 areas of the brain during the MRI
    - The areas that you receive stimulation at this visit is by chance
  - A medical doctor on the research team will be present while you receive ultrasound stimulation
- After the MRI scans, you will be asked about how you felt when the ultrasound device was on or any side effects you may have from the ultrasound stimulation
- Research staff will ask you about symptoms of depression and anxiety, as well as other questions related to your mental health
- You will also be asked to complete questionnaires related to depression and anxiety symptoms
- A medical doctor on the research team will do a neurological exam
- Total time for visit 3 is about 4 hours

Visit 4: The fourth study visit will happen one day after you receive ultrasound stimulation at visit 3. It will include a brain scan and examinations by medical doctors.

- You will receive an MRI scan at this visit
  - The MRI scan uses magnets to take pictures of your brain and its activity
  - You will be asked to lie on a bed and hold still in the MRI scanner
  - Some of the pictures from the MRI scan may become part of your medical record
  - The MRI scan will take about 30-45 minutes
- Research staff will ask you about symptoms of depression and anxiety, as well as other questions related to your mental health
- A medical doctor on the research team will do a neurological exam
- You will be asked to complete questionnaires that ask questions about symptoms related to posttraumatic stress, depression, and anxiety

- You will also be asked to complete a series of tasks, such as drawing lines or remembering words
  - Research staff will instruct you in each of these tasks before you do them
- You will be asked about any side effects you may feel are from the ultrasound stimulation you previously received
- Total time for visit 4 is about 4 hours

Visit 5: The fifth study visit will happen one week after you receive ultrasound stimulation at visit 3. It will follow the same steps as visit 4. The total time for visit 5 is about 4 hours.

Visit 6: The sixth study visit takes place as close to visit 5 as possible (may be on the same day with breaks). This visit includes the second ultrasound stimulation session (to the area that was not stimulated at Visit 3) and will follow the same steps as visit 3. The total time for visit 6 is about 4 hours.

Visit 7: The seventh study visit will take place one day after you receive ultrasound stimulation at visit 6. It will follow the same steps as visits 4 and 5. The total time for visit 7 is about 4 hours.

Visit 8: The eighth study visit will take place one week after you receive ultrasound stimulation at visit 6. It will follow the same steps as visits 4, 5, and 7. The total time for visit 8 is about 4 hours. Unless you require extended follow-up visits (please reference see *Other visits*, below), this is the FINAL STUDY VISIT.

Other visits:
If you have changes in mental health (good or bad) at visit 3 or 6, we may ask you to attend other study visits, outside those listed above. These visits would occur during the "Extended Follow-up Phase" (see ***Table 2***). In such instances, **Follow-up 6** will be your LAST STUDY VISIT.

TABLE 2. Overview of Extended Follow-up Visits

Extended Follow-up Phase						
Visit	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**	**Follow-up 4**	**Follow-up 5**	**Follow-up 6**
Purpose	2-weeks post LIFU*	3-weeks post LIFU*	4-weeks post LIFU*	5-weeks post LIFU*	3 months post LIFU*	6 months post LIFU*
Activities	•MRIs (up to 1.5 hours) •Short mental tasks			•Questionnaires/ Assessments •Questions about mental health		
Compensation	Up to $150 per visit (See compensation section for details)					
Duration (maximum)	4 hours (per follow-up)					

**Follow-up occurs in relation to final LIFU session (either visit 3 or 6)*

- If research staff find changes in your physical or mental health after the first round of ultrasound stimulation, the investigator may decide it is better for

you not to receive the second round of stimulation. Investigators will make this determination at your 1-week follow-up (i.e., visit 5). Additionally, you may be asked to come back for additional follow-ups (up to 6) after visit 5.

- If research staff find changes in your physical or mental health after the second round of ultrasound stimulation, you may be asked to come back for additional follow-up visits (up to 6). This determination will be made by the investigators at your 2nd 1-week follow-up (i.e., visit 8).

Optional NDA participation: *Participants may choose to share their data with the National Institute of Mental Health Database (NDA) at the National Institute of Health (NIH). NDA is a large database where deidentified study data from many National Institute of Mental Health (NIMH) studies is stored and managed. Deidentified study data means that all personal information about you (such as name, address, birthdate and phone number) is removed and replaced with a code number. Your personal information will not leave the VA. Sharing your deidentified study data helps researchers learn new and important things about mental health more quickly than before.*

If you opt-in to this optional study component, during and after the study, the study researchers will send deidentified and limited (i.e., MRI and CT images include the date that they were collected) study data to the NDA. Other researchers across the world can then request to use the deidentified study data for other research. Every researcher (and institutions to which they belong) who requests to use or see the deidentified and limited study data must promise to keep the data safe and promise not to try to learn your identity. Experts at the NIH who know how to keep your data safe will review each request carefully to reduce risks to your privacy. Sharing your study data does have some risks, although these risks are rare. Your study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity.

A global unique identifier (GUID) is used to upload your study data to the NDA. A GUID consists of a series of randomly generated letters and numbers, and is used to de-identify your study data. Additionally, a GUID is unique to you, which means that if you have previously, or in the future, participate(d) in NIMH research studies, all of your data within the NDA is labeled with the same GUID. In order for the research team to create or verify your GUID, you will need to provide staff specific personally identifiable information (e.g., full name, date of birth, city/municipality of birth). The information you provide our team will be coded, in a way that makes it impossible to link the code back to you, before being sent to the National Institute of Health (NIH). The NIH will then use that coded information to generate and return your GUID. The information used to generate or verify your GUID, will not be stored.

You may not benefit directly from allowing your study data to be shared with NDA. The study data provided to NDA may help researchers around the world learn more about mental health and how to help others who have problems with mental health.
NIMH will also report to Congress and on its website about the different studies using NDA data. You will not be contacted directly about your study data that was contributed to NDA.

You may decide now or later that you do not want your study data to be added to the NDA. You can still participate in this research study even if you decide that you do not want your data to be added to the NDA. If you know now that you do not want your data in the NDA, please tell the study researcher before leaving the clinic today.

If you decide any time after today that you do not want your data to be added to the NDA, call or email the study staff who conducted this study, and they will tell NDA to stop sharing your study data. Once your data is part of the NDA, the study researchers cannot take back the study data that was shared before they were notified that you changed your mind. If you would like more information about NDA, this is available on-line at http://nda.nih.gov

_____**Initial here to opt-in to the NDA Data Sharing Component**

_____**Initial here to opt-out of the NDA Data Sharing Component**

Your choice to participate or not in this study will not affect your clinical treatment. You are encouraged to continue any medical or mental health treatments that you were receiving prior to enrollment in this study. The study team will ask you about your treatment(s) and/or medication(s) at the 1st study visit. Prior to each study visit, we will review your medical record for any change(s) in medications or mental health treatment.

Other information including your name, address, date of birth, and information from your medical records such as medical history, allergies, and lab results may also be accessed and collected as part of study procedures. Study staff may add your current mental health, primary care, and other relevant providers as co-signers on any study visit note. The study Principal Investigator or designee may communicate directly with your relevant providers.

WHAT IS EXPECTED OF ME IF I TAKE PART IN THIS STUDY?

- Keep your study appointments. If you miss an appointment, please contact the investigator or research staff to reschedule as soon as you know you will miss the appointment. Notify study staff of any planned travel or ongoing scheduling conflicts that could possibly conflict with follow-up visits.
- Tell the investigator or research staff if you believe you might be pregnant.
- Complete your questionnaires as instructed.
- Complete assessments and computerized tasks to the best of your ability.
- Ask questions as you think of them.

- *o* While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra X-rays or potential treatment interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.
- *o* Tell the investigator or research staff if you notice any changes (good or bad) after receiving ultrasound stimulation.
- *o* Avoid any medication or treatment change(s) during study participation. Please make sure to tell the study team if you run out of your medications, forget to take dose(s), or start new medication(s) at the start of each study visit. Notify the study investigator if doctor(s) not involved in this research project determine that it is in your best interest to modify your medication(s) or treatment(s) during course of study participation.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

- **General Risks of Participation and Potential Side Effects – *clinical symptoms***

  - **Changes from Baseline**
    The study team will ask you about current and past medical diagnoses, ongoing treatment(s), and active symptoms or problems that you experience at your initial study visits (1 & 2). It is possible that medical conditions, symptoms, and/or problems may change or worsen during your study participation. These changes could be unrelated, or related study participation. It is important that you notify the study team if you experience any changes in problems or symptoms during your participation. Members of the study team may ask you additional questions about your symptoms and experiences to determine if changes may be related to study participation.

  - **New Symptoms or Problems**
    It is possible that you may experience new problems or symptoms while participating in this study. It is important that you notify the study team if you experience any new problems or symptoms so that the Principal Investigator (Dr. Noah S. Philip) and other study clinicians can determine whether these may be related to study participation.

  It is possible that you may experience mild changes (increase or decrease) related to:
  - Mood: anxiety, depression symptoms, irritability, feelings of excitement, etc.
  - Cognition: thinking, concentration, remembering things, worsening performance on mental tasks, etc.

- Physical: aches and pains, or headache
- Sleep and Overall Energy: feeling fatigue, easily tiring, drowsiness during the day, or changes in sleep (e.g., falling or staying asleep, waking earlier or later than normal)

- **Ultrasound**

Ultrasound have been safely used for diagnostic imaging for many years. The settings used in this study are similar to those used to monitor blood flow in various tissues (including brain) in regular medical settings. You may hear or feel a buzz from the Brainsonix Pulsar 1002 low-intensity focused ultrasound (LIFU) device. A medical doctor on the research team will do an exam before and after your focused ultrasound stimulation, and research staff will ask you questions to check for any effects of the ultrasound stimulation. Not all the risks of using ultrasound to change brain activity are known. There is a risk that the energy from the device could cause injury. The energy will be kept below the limit used for clinical ultrasound to reduce the risk of injury. The FDA has deemed this to be a significant risk device study.

  - A disc (similar in size and shape to a hockey puck), called a transducer, is connected to ultrasound source to deliver LIFU. The transducer is held to the scalp, using a holder with padded Velcro straps that wrap around the head (front, back and top) and under the chin.
    - It is important that transducer movement is limited during ultrasound sessions. Research staff will tighten the Velcro straps to make sure the transducer stays in the correct place.
      - Tell the research team if you experience any discomfort from the straps or transducer holder. The team will do their best to decrease the risk of discomfort prior to MRI and LIFU procedures.
      - You may experience mild irritation or redness from the Velcro straps. A study physician will check to make sure any irritation or redness resolve before the end of your study visit.
    - The transducer will be fitted and aligned to your head at Visit 2. This will help you to feel comfortable with the set-up before ultrasound sessions.
  - Possible LIFU-related side effects may include new or worsening:
    - Headache
    - Sleep disturbances (e.g., problems falling asleep, difficulty staying asleep, feeling sleepy or drowsy during the day, waking earlier than normal)
    - Cognitive and Attention problems (e.g., brain fog, difficulty with concertation or focus).
    - Mild changes in emotions or feelings (e.g., irritability, depressed mood, anxiety symptoms)
  - Less common risks that are possibly related to LIFU include:
    - Decreased appetite or self-reported weight loss
    - Feeling sweaty or experiencing dry mouth during ultrasound
    - More than mild changes in depression symptoms.

- Dissociative symptoms, such as feeling “spacey” or like your mind and body are separate from each other.
- Feeling fatigue during or after ultrasound
- Numbness or tingling sensation(s)
- Head pain or discomfort during ultrasound sonication
- Vision changes
- Dizziness
- Gait effects
- Nausea

It is important that you notify the study team if you experience any of these risks, or any other discomfort, changes, or adverse experiences during or after LIFU sessions, so that the Principal Investigator (Dr. Noah S. Philip) and other study clinicians can determine whether these may be related to the study device.

- **MRI**

MRI is generally considered safe, although there have been accidents resulting in serious injury and death. These accidents mostly result from failure to follow established safety guidelines for the MR environment. All research staff are knowledgeable and trained in MRI safety. You will be screened for MRI safety and will not be enrolled if the researchers identify safety concerns. Some people experience a 'closed-in' feeling due to the relatively restricted space within the MRI machine. You may experience discomfort from lying in one position for a long time. You may not be able to have the MRI procedure if you have certain metal, surgical clips, or implants, including a brain aneurysm clip or a pacemaker, in your body, because during the MRI procedure metal can heat up and move, or clips and implants stop working. Dental fillings are not a problem. If there is any question about whether or not there is metal in your body, you may be requested to have an X-ray to determine this; the X-ray will become part of your medical record. If you are pregnant, you should delay having an MR scan. You will need to remove all jewelry or clothing with metal before having the MRI. All of these precautions will be reviewed with you immediately before you have the MRI.

- **CT**

CT uses X-ray radiation. You are exposed to radiation on a daily basis, both from natural (sun and earth) and manmade sources. The estimated radiation dose that you will receive as a participant for this study is low and is not expected to be harmful. You may also be bothered by a ‘closed-in’ feeling or discomfort from lying in one position for a long time.

- **Questionnaires**

Some people become uncomfortable at being asked questions about their physical and emotional health. You may discuss any discomfort with one of the researchers. If, for any reason, you wish not to answer specific questions or you

wish to terminate the session, you will be able to do so. If you become distressed and require additional support, a study staff member will put you in touch with a mental health care provider (if you do not have one), or may contact your mental health provider.

- **Medical examination**
  Some people become uncomfortable when having a physical examination. If, for any reason, you wish not to answer specific questions or you wish to terminate the session, you will be able to do so.

- **Mental tasks**
  You may become frustrated or bored while completing the mental tasks. If, for any reason, you wish to terminate the session, you will be able to do so.

- **Risk of loss of confidentiality**
  While every effort will be made to maintain your confidentiality, it is possible that complete confidentiality will not be maintained. There are safeguards in place to protect your private information. These safeguards are described under the heading "How Will My Private Information Be Protected?"

  Sharing your study data does have some risks, although these risks are rare. Your study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity.

- ***Inclusion of Women of Childbearing Potential***
  The safe use of LIFU in the brain in pregnant women and nursing mothers has not been established. Consequently, there may be risks to you (or to your embryo or fetus) if you are or may become pregnant that are unknown. Women of childbearing potential enrolling in this study must (i) have been using a birth control measure (an intrauterine device (IUD), birth control pills or shots, a condom, diaphragm, or abstinence) for the previous three months, (ii) must have a negative pregnancy test, and (iii) must agree to continue to use a birth control measure for the duration of the study. If, while participating in the study, you suspect you have become pregnant, please contact the study physician immediately. Women are considered to be of childbearing potential unless they have been surgically sterilized (for example tubal ligation or hysterectomy) or are post-menopausal, that is, no menstrual period for more than 6 months. Nursing mothers may not participate in this study.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your mental health, primary care, and/or other providers if you have any questions about the risks of usual care, which are not involved in this research study.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

You will not receive direct benefits for participating in this research study.

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

Every effort to maintain confidentiality will be made. You will not be identified in any reports or publications that may result from this study. The confidentiality of the information you provide will be maintained on a secure research server. Paper data will be stored in a locked cabinet inside a locked VA office. Identifiable information gathered during the course of this study will not be shared outside study personnel except where permitted by law.

The identifiers might be removed from the identifiable private information and, after such removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or or your Legally Authorized Representative (LAR). If you decide to participation in the ***optional NDA component***, your data will be shared with the NIMH, and may be used by other researchers in the future.

There are times when we might have to show your records to other people. For example, someone from the Office of Human Research Protections, the Government Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, the VA Institutional Review Board (IRB), our local Research and Development Committee, Food and Drug Administration, and other study monitors may look at or copy portions of records that identify you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Health Information Portability and Accountability Act (HIPAA)

There are rules to protect your private information. Federal laws and the federal medical or HIPAA Privacy Rule also protect your privacy. By signing this form, you provide your permission called your 'authorization,' for the use and disclosure of information protected by these laws and the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. Other information such as HIV status, drug, alcohol or STD treatment, genetic test results or mental health treatment may be viewed or collected, if necessary or if there are interviews or surveys where you, as the research subject, provide that information to the research team.

The research team may also need to disclose or share your information to others as part of the research and study progress. Others may include the following: *the Focused Ultrasound Foundation, National Institute of Mental Health (NIMH), Food and Drug Administration (FDA), Office of Human Research Protections (OHRP), the VA Office of Research Oversight (ORO), the Government Accountability Office (GAO),* the VA Institutional Review Board, and the local VA medical facility Human Research Protections Program.

Your health information disclosed pursuant to this authorization may no longer be protected by Federal laws or the HIPAA Privacy Rule regulations and may be subject to re-disclosure by the recipient.

While this study is being conducted you will have access to your research related health records. This will not affect your VA healthcare, including your doctor's ability to see your records as part of your normal care and will not affect your right to have access to the research records after the study is completed.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you can ask a member of the research team to give you a form to revoke your authorization in writing. Your written request will be valid when the research team receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your rights as a VHA patient to treatment or benefit outside of the study.

If you revoke this authorization, **Dr. Noah S. Philip** and his or her research team can continue to use information about you which the research team has relied upon for the research and that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization. This authorization will expire at the end of the research study unless revoked prior to that time.

WHAT ARE THE COST TO ME IF I TAKE PART IN THIS STUDY?

You or your insurance will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

WHAT COMPENSATION IS OFFERED FOR PARTICIPATION IN THE STUDY?

You will be compensated for your time and effort in completing study procedures (see ***Table 1***). Research staff will provide compensation after each study visit according to the following schedule:

- You will be compensated $100 each MRI session at visits 2, 3, 4, 5, 6, 7, and 8
- You will be compensated $50 for the medical examinations, questionnaires, and tasks at visits 2, 3, 4, 5, 6, 7, and 8
- You will be compensated for any additional (6) visits (i.e., Extended Follow-up visits) at the same amounts visits 2 thru 8
  - See ***Table 2. Overview of Extended Follow-Up Phase***
  - If applicable, total compensation for these 6 visits is $900
- Total compensation for the 8 standard study visits is $1,050
- Total compensation for the 8 standard visits, plus the 6 extended follow-ups, is $1,950

You will be compensated using gift cards (e.g., VISA, Mastercard, American Express). *You may be issued an Internal Revenue Service Form 1099-MISC for the payment(s) you receive in this study, which would require us to share your social security number with the Ocean State Research Institute (OSRI), as they will be issuing the payments.*

If clinical care is needed after participation, those visits will not be additionally compensated. In response to injury or mental health changes, you will receive the standard of care in responding to these injuries or mental health changes.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

If you are injured as a result of being in this study, the VA will provide the necessary medical treatment in accordance with applicable federal regulations (38 CFR 17.85).

Many of the procedures for this study are used to detect if any injury or change to your mental health occurs. If you are injured or your mental health changes from being in this study, research staff will schedule additional follow-up visits. Medical doctors on the research team will also discuss these changes with your mental health and primary care providers. If you have been injured or have changes in your mental health during the study, the standard of care will be provided to you after your participation. If necessary, study physicians (psychiatrists and/or neurologists) may also provide you with a referral for clinical care after you complete your study participation.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY:

Dr. Noah Philip at (401) 273-7100 ext. 16200 and

AFTER HOURS:

Call (401) 273-7100 and ask the operator to contact Dr. Noah Philip _____

Emergency and ongoing medical treatment will be provided as needed.

DO I HAVE TO TAKE PART IN THE STUDY?

- No. Participation in this study is completely voluntary. If you decide to take part in the study, it should be because you really want to volunteer.
- You will not lose any services, benefits or rights you would normally have if you choose not to participate.
- Your decision to participate or not participate in this study will not affect your treatment at the Providence VA Medical Center
- If you choose to participate in the study, you may withdraw at any time. Information collected before you withdraw may still be reviewed, but no new data will be collected.
- If you choose to withdraw from participation in the study, any treatment you receive now or in the future at the Providence VA Medical Center will not be affected. Compensation will be for the number of sessions that you complete.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

The investigator may decide to end your participation in the research study. The investigator would end your participation in the research study if he decides that it is not safe for you to receive ultrasound stimulation or other study procedures. This may be for one of the following reasons:

- You injure your head before either ultrasound visit (visits 3 or 6)
- The CT scan done at visit 2 shows a condition that would be unsafe for ultrasound
- You have a significant change in your mental health before the ultrasound visit (visit 3)
- You experience or display side effects that, in the investigator's opinion, may be or are related to ultrasound stimulation before the second ultrasound session (visit 6).

The investigator and his research team may also decide it is not safe for you to receive ultrasound stimulation or other study procedures for reasons not listed above.

If the investigator and his research team decide to end your participation in the research study, someone on the research team will explain the reason for ending your participation. If your participation is ended for a health-related reason, the research team may also discuss this with your mental health, primary care, and other relevant providers. You will be thanked for your participation in the research study and be compensated for the study procedures you completed. Your participation in the study will then be complete.

If you are injured or your mental health changes after the ultrasound visit, you will remain in the study. Research staff may ask you to come back for additional follow up visits every week up to one month after the ultrasound visit. Medical doctors on the research team will also discuss these changes with your mental health, primary care, and other relevant providers.

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the Institutional Review Board (IRB) at the Providence VA Medical Center. This is the Board that is responsible for overseeing the safety of human participants in this study. You may call Research Administration at (401) 457-3066 or the Providence VAMC Patient Advocate at 401-457-3093 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

Research staff will tell you any new information about using ultrasound to change brain activity while you are participating in the study. This could include information about the risks of using ultrasound to change brain activity.

You will be examined by medical doctors on the research team as part of this study. The medical doctors may find information about your health that makes you ineligible to participate in the study. The medical doctors may tell you and your mental health, primary care, and other relevant providers about that information. The medical doctors will also examine you after you receive ultrasound energy. If your physical or mental health changes after the ultrasound energy, medical doctors on the research team will discuss the change with you and your mental health, primary care, and other relevant providers.

FUTURE USE OF DATA AND RE-CONTACT

Please see section **"What will happen if I take part in the study?"** (above) for information about data stored in the NDA, including storage, access, and future use.

Participant Name: _____ Date: _____

Title of Study: Low Intensity Focused Ultrasound: A New Paradigm for Depression & Anxiety

Principal Investigator: Noah S. Philip, MD VA Facility: Providence 650

Study Group: Participants with Depression

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr. Noah Philip or his research staff has explained the research study to me. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me. I have been given the chance to ask questions and obtain answers.

By signing this document below, I voluntarily consent to participate in this study and authorize the use and disclosure of my health information for this study. I also confirm that I have read this consent, or it has been read to me. I will receive a copy of this consent after I sign it. A copy of this signed consent will also be put in my medical record.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Name of Staff Obtaining Consent	_____ Staff Signature	_____ Date