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Repetitive Transcranial Magnetic Stimulation to Improve Cognitive Function in TBI

Approval Date by IRB: December 11<sup>th</sup>, 2018



**RESEARCH CONSENT FORM**

Title of Study: Repetitive Transcranial Magnetic Stimulation to Improve Cognitive Function in TBI

Principal Investigator: Maheen Mausooof Adamson

VAMC: VA Palo Alto HCS

**rTMS for the Improvement of Cognitive Function and Other Outcomes in TBI**

**Informed Consent**

Are you participating in other research studies? \_\_\_ Yes \_\_\_ No

**PURPOSE OF RESEARCH**

You are invited to participate in a research study to determine if repetitive Transcranial Magnetic Stimulation (rTMS) is an effective treatment for improving cognitive function and other outcomes. You were selected as a possible subject in this study because: 1) you have indicated that you have had a traumatic brain injury (TBI); and 2) you are a Veteran.

This study is being done by researchers at VA Palo Alto. This research study is looking for 100 participants, including Veterans, Military personnel, and civilians, who experience cognitive problems and other outcomes.

The primary aim for this study is to assess the effectiveness of rTMS on improving cognitive function. We will also be assessing whether there are changes to quality of life, fatigue and PTSD, headache and pain secondary to improvements in cognition.

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

**VOLUNTARY PARTICIPATION**

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

**DURATION OF STUDY INVOLVEMENT**

This entire research study is expected to be conducted over approximately 2 years. Each participant will undergo 20 rTMS treatment sessions of 30-60 minutes over the course of 2 to 6 weeks. There will also be follow-up activities at post-treatment, and 6 months.



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**PROCEDURES**

Patients who sign this informed consent and meet the study eligibility criteria will be enrolled into the study and will be randomized into one of 2 treatment groups: active “real rTMS” or sham (placebo) rTMS. Patients who fail screening may be re-screened at a later time at the discretion of the Protocol Director.

If you choose to participate, Dr. Adamson and her research study staff will ask you to participate in the activities described below. All study procedures will be completed by trained professionals and research staff. This study has 4 phases: screening (1 hour telephone screen, and 6 hours on-site screen), baseline (8 hours), intervention (2-6 weeks), and follow-up post-intervention (9 hours), and at 6 months (10 hours).

**1. SCREENING PHASE**

If you agree to be in this study, you will complete a number of tests to make sure that you are eligible and healthy enough to participate. You will read and sign this informed consent form before you begin the screening phase. The on-site screening phase will take approximately 6 hours to complete. It may be done in one day or over several days.

During the screening phase and before you begin the baseline and intervention phases, the following will happen:

- If you are a woman of childbearing age, a urine sample will be used to test for pregnancy. Some parts of this research may have negative effects on a fetus and should not be done during pregnancy. Because of this risk, it is necessary that a pregnancy test be done first, as a positive test would exclude you from participation in this study. Additionally, it is important for you to tell us if, to your knowledge, you are pregnant or breast-feeding at the time of this study.
- You will be given a physical examination. A clinician will assess your medical history, your pain, and also your mood.
- Study staff will review with you any medications (prescriptions, “natural food products,” supplements, and “over the counter” medications) that you are taking or have taken in the past. During the study, you will not be able to take any medications known to increase the risk of seizures. Your primary physician may adjust your medications as needed.
- You will complete several assessments about your health, cognitive function, your pain, your mood, your use of alcohol and other substances, and any possible traumatic experiences you may have had.
- A blood sample of about 4 tablespoons will be taken to check how various systems in your body, like your liver and kidneys, are working. If you have a liver function test that is abnormal, you may need to return for additional tests. They will also be used for



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assessment of plasma proteins and genetic information. Any samples left over after analysis will be stored.

- You will be asked to provide a urine sample. This sample will be screened for the use of drugs. Positive results may require that you be excluded from this study. If you are able to stop using these drugs, you may be re-screened later.
- You will have a breathalyzer to measure your alcohol level. This will be for the screening of alcohol use. Positive results may require that you be excluded from this study. If you are able to limit your alcohol consumption per the study guidelines, you may be re-screened later.
- You will be provided with the results of these blood, urine, and breathalyzer tests, if you request them.
- You will be tested with an rTMS coil in order to find the settings that will be used for your treatments. This is called a “motor threshold” and is the amount of magnetic power required to make your right thumb move by stimulating your brain. We will attach pads to your right thumb and hand with non-permanent adhesive. The pads will be connected to a machine which measures the movement in your hand. We will use this machine, called an electromyography or EMG, to find your motor threshold.

**2. BASELINE PHASE**

Upon successful completion of the screening phase, and after careful review of all labs, exams, and assessments to ensure your safety and suitability for the duration of the study, you will complete the baseline phase. The baseline phase will take approximately 8 hours to complete. It may be done in one day or over several days. During the baseline phase, the following will happen:

- You will have a hearing test to measure your level of hearing.
- You will complete several assessments, as well as a series of cognitive assessments.
- MRI of your brain will be taken.
- A blood sample of about 4 tablespoons will be taken and used for assessment of plasma proteins. Any samples left over after analysis will be stored.

**About MRI (Magnetic Resonance Imaging)**

MRI machines use strong magnet and radiofrequency fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for approximately one hour while the machine gathers data. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance (MR) scanner. We will provide earplugs or headphones that you will be required to wear. The space within the large



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magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

Tissue Sampling for Genetic Testing

Genetic tests will be conducted on your samples. The tests we plan to do will allow us to study potential predisposition to metabolic, neurological, or immunological disease and responses to the treatment offered as an intervention in this study. Research using blood or tissues is an important way to try to understand traumatic brain injury and/or the role genes play in the health problems associated with traumatic brain injury.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

We will protect the confidentiality of your samples and information about you. Your samples will be stored in a locked area and all information about you will be stored in a locked file cabinet or on a password protected secure computer.

Tissue Banking for Future Research

As part of this research we would like to save any leftover blood samples for future research. Your blood samples will be stored at the Palo Alto VA and will be used for future research on traumatic brain injuries and related health problems. Your samples will be stored until the sample is all used up or until this research study is completed or on December 31, 2075. Your sample and information about you will be labeled with a code that does not contain your name, initials, SSN, date of birth, or other ways that identify who you are. The research we conduct with your blood is being done for research purposes only and we will not tell you or your doctor about the results of the research.

You may withdraw your permission for us to use your blood for future research at any time. Contact the Dr. Maheen Mausoo Adamson, PhD, at (650)493-5000 x 62179 to withdraw your permission. If you take back your permission, the research team can continue to use information about you collected before you decided to take back your permission, but they will not collect any information about you going forward and any remaining samples will be destroyed.

The research we conduct using your blood may result in inventions or discoveries that could be used to make new products or diagnostic or therapeutic agents. These inventions and discoveries may become financially valuable. You will not receive any money or other benefits from any commercial or other products that are made using your specimens.



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\_\_\_\_\_ Yes, I give permission for my samples to be saved for future research, as set forth above.

\_\_\_\_\_ No, I do not give permission for my samples to be saved for future research.

**3. INTERVENTION PHASE**

If you agree and are eligible to participate in this research study, you will be enrolled in the intervention phase of the study. This phase will last up to 6 weeks. You will come to the clinic for 20 sessions of rTMS treatments. Each session will last approximately 30-60 minutes, which includes 20 minutes of rTMS treatment, plus some brief assessments. There will normally be between one to three daily sessions, Monday through Friday. During the intervention phase, the following will happen:

- You will have been randomized to either active “real rTMS” treatment or to sham treatment. Randomization is a process that is similar to flipping a coin where one side of the coin is active and the other side is sham. There is a 50:50 chance of being randomized to either treatment group. You will have a fifty percent chance of receiving the “real rTMS” treatment. In active treatment “real rTMS”, brief pulses of magnetic energy are used to stimulate nerve cells in your brain. In sham treatment, the same machine is used but the nerve cells are not stimulated.

Neither you nor your treatment provider will know which treatment you are getting until the study is over. This type of study is called a double blind trial and this study type is being used so that your treatment and evaluation won't be affected by someone knowing whether or not you are getting active “real rTMS” or sham treatment. The study machine will know which treatment you are getting so that you will receive the same treatment at each visit. Additionally, for each treatment session, whether sham or active, each patient shall wear scalp electrodes through which a low-voltage, low electric current will be passed in order to provide cutaneous stimulation. At the same time, the Noise Generator is used to hide the click noise produced by the rTMS. That is, when a magnetic stimulation pulse is fired, white noise is sent to the ears of the patient. This sham (white) noise will hide the click noise from the participant (active or placebo). If your treatment provider needs to know which treatment you are getting, he or she will be able to get that information. Before the first treatment, we will ask you whether you believe you will receive the active “real rTMS” or the sham treatment. After the first treatment, and after the final treatment, we will ask you whether you believe you received the active “real rTMS” or the sham treatment.



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- You will be retested to find your motor threshold on the first day of treatment, and then approximately weekly after that. You will be tested with an active coil to find the settings that will be used for you.
- Brief assessments will be administered.
- You will be asked about any other drugs that you are taking and about side effects that may have occurred since your last visit. These may or may not be related to the study treatment. You will also be asked about the amount of alcohol or other substances you have consumed since your last visit, and about how much sleep you got the night before your treatment. These questions will be asked at every session.
- You may be asked to provide a urine sample several times randomly during this phase. This sample will be screened for the use of drugs. Your urine screen results may be disclosed to your primary physician if we think that you are using drugs in a risky manner. You may also not be allowed to receive your rTMS treatment.
- If you are a woman of childbearing age, you will have a urine pregnancy test every four weeks through the end of the intervention phase to be sure that you are not pregnant. You may have a breathalyzer to determine your blood alcohol level several times randomly during this phase. This will be for the screening of alcohol use. Your results may be disclosed to your primary physician if we think that you are using alcohol in a risky manner. You may also not be allowed to receive your rTMS treatment.
- A blood sample of about 4 tablespoons will be taken and used for assessment of plasma proteins every 5 rTMS treatments. Any samples left over after analysis will be stored.

***The following is a description of the treatment procedure:***

- You will be awake and alert throughout the treatment session.
- You will be reclined in a chair. You will be provided with headphones. You will have electrodes placed on your forehead. Your head will be placed in a holder so that it is correctly positioned. You may close your eyes and rest, but not sleep.
- A metal coil in a plastic case will be held against the scalp on the left side of your head. There is a clicking noise as magnetic pulses are produced, but you will hear white noise through the headphones.
- Participants may feel a tingling sensation on the head.
- Depending on the treatment group that you have been assigned to, you will receive either active “real rTMS” or sham treatments.
- You may drive yourself to and from treatment sessions and attend to your normal daily tasks.



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**4. FOLLOW-UP PHASE**

During the follow-up phase, you will meet with study staff to complete study tests and assessments. The amount of time required will be approximately 9 hours for the immediate post-intervention follow up, and 10 hours for the 6 month follow-up. Some of the immediate post-intervention assessments may be completed at your final treatment session. During the follow-up phase, the following will happen:

- You will have a hearing test done to measure your level of hearing.
- You will complete several assessments about your health, your pain, your mood, your use of alcohol and other substances, your sleep, and any possible traumatic experiences you may have had, and a series of cognitive assessments.
- MRI scans of your brain will be taken at the immediate post-treatment follow-up visit and at the 6-month follow up visit.
- You may be asked to provide a urine sample at the immediate post-treatment follow-up visit. This sample will be screened for the use of drugs. Your urine screen results may be disclosed to your primary physician if we think that you are using drugs in a risky manner.
- If you are a woman of childbearing age, you will have a urine pregnancy test every four weeks through the end of the intervention phase to be sure that you are not pregnant.
- You may have a breathalyzer to determine your blood alcohol level at the immediate post-treatment follow-up visit. This will be for the screening of alcohol use. Your results may be disclosed to your primary physician if we think that you are using alcohol in a risky manner.
- A blood sample of about 4 tablespoons will be taken and used for assessment of plasma proteins. Any samples left over after analysis will be stored.

**5. FOR ALL STUDY PHASES**

- It is important for study staff to be aware of any changes in your medications during your participation in the study. If there are changes to your medications or you take them not as prescribed prior to a treatment session, study staff may choose to cancel or reschedule that session.
- You will interact with members of the entire study team. This includes a psychiatrist or neurologist, a nurse or physician assistant rTMS Operator, and a Study Coordinator. The study takes place at the VA Palo Alto Health Care System (VAPAHCS) during normal business hours, Monday through Friday, 8am to 4:30pm. If asked, we will provide a note for your employer that you were receiving medical treatment. We will not compensate for missed work time.





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- You will be asked about adverse events whenever you are seen by study staff for treatment, evaluation, and follow-up visits. An adverse event is anything bad that happens with you and may or may not be related to your participation in this study. An independent committee will be told about all adverse events at least once every six months. If they believe that any aspect of this study is unsafe, they will recommend that changes be made to eliminate the safety problem.

**PARTICIPANT'S RESPONSIBILITIES**

You should:

- Follow the instructions of the investigators and study staff.
- Complete your questionnaires as instructed. You are free to skip any questions that you prefer not to answer.
- Ask questions as you think of them.
- Tell the investigator or research study staff if you stop using birth control or think you might be pregnant.
- Tell the investigator or research staff if you change your mind about staying in the study.
- While participating in this research study, do not take part in any other research study without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing or potential drug interactions. Taking part in other research studies without approval from the investigators may invalidate the results of this research, as well as that of the other studies.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigator or study staff to reschedule as soon as you know you will miss the appointment.
- It is important that you not give false, incomplete, or misleading information about your medical history, including past and present drug use, because this could have serious consequences for your well-being.
- The effects of alcohol and substance use while undergoing rTMS are not well known at this time. Alcohol use will be limited to 1 alcoholic beverage, defined as 12 oz. beer, 5 oz. wine, or 1.5 oz. hard liquor, a day. You cannot use illegal substances, such as marijuana, cocaine, and amphetamines, during your participation in the study. If you begin to use substances during your participation in this trial, you may be removed from the study. If you report consuming more than one alcoholic beverage or using substances prior to your treatment session, study staff may choose to reschedule that session.



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**WITHDRAWAL FROM STUDY**

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled (if applicable) and your decision will not affect your ability to receive medical care for your condition.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling Dr. Adamson at 650-493-5000 x62179.

The investigators may also withdraw you from the study without your consent for one or more of the following reasons: Failure to follow the instructions of the Protocol Director and/or study staff; if the Protocol Director decides that continuing your participation could be harmful to you; pregnancy; if you need treatment not allowed in the study; if the study is cancelled; for other administrative reasons; or for other unanticipated circumstances.

**POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES**

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions. This study involves the following risks, discomforts, and possible inconveniences:

**rTMS**

A few patients receiving rTMS have had a seizure. All of the reported seizures resolved promptly on their own and none had any lasting effects or adverse impact on the patients. There is little evidence of risk of seizures using rTMS the way it will be used in this study.

In the unlikely event that a seizure does occur, you will be closely monitored and treated for any medical or psychological consequences. Lab tests will be drawn and you will be seen by a neurologist as soon as possible. The facility where the rTMS studies are performed are fully equipped to safely handle a seizure. You will be given a letter regarding the seizure to share with your primary health care provider. The letter will indicate that the seizure during rTMS does not increase your risk for future seizures.

rTMS treatment can result in mild to moderate headaches in as many as 30 out of 100 of patients. Some people also report discomfort at the site of rTMS stimulation. This occurs in around 15 out of 100 of patients. Headaches and site discomfort usually readily respond to acetaminophen or ibuprofen. Painfulness improves over time or goes away. Often patients fall asleep in the second week while receiving the same treatment that on the first day was reported as very painful.

There is a small risk of dental pain with rTMS, during or immediately after the treatment. If this occurs, let your study doctors and nurses know and they may be able to move the rTMS coil position or provide you with a bite block to reduce this pain or make it not happen.



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rTMS treatment may produce movement or tingling of the arm, leg, face or scalp. You may also experience a temporary feeling of numbness in the face.

There is a possible risk of hearing loss due to the light clicking sounds made by the device. You will wear ear protection during your rTMS sessions. This should greatly reduce the possibility of hearing loss. Your hearing will be tested at baseline, and at each follow-up visit to see if any hearing loss has occurred.

The rTMS operator will monitor you for ear protection, coil placement, and seizure activity during all sessions.

In some people, daily prefrontal rTMS can cause them to have increased energy, no need for sleep, and rapid racing thoughts. This is called mania. If you notice these changes let your primary physician and the study team know.

Your study investigator will be monitoring you during your participation to see if you are experiencing any side effects. It is important that you report promptly any side effect to study staff. If you feel, or your study investigator feels, that the side effects are not well tolerated, treatment may be stopped altogether and you may be withdrawn from the study.

The possibility of long-term risks is unknown. In previous studies, animal and human brains have shown no evidence of any kind of damage from rTMS. As with any experimental treatment, there may be unforeseen risks associated with this device. You will be informed of any new information that is developed during the study that might affect your willingness to continue your participation.

There is a chance that the pictures of your brain, laboratory results, or other medical tests will show an abnormality that you did not know about. This abnormality could be life-threatening or not serious at all. Abnormal results might lead to more tests. If you are not eligible for VA care or benefits for the evaluation of these findings, we will, with your consent, send this information to your personal (Non-VA) physician. Your consent to this study serves as consent to contact your personal (Non-VA) physician. You and your physician can arrange the necessary work-up and treatment. If you are not eligible for VA care for the evaluation of the unanticipated abnormality, the evaluation might cost you money out-of-pocket. Abnormal results also might lead to loss of insurability or loss of employment.

**MRI**

Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be



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removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator.

Before you enter the scanner, we will ask you questions about whether you have any non-removable metal in your body. In addition, we may ask your permission to communicate with your physician to obtain information about your medical history if we need additional information to determine whether you should or should not have the MRI scan. If there is a good reason to suspect that you have metal in a part of your body (e.g., previous surgery in which the surgical report is not clear regarding implanted screws or wires), or if you have ever worked in a metal shop, we may arrange for you to have an x-ray to check that there are no metal fragments. The radiation exposure from this x-ray is equivalent to that occurring from natural sources over two months.

You should also notify the operator/investigator if you have any tattoos on your body, including eyeliner and other permanent makeup. Tattoos could become warm and irritated during the scan and remain so for several days. If you would prefer not to participate in the MR scan due to the presence of tattoos on your body, please inform a research team member.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is expected and should not be painful.

There is a risk of heating from radiofrequency imaging coils and their cables, button response boxes and their cables, and the cables from monitoring devices that record physiologic processes such as heartbeats per minute or electrical activity of the brain. Please report any heating sensation immediately. You may have the scan stopped at any time if this occurs.

Dizziness or nausea may occur if you move your head rapidly within the magnet.

If you have kidney problems, please tell the operator.

**IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.**

**X-ray**

This research study may involve exposure to radiation from one skull x-ray. This radiation exposure is not necessary for your medical care and is for research purposes only. The additional amount of radiation is approximately equal to 50 days of radiation exposure from natural sources like the sun, ground and water. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

**Other**

If you are taking any drugs that may increase the risk of having a seizure, you will need to be taken off those drugs before you can participate. You and your physician will need to



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discuss the feasibility of your discontinuing any such medication. Withdrawal from such drugs may cause discomfort or illness.

Risks of the usual care you receive are not risks of the research. They are not included in this consent form. You should talk with your health care providers about risks of usual care.

There are virtually no risks involved in the cognitive testing and psychosocial measurements other than the anxiety that can be associated with any test. However, these questions may bring on uncomfortable thoughts, feelings, and lead to recalling troubling memories. It is possible that you might become tired or frustrated by some of our testing. You may find answering the questionnaires annoying, boring, or repetitive. If this happens, please tell us and we will take a break or continue the questions another day.

Drawing blood is a routine procedure involving the possibility of slight bruising and/or infection at the needle puncture site. There may be some discomfort during insertion of the tube for withdrawing blood. On rare occasions some patients have fainted while having their blood drawn. A clot could also form in the vein, resulting in temporary pain or tenderness in the area where the tube was placed. Infection is rare. To minimize these risks, experienced medical personnel will handle all the blood drawing procedures. There is also a risk of scarring at the site of needle insertion with individuals having more pigmented skin having a greater risk of this occurring.

If, in an interview, you disclose that (a) you intend to harm yourself or someone else, (b) that a child had been abused or neglected, or (c) that an elder or dependent had been abused, we are required by California law to notify the appropriate authorities.

**For Women of Child-bearing Potential**

For safety reasons, pregnant women will not be allowed to participate in this study. This is because the effects of rTMS on an unborn child are not known. There may be unforeseeable (unanticipated) risks to the participant (or to the fetus) if the participant is pregnant or becomes pregnant during the study.

You will have a urine pregnancy test within 7 days prior to your starting study treatment. Thereafter, you will have a urine pregnancy test every four weeks through the end of the study as well as when you have a six month follow-up visit to be sure that you are not pregnant.

**You must agree to use a medically acceptable form of birth control while participating in the study. Acceptable forms of birth control are:**

- Complete abstinence (not having sexual intercourse with anyone)
- An oral contraceptive (birth control pills)
- Norplant
- Depo-Provera
- A condom with spermicide



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- A cervical cap with spermicide
- A diaphragm with spermicide
- An intrauterine device
- Surgical sterilization (having your tubes tied)

If you become pregnant during the intervention phase of the study, you will not be able to continue the study treatments. You will also be referred to a Women’s Health Clinic. If you become pregnant during the follow-up phase of the study, you will continue to come in for all remaining follow-up phase visits and will complete all assessments as you normally would.

If you become pregnant at any time during the study, you will be asked to sign a release of information form for study staff to access medical records to obtain information regarding the outcome of your pregnancy. No pediatric records will be reviewed.

There is no likely effect on sperm count or the motility of sperm or other reproductive risks associated with fathering a child, although this has not been formally tested in humans. Likewise, there are no known risks on sperm and ova (eggs).

**POTENTIAL BENEFITS**

We can’t promise that you will get any benefits from taking part in this research study. However, possible benefits may include relief from pain and improvement in quality of life. The information that is obtained during this study may be scientifically useful and may lead to greater knowledge about the treatment of cognitive function with TBI.

The medical testing done in this study could reveal a medical condition that you might not have previously been aware of and for which you may need treatment. Study staff will refer you for additional treatment if such problems are identified but the study will not pay for the treatment of any such identified problems. If you are not eligible for VA care or benefits for the evaluation of these findings, we will, with your consent, send this information to your personal (Non-VA) physician. Your consent to this study serves as consent to contact your personal (Non-VA) physician. You and your physician can arrange the necessary work-up and treatment.

**WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY DIRECT BENEFITS FROM THIS STUDY.**

**ALTERNATIVES**

You may choose not to participate in this study. If this is your decision, there are other choices including the standard treatments provided by a local clinic. Your study investigator will discuss any alternatives with you before you agree to participate in this study. Alternative treatments include behavioral medicine, exercise, diet change and cognitive rehabilitation.



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Principal Investigator: Maheen Mausoo Adamson

VAMC: VA Palo Alto HCS

**PARTICIPANT'S RIGHTS**

Your participation is voluntary. You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. You have the right to refuse to answer particular questions.

If you decide not to participate, tell the Protocol Director. You will still receive care for any disease and will not lose any benefits to which you would otherwise be entitled.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

**CONFIDENTIALITY**

We will keep your name and all the information you tell us in this study as confidential as possible. Your laboratory results, including your urine drug screen results, will be accessible in your VA medical record (CPRS). The responses to questions concerning illegal drug use could be self-incriminating and harmful to you if they became known outside the study. As mentioned earlier, your urine screen results for drug use may be disclosed to your primary physician if we think that you are using drugs in a risky manner. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number, address, telephone number, or any other direct personal identifier. Also, other federal agencies as required, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information.

Because this study involves an investigational device, the Food and Drug Administration may also have access to information about you collected in this study.

**FINANCIAL CONSIDERATIONS**

**Payments**

**There will be no payment for participation in this study. Costs**

You will not have to pay anything to be in this study.

**Sponsor**

The Department of Veterans Affairs is providing financial support and/or material for this study.

**CONTACT INFORMATION**

**Questions, Concerns, or Complaints**

If you have any questions, concerns or complaints about this research study you should ask the Principal Investigator, Dr. Maheen Mausoo Adamson. You can call her at 650-493-



**IRB USE ONLY**

Approval Date: December 11, 2018

Expiration Date: February 13, 2019

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5000 ext. 62179. You should also contact her at any time if you feel you have been hurt by being a part of this study.

**Appointment Contact**

If you need to change your appointment, please contact study staff at 650-493-5000 ext 62930.

**Independent Contact**

If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, and would like to speak with a person who is independent of the research, call the Stanford Institutional Review Board (IRB) at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

**COMPENSATION for Research Related Injury**

If you are injured as a direct result of being in this study, medical treatment will be available. If you are eligible for Veteran’s benefits, the cost of such treatment will be covered by the VA. If not, the cost of such treatments may still be covered by the VA depending on a number of factors. In most circumstances, the treatment must be provided in a VA medical facility. No other form of compensation for injuries is available. However, by signing this form you have not released the VA from liability for negligence. For further information, you may call the Human Protections Administrator at (650) 493-5000, ext. 67593 or the V.A. Regional Counsel at (415) 750-2288.

**EXPERIMENTAL SUBJECT’S BILL OF RIGHTS**

As a human subject you have the following rights. These rights include but are not limited to the subject's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;





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- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you (by phone or letter) about related studies that may be of interest to you?

\_\_\_\_\_ Yes. I would like to be contacted for future research opportunities.

\_\_\_\_\_ No. Do not contact me about future research opportunities.

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Print name of Participant

**Person Obtaining Consent:**

\_\_\_\_\_  
Signature of Person Obtaining Consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Print Name of Person Obtaining Consent



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HIPAA regulations require the participant to give separate written permission (signature) for the use of their protected health information.

Person Obtaining Consent HIPAA Authorization confirmation:

     Confirm the participant signed the VA HIPAA Authorization (VA 10-0493)

# STANFORD UNIVERSITY

Stanford, CA 94305 [Mail Code 5579]

David Spiegel, M.D.  
CHAIR, PANEL ON MEDICAL HUMAN SUBJECTS

(650) 724-9815  
(650) 725-6766

## Certification of Human Subjects Approvals

**Date:** December 11, 2018

**To:** Maheen Mausoo Adamson, PhD, Psychiatry and Behavioral Sciences

Karen Cullen MS, Maya Yutsis PhD, Nyzia E Licon MPH, Jerome A Yesavage MD, Theresa Louise-Bender Pape Dr.PH, MA, CCC-SLP/L, Amit Etkin, Ansgar Furst PhD, John Wesson Ashford M.D., Ph.D. (VA), Brian Yochim, David J. Clark, Esmeralda Madrigal, Molly Timmerman, Odette Althea Harris M.D., M.P.H.(VA), Allyson Rosen, Valerie Darcy

**From:** David Spiegel, M.D., Administrative Panel on Human Subjects in Medical Research

**eProtocol Title:** Repetitive Transcranial Magnetic Stimulation to Improve Cognitive Function in TBI

**eProtocol #:** 29889

**IRB 3 (Registration #: 350)**

The IRB approved human subjects involvement in your research project on 12/11/2018. **'Prior to subject recruitment and enrollment, if this is: a Cancer-related study, you must obtain Cancer Center Scientific Review Committee (SRC) approval; a CTRU study, you must obtain CTRU approval; a VA study, you must obtain VA R and D Committee approval; and if a contract is involved, it must be signed.'**

The expiration date of this approval is 02/13/2019 at Midnight. If this research is to continue beyond that date, it is your responsibility to submit a Continuing Review application in eProtocol. Research activities must be reviewed and re-approved on or before midnight of the expiration date. The approval period may be less than one year if so determined by the IRB. Proposed changes to approved research must be reviewed and approved prospectively by the IRB. No changes may be initiated without prior approval by the IRB, except where necessary to eliminate apparent immediate hazards to subjects. (Any such exceptions must be reported to the IRB within 10 working days.) Unanticipated problems involving risks to participants or others and other events or information, as defined and listed in the Report Form, must be submitted promptly to the IRB. (See Events and Information that Require Prompt Reporting to the IRB at <http://humansubjects.stanford.edu>.) Upon completion, you must report to the IRB within 30 days.

Please remember that all data, including all signed consent form documents, must be retained for a minimum of three years past the completion of this research. Additional requirements may be imposed by your funding agency, your department, HIPAA, or other entities. (See Policy 1.9 on Retention of and Access to Research Data at <http://doresearch.stanford.edu/policies/research-policy-handbook>)

This institution is in compliance with requirements for protection of human subjects, including 45 CFR 46, 21 CFR 50 and 56, and 38 CFR 16.

Waiver of Individual Authorization for recruitment under 45 CFR 164.512(i)(2)(ii)(A),(B),(C), pursuant to information provided in the HIPAA section of the protocol application.



David Spiegel, M.D., Chair

**Approval Period:** 12/11/2018 - 02/13/2019

**Review Type:** REGULAR - MODIFICATION

**Funding:** VA

**Assurance #:** FWA00000935 (SU), FWA00000934 (SHC), FWA00000929 (VA)

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<b>Modification</b>
<p><b>1. Summarize your proposed changes.</b></p> <p>1. Personnel Info</p> <p>Girish R. Swaminath was removed from Admin Contact and Karen Cullen was added as the new Admin Contact. We add under other personnel: Esmeralda Madrigal and Molly Timmerman.</p> <p>Protocol Information</p> <p>1. Purpose</p> <p>Part A</p> <p>It was updated (see the underlined text below) Repetitive Transcranial Magnetic Stimulation (rTMS) to Improve Cognitive Function in TBI: The proposed study will evaluate the safety, durability and efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) as a promising non- invasive therapeutic treatment for executive function (EF)deficits and other outcomes (such as: headache, pain, etc) seen in 100 Veterans, Military personnel and Civilians with mild to moderate Traumatic Brain Injury (TBI).</p> <p>Part B</p> <p>Under Secondary Objective we added:</p> <p>6. To evaluate improvement in headaches and pain reporting following rTMS treatment using responses on the assessment HIT-6 (HIT-6 has been included with the original protocol on Section 16)</p> <p>2. Study Procedure</p> <p>Please see the underlined text below (updates</p> <ul style="list-style-type: none"><li>• Headache and Pain self-report will be recorded before and after every treatment session.</li></ul> <p>8. Participant population</p> <p>Please see the underlined text below (updates)</p> <ul style="list-style-type: none"><li>(i) 100 participants are expected to be enrolled</li><li>(ii) 100 participants at VAPAHCS</li><li>(iii) all participants will be Veterans, Military personnel and Civilians.</li></ul> <p>13. Consent</p> <p>The consent was modified. See yellow highlighted sections.</p>
<p><b>2. Indicate Level of Risk</b></p> <p>No Change</p>
<p><b>3. Update the Conflict of Interest (COI) section if any changes in COI have been made since the last protocol submission.</b></p> <p>N Is there a change in the conflicting interest status for any existing personnel on this protocol?</p>

<b>Protocol Director</b>		
<b>Name</b> Maheen Mausoo Adamson	<b>Degree (Program/year if student)</b> PhD	<b>Position, e.g. Assistant Professor, Resident, etc.</b> Clinical Assistant Professor (Affiliated) [VAPAHCS]

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<b>Department</b> Psychiatry and Behavioral Sciences	<b>Mail Code</b> 151Y	<b>Phone</b> 650-493-5000 x62179	<b>Fax</b>	<b>E-mail</b> madamson@stanford.edu
<b>CITI Training current</b>				Y

**Admin Contact**

<b>Name</b> Karen Cullen	<b>Degree (Program/year if student)</b> MS		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Research Associate	
<b>Department</b> Neurology	<b>Mail Code</b>	<b>Phone</b> 650493500 X 66444	<b>Fax</b>	<b>E-mail</b> karen.cullen@va.gov
<b>CITI Training current</b>				Y

**Investigator**

<b>Name</b> Maya Yutis	<b>Degree (Program/year if student)</b> PhD		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Clinical Assistant Professor (Affiliated) [SHC]	
<b>Department</b> Neurology	<b>Mail Code</b> 3076	<b>Phone</b> 6504935000	<b>Fax</b>	<b>E-mail</b> myutis@stanfordhealthcare.org
<b>CITI Training current</b>				Y

**Other Contact**

<b>Name</b> Nytzia E Licon	<b>Degree (Program/year if student)</b> MPH		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Clinical Research Coordinator	
<b>Department</b> Neurology	<b>Mail Code</b>	<b>Phone</b> 650-493-5000	<b>Fax</b>	<b>E-mail</b> nytzia.licon@va.gov
<b>CITI Training current</b>				Y

**Academic Sponsor**

<b>Name</b> Jerome A Yesavage	<b>Degree (Program/year if student)</b> MD		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Professor	
<b>Department</b> Psychiatry VA Research	<b>Mail Code</b> 5550	<b>Phone</b> (650) 852-3287	<b>Fax</b> (650) 852-3297	<b>E-mail</b> yesavage@stanford.edu
<b>CITI Training current</b>				Y

**Other Personnel**

<b>Name</b> Allyson Rosen	<b>Degree (Program/year if student)</b>		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Instructor	
<b>Department</b>	<b>Mail Code</b>	<b>Phone</b>	<b>Fax</b>	<b>E-mail</b>

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Psychiatry VA Research		(650) 493-5000	(650) 852-3297	rosena@stanford.edu
<b>CITI Training current</b>				Y
<b>Name</b> Valerie Darcy		<b>Degree (Program/year if student)</b>		<b>Position, e.g. Assistant Professor, Resident, etc.</b>
<b>Department</b> Vice Provost and Dean of Research - Research Compliance	<b>Mail Code</b> 151Y	<b>Phone</b> 650-493-5000 x61340	<b>Fax</b>	<b>E-mail</b> valerie.darcy@va.gov
<b>CITI Training current</b>				Y
<b>Name</b> Amit Etkin		<b>Degree (Program/year if student)</b>		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Asst Professor
<b>Department</b> Psychiatry and Behavioral Sciences	<b>Mail Code</b> 5717	<b>Phone</b> (650) 725-5736	<b>Fax</b> (650) 725-3762	<b>E-mail</b> amitetkin@stanford.edu
<b>CITI Training current</b>				Y
<b>Name</b> Brian Yochim		<b>Degree (Program/year if student)</b>		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Clinical Assistant Professor (Affiliated) [VAPAHCS]
<b>Department</b> Psychiatry VA Research	<b>Mail Code</b>	<b>Phone</b>	<b>Fax</b>	<b>E-mail</b> byochim@stanford.edu
<b>CITI Training current</b>				Y
<b>Name</b> John Wesson Ashford		<b>Degree (Program/year if student)</b> M.D., Ph.D. (VA)		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Clinical Professor (Affiliated)
<b>Department</b> Psychiatry and Behavioral Sciences	<b>Mail Code</b> 5550	<b>Phone</b> (650) 493-5000	<b>Fax</b> (650) 852-3297	<b>E-mail</b> ashford@stanford.edu
<b>CITI Training current</b>				Y
<b>Name</b> David J. Clark		<b>Degree (Program/year if student)</b>		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Professor-Med Ctr Line
<b>Department</b> Anesthesia	<b>Mail Code</b> VA 112A	<b>Phone</b>	<b>Fax</b> (650) 852-3423	<b>E-mail</b> djclark@stanford.edu
<b>CITI Training current</b>				Y
<b>Name</b> Theresa Louise-Bender Pape		<b>Degree (Program/year if student)</b> Dr.PH, MA, CCC-SLP/L		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Co-Investigator

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<b>Department</b>	<b>Mail Code</b>	<b>Phone</b>	<b>Fax</b>	<b>E-mail</b> Theresa.Pape@va.gov
<b>CITI Training current</b>				Y
<b>Name</b> Odette Althea Harris		<b>Degree (Program/year if student)</b> M.D., M.P.H.(VA)		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Assoc Prof-Med Ctr Line
<b>Department</b>	<b>Mail Code</b>	<b>Phone</b> (650) 723-5574	<b>Fax</b>	<b>E-mail</b> odette@stanford.edu
<b>CITI Training current</b>				Y
<b>Name</b> Ansgar Furst		<b>Degree (Program/year if student)</b> PhD		<b>Position, e.g. Assistant Professor, Resident, etc.</b> Clinical Associate Professor (Affiliated) [VAPAHCS]
<b>Department</b> Psych/Public Mental Health & Population Sciences	<b>Mail Code</b>	<b>Phone</b>	<b>Fax</b>	<b>E-mail</b> ajfurst@stanford.edu
<b>CITI Training current</b>				Y
<b>Name</b> Esmeralda Madrigal		<b>Degree (Program/year if student)</b>		<b>Position, e.g. Assistant Professor, Resident, etc.</b>
<b>Department</b>	<b>Mail Code</b>	<b>Phone</b>	<b>Fax</b>	<b>E-mail</b> Esmeralda.Madrigal@va.gov
<b>CITI Training current</b>				Y
<b>Name</b> Molly Timmerman		<b>Degree (Program/year if student)</b>		<b>Position, e.g. Assistant Professor, Resident, etc.</b>
<b>Department</b> Orthopaedic Surgery	<b>Mail Code</b>	<b>Phone</b>	<b>Fax</b>	<b>E-mail</b> mollyt1@stanford.edu
<b>CITI Training current</b>				Y

**Participant Population(s) Checklist**

**Yes/No**

- Children (under 18) N
- Pregnant Women and Fetuses N
- Neonates (0 - 28 days) N
- Abortuses N
- Impaired Decision Making Capacity N
- Cancer Subjects N
- Laboratory Personnel N
- Healthy Volunteers N
- Students N
- Employees N

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- Prisoners N
- Other (i.e., any population that is not specified above) Y

**Study Location(s) Checklist**

**Yes/No**

- Stanford University Y
  - Clinical & Translational Research Unit (CTRU) Y
  - Stanford Hospital and Clinics Y
  - Lucile Packard Children's Hospital (LPCH) Y
  - VAPAHCS (Specify PI at VA) Y
- Maheen Mausooof Adamson, PhD
- Other (Click ADD to specify details)

**General Checklist**

**Multi-site**

**Yes/No**

- Is this a multi-site study? A multi-site study is generally a study that involves one or more medical or research institutions in which one site takes a lead role.(e.g., multi-site clinical trial) N

**Collaborating Institution(s)**

**Yes/No**

- Are there any collaborating institution(s)? A collaborating institution is generally an institution that collaborates equally on a research endeavor with one or more institutions. N

**Cancer Institute**

**Yes/No**

- Cancer-Related Studies (studies with cancer endpoints), Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Specimens (e.g., blood, tissue, cells, body fluids with a scientific hypothesis stated in the protocol). N

**Clinical Trials**

**Yes/No**

- Investigational drugs, biologics, reagents, or chemicals? N
- Commercially available drugs, reagents, or other chemicals administered to subjects (even if they are not being studied)? N
- Investigational Device / Commercial Device used off-label? Y
- IDE Exempt Device (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices) N
- Will this study be registered on# clinicaltrials.gov? ( See Stanford decision tree ) Y



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- Is Stanford responsible for ClinicalTrials.gov registration? (See Stanford decision tree) NCT# N

**Tissues and Specimens**

**Yes/No**

- Human blood, cells, tissues, or body fluids (tissues)? Y
- Tissues to be stored for future research projects? Y
- Tissues to be sent out of this institution as part of a research agreement? For guidelines, please see <https://sites.stanford.edu/ico/mtas> N

**Biosafety (APB)**

**Yes/No**

- Are you submitting a recombinant DNA vector or Human Gene Transfer investigation using biological agents? If yes, please complete and attach the Gene Transfer Protocol Application Supplemental Questions to section 16 of the eProtocol application. N
- Are you submitting a Human study using biohazardous/infectious agents? If yes, refer to the <http://www.stanford.edu/dept/EHS/prod/researchlab/bio/index.html> Administrative Panel on BioSafety website prior to performing studies. N
- Are you submitting a Human study using samples from subjects that are known or likely to contain biohazardous/infectious agents? If yes, refer to the <http://web.stanford.edu/dept/EHS/prod/researchlab/bio/index.html> Administrative Panel on BioSafety website prior to performing studies. N

**Human Embryos or Stem Cells**

**Yes/No**

- Human Embryos or Gametes? N
- Human Stem Cells (including hESC, iPSC, cancer stem cells, progenitor cells) N

**Veterans Affairs (VA)**

**Yes/No**

- The research recruits participants at the Veterans Affairs Palo Alto Health Care System(VAPAHCS). Y
- The research involves the use of VAPAHCS non-public information to identify or contact human research participants or prospective subjects or to use such data for research purposes. Y
- The research is sponsored (i.e., funded) by VAPAHCS. N
- The research is conducted by or under the direction of any employee or agent of VAPAHCS (full-time, part-time, intermittent, consultant, without compensation (WOC), on-station fee-basis, on-station contract, or on-station sharing agreement basis) in connection with her/his VAPAHCS responsibilities. Y
- The research is conducted using any property or facility of VAPAHCS. Y

**Equipment**

**Yes/No**

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- Use of Patient related equipment? If Yes, equipment must meet the standards established by Hospital Instrumentation and Electrical Safety Committee (650-725-5000) N
- Medical equipment used for human patients/subjects also used on animals? N
- Radioisotopes/radiation-producing machines, even if standard of care? Y  
[http://www.stanford.edu/dept/EHS/prod/researchlab/radlaser/Human\\_use\\_guide.pdf](http://www.stanford.edu/dept/EHS/prod/researchlab/radlaser/Human_use_guide.pdf) More Info

**Payment**

**Yes/No**

- Subjects will be paid/reimbursed for participation? See payment considerations. N

**Funding**

**Yes/No**

- Training Grant? N
- Program Project Grant? N
- Federally Sponsored Project? Y
- Industry Sponsored Clinical Trial? N

**Funding**

<b>Funding - Grants/Contracts</b>	
<b>Funding Administered By :</b> VA	<b>SPO # (if available) :</b>
<b>Grant # (if available) :</b>	<b>Funded By (include pending) :</b> VA
<b>Principal Investigator :</b> Maheen Mausooof Adamson	
<b>Grant/Contract Title if different from Protocol Title :</b> _____	
Y	For Federal projects, are contents of this protocol consistent with the Federal proposal?
N	Is this a Multiple Project Protocol (MPP)?
N	Is this protocol under a MPP?

<b>Funding - Fellowships</b>
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<b>Gift Funding</b>
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<b>Dept. Funding</b>
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<b>Other Funding</b>
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**Resources :**

- a) **Qualified staff.**

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**Please state and justify the number and qualifications of your study staff.**

VA War Related Illness and Injury Study Center (WRIISC), Mental Illness Research and Education Center (MIRECC), and Polytrauma VAPAHCS staff will be actively involved in the administration of the study and in patient visits and data collection. These include:

Maheen Adamson, PhD: will oversee all data collection, study and staff management and analysis. Also may consent participants.

Co-Protocol director: Maya Yutsis, PhD will ensure the exclusion/inclusion criteria for the participants.

Neuropsychologists: Brian Yochim and Allyson Rosen will train and manage the neuropsych battery.

Valerie Darcy, RN: Nurse or Nurse Practitioner's primary task is to administer the rTMS treatment and document encounters.

Research Health Science Specialist (GS-9) TBD: When hired the rTMS Study clinical research project coordinator will manage the study, may conduct some assessments, and consent participants.

Additional support staff will be provided by WRIISC if needed. Consultants (Amit Etkin, Wes Ashford, Jerome Yesavage and Mark George) will be contacted quarterly and as needed.

**b) Training.**

**Describe the training you will provide to ensure that all persons assisting with the research are informed about the protocol and their research-related duties and functions.**

All staff, both present and future, will be trained in human subjects protections, computer security and privacy regulations.

All staff who administer the rTMS treatment will be fully trained and certified.

**c) Facilities.**

**Please describe and justify.**

The data will be collected at study visits at the VA Palo Alto Health Care System (VAPAHCS) War Related Illness and Injury Study Center (WRIISC). All collections will take place in the clinic setting. The data will be stored on VA servers administered by VA staff. The Data will also be analyzed on VA computers on VA networks. Some neuroimaging data will be analyzed on Stanford LAN connection.

**d) Sufficient time.**

**Explain whether you will have sufficient time to conduct and complete the research. Include how much time is required.**

This project is expected to last for 2 years. The duration of the study will be two years, with 18 month enrollment period, and the last six months will be strictly for follow-up. 20 participants will be recruited in the first year and 20 will be recruited in the second year. Each participant will be in the trial for a total of approximately 28 weeks (1-2 weeks screening, 2 weeks acute treatment phase (depending on scheduling constraints) and a follow-up visit at 26 weeks post-treatment. The last 6-8 months of the study will also be spent analyzing data and writing up results.

**e) Access to target population.**

**Explain and justify whether you will have access to a population that will allow recruitment of the required number of participants.**

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The WRIISC is a national referral center established to further diagnosis and provide treatment options for veterans suffering from military related injuries and illnesses. We have seen a number of local Veterans from various conflict eras with TBI through our clinic locally. Our collaboration with Maya Yutsis, who works in VAPAHCS polytrauma center will also provide us with study participants. We are confident that there are a sufficient number of Veterans with mild and moderate TBI in the Northern CA area.

**f) Access to resources if needed as a consequence of the research.**

**State whether you have medical or psychological resources available that participants might require as a consequence of the research when applicable. Please describe these resources.**

The project will have sufficient medical or psychological resources available. There will be neurologists, psychologists, nurses, psychiatrists and educational resources available for all Veterans that are part of this study.

**g) Lead Investigator or Coordinating Institution in Multi-site Study.**

**Please explain (i) your role in coordinating the studies, (ii) procedures for routine communication with other sites, (iii) documentation of routine communications with other sites, (iv) planned management of communication of adverse outcomes, unexpected problems involving risk to participants or others, protocol modifications or interim findings.**

## 1. Purpose

**a) In layperson's language state the purpose of the study in 3-5 sentences.**

Repetitive Transcranial Magnetic Stimulation (rTMS) to Improve Cognitive Function in TBI: The proposed study will evaluate the safety, durability and efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) as a promising non- invasive therapeutic treatment for executive function (EF) deficits and other outcomes (such as: headache, pain, etc) seen in 100 Veterans with mild to moderate Traumatic Brain Injury (TBI).

**b) State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.**

Many returning OEF/OIF Veterans with concussion histories report cognitive problems that may last for months or even years (Schneiderman et al., 2008; Hoge et al., 2008). Although deployment itself can be associated with cognitive problems (Vasterling et al, 2006), having co-morbid conditions such as post traumatic stress disorder (PTSD) and depression may prolong the symptoms of TBI resulting in lowered attention, processing speed, learning and memory (Nelson et al., 2012; Caeyenberghs et al., 2012). Strong evidence also suggests that a history of TBI increases risk for developing PTSD (Eckart et al., 2011). Significant progress has been made towards understanding the pathophysiology and neuropsychological changes associated with the acute and long term sequelae of TBI, including its complicated relationship with PTSD (Brenner et al., 2011; Hallbauer et al.,

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2009;  
Villamar et al., 2012). However, few studies have addressed what mechanisms of TBI may be responsive to therapeutic treatment.

The most common cognitive difficulties faced by Veterans with TBI include executive function deficits such as impaired attention, verbal fluency, poor planning, reduced working memory, and mental flexibility (Godefroy et al., 2003). A survey of Army infantry who suffered from TBI reported that 31.4% complained of concentration problems and 24.6% complained of memory problems (Nelson et al., 2012). Numerous studies confirm that Dorso Lateral Prefrontal Cortex (DLPFC) is involved in inhibition, planning and set-switching - key components of executive function (Vanderhasselt et al., 2006). Deficits in executive function following mild TBI (mTBI) are also associated with injury to the axons and involve the DLPFC (Lipton et al., 2009). In fact, patients with focal lesions in this brain region performed significantly worse than controls on the Trail Making Test (TMT: primary outcome measure) suggesting impaired cognitive set-shifting (Yochim et al., 2007). Moreover, control participants performed significantly better on TMT than patients with mTBI (Brooks et al., 1999). We hope to demonstrate improvement of this deficit in Veterans with mild and moderate TBI through rTMS treatment. Additionally we would also report on the efficacy of using functional brain connectivity (thru advanced neuroimaging) as a biomarker to capture this improvement in executive function.

Previous studies have documented the relationship between injury severity, cognitive impairment and functional status (Bush et al., 2003; Senathi-Raja et al., 2010). In fact, Bercaw et al, (2011) reported that neuropsychological performance at year 1 post-injury predicted functional outcomes in year 2. Although reports of mild TBI patients returning to baseline functioning one year post-injury have been documented, 7% to 33% of these patients experience persistent symptoms (Belanger et al., 2005). Note that regardless of injury severity, one of the most frequently reported post-TBI sequelae is cognitive dysfunction (e.g, memory problems and executive function: Terrio et al., 2009; Senathi-Raja et al., 2010). Among these patients

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there is often little correlation between subjective (e.g, self-report) and objective markers (eg, neuropsychological test performance) of such dysfunction (Brenner et al., 2011). Moreover these cognitive complaints have been associated with poorer psychosocial functioning (eg, return to work; Benedictus et al., 2010).

**Specific Aims are:**

To assess the efficacy and durability of benefits of repetitive Transcranial Magnetic Stimulation (rTMS) as a promising non-invasive therapeutic treatment for executive function deficits seen in Veterans with mild to moderate TBI.

**Primary Hypothesis:**

Veterans with mild to moderate TBI receiving active rTMS treatment will show improvement of > 1 SD on performance between baseline and post-treatment on any one of the following: the Trail Making Test part B, D-KEFS Verbal Fluency and/or D-KEFS Color-Word Interference Test) than Veterans receiving sham rTMS.

**Primary Objective:**

To assess the efficacy of rTMS in improving executive functioning in Veterans with mild to moderate TBI in order to maximize rehabilitation outcomes.

**Secondary Hypotheses:**

1. Sustained Improvement. At the end of the 6-month post treatment follow-up, TBI patients who received rTMS would be more likely to continue to have reduced symptoms, i.e. greater "executive function improvement" than patients who received sham rTMS.
2. Secondary consequences of TBI will improve with rTMS treatment, i.e. scores on Quality of Life (QOL) scale will show significantly greater improvement in patients with mild to moderate TBI who received rTMS treatment.
3. Moderators of Response. Age, severity of symptoms at baseline, type of comorbidity (PTSD, time since injury, sleep, depression substance abuse, medication use, cognitive exercises, fatigue or any combinations of these), TBI type, duration of

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illness and prior treatment resistance (rTMS/ECT): may affect or "moderate" treatment response.

4. Greater functional connectivity will be observed in hub centers of the Default Mode Network (DMN), particularly the precuneus/posterior cingulate area as measured by resting state fMRI at follow-up compared to baseline in those TBI patients treated with rTMS compared to those treated with sham.

5. Mediators of Response to Treatment: to establish a preliminary understanding of the underlying mechanisms related to rTMS modulation of synaptic repair in TBI we will also look at Brain Derived Neurotrophic Factor (BDNF) plasma samples in our population.

#### B. Secondary Objectives

1. To evaluate the durability of benefit of rTMS in treatment of executive function deficits (patients receiving rTMS are more likely to show significant improvement at 6 months post treatment than those receiving sham).

2. To evaluate post treatment the impact of rTMS treatment on everyday functioning as defined by the Quality of Life (QOL) scale, a frequently used clinical measure.

3. To evaluate other moderators of response to rTMS treatment such as age, time since injury and severity of PTSD (assessed by PCL-checklist score) as well as depression, sleep substance abuse, fatigue or any combinations of these factors.

4. To evaluate resting state functional MRI (fMRI) as a biological marker of response to rTMS treatment.

5. To evaluate underlying biological mechanisms involving BDNF in synaptic repair and/or change in network connectivity resulting from rTMS treatment.

6. To evaluate improvement in headaches and pain reporting following rTMS treatment using responses on the assessment HIT-6 (HIT-6 has been included with the original protocol on Section 16)

- c) **Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific**

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**behavioral traits in humans in classroom or other environment)**

The purpose of this project is to study and make recommendations regarding treatment of executive dysfunction in humans.

**2. Study Procedures**

- a) **Please SUMMARIZE the research procedures, screening through closeout, which the human subject will undergo. Refer to sections in the protocol attached in section 16, BUT do not copy the clinical protocol. Be clear on what is to be done for research and what is part of standard of care.**

List of Procedures for the rTMS protocol:

Screening Measures:

- Telephone screening call: 1 hr
- Consenting and on-site screening: approx. 6 hrs
- Physical exam, medical history
- Medication review
- Interviews, self-report questionnaires  
Clinical TBI Evaluation
- Blood (60 cc), urine, and breath tests
- Determination of TMS motor threshold (markings on the cap will be marked with "MT" for motor threshold and "Tx" for treatment site.
- Eligibility determination
- Randomization to active or sham treatment

Baseline measures: approx. 8 hrs

- Interviews, self-report questionnaires, tasks (pain, fatigue, sleep, malingering, depression, PTSD, TBI, suicide, cognition);
- Cognitive testing (including main outcome measure for executive function) and webneuro computerized testing
- Neuroimaging: Diffusion Tensor Imaging (DTI), functional MRI (fMRI); structural MRI
- If indicated, and prior to MRI scan, an MRI X-ray screen will be performed if there is suspicion that participant may have metal in their body
- Pure Tone Audiometry

Intervention Measures:

- rTMS or sham treatment: up to 3 treatments a day for up to 5 days/week, 2-6 weeks = 20 sessions. Each session lasting 30-60 minutes in length. Depending on schedule, and at the physician's discretion, up to three rTMS sessions can be scheduled per day with a one hour interval between sessions, shortening treatment duration to 1.5 weeks.
- TMS motor threshold determination prior to the first treatment and every 5th day of treatment thereafter (at least weekly).
- Random breathalyzer and urine tests will be administered during the intervention phase to screen for drug and alcohol use; depending on results, participant may not be allowed to receive



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additional rTMS treatment for safety reasons

- Blood samples (60 cc) will be taken every 10 rTMS

treatment

for processing of BDNF from blood plasma.

- Headache and Pain self report will be recorded before and after every treatment session.

Follow-up (post treatment and 6 months): approx. 8.5 hrs

- Interviews, Self-Report Questionnaires (same as above);
- Pure Tone Audiometry;
- Cognitive testing including executive function main

outcome measure and webneuro computerized testing

• Neuroimaging: Diffusion Tensor Imaging (DTI), Functional MRI (fMRI), structural MRI

• Blood samples (60 cc) will be taken for processing of BDNF from blood plasma.

- b) Explain how the above research procedures are the least risky that can be performed consistent with sound research design.**

The study design involves minimal risk to participants. This research project is a placebo control study design.

- c) State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).**

Deception will not be used.

- d) State if audio or video recording will occur. Describe what will become of the recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.**

None will occur.

- e) Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).**

There are many alternative procedures/courses of improving executive function including cognitive training, weight loss, exercise, etc although their clinical feasibility can be questioned. No standard treatments for improving executive function are being withheld from potential participants in this study.

- f) Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?**

If rTMS is found to be effective for improving cognitive function, it may be possible to have patients return for booster sessions.

- g) Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the study be terminated before the projected total participant population has been enrolled? When will the study end if no important differences are detected?**

Study Personnel will generate tabulations of Serious Adverse Events

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(SAEs) and Unanticipated Adverse Device Effects (UADEs) and present a summary of these to the Data Monitoring Committee (DMC) on a schedule set by the DMC. The DMC will also determine when they should be unblinded to treatment assignment for the reviewing of adverse event data. The DMC will advise the PI concerning whether the study should continue or be stopped for safety reasons.

### 3. Background

#### a) Describe past experimental and/or clinical findings leading to the formulation of the study.

Overview of rTMS in Cognitive Dysfunction in mild and Moderate TBI  
 Repetitive TMS is a method of delivering therapeutic, non-invasive brain stimulation. While not yet utilized in TBI research on a large scale, rTMS is well suited for this pilot project given the clinical and research expertise in rTMS trials for various other common Veteran complaints (e.g., team of 5 MD's, 1 RN, 3 clinical neuropsychologists and 2 neuroimaging researchers in the VA). rTMS is currently being used at the VA Palo Alto and Stanford University in the treatment of: pain (VA Rehabilitation grant funded: PI: Dr. Ashford & Co-I/Co-Protocol Director: Dr. Adamson), depression (VA Co-op studies funded, PI: Dr. Rosen; Co-op studies funded, PI: Dr. Yesavage), and PTSD (NIH funded project: Dr. Etkin). At present it is an FDA-approved for treatment for major depression (Oreardon et al., 2007; George et al., 2010; Dr. George, current consultant). A recent VA study reported improvements in PTSD and related symptoms in Veterans with PTSD who received rTMS (Watts et al., 2012). Also of relevance in our TBI Veterans, a major industry trial of rTMS in Treatment Refractory Major Depression (TRMD) has been completed. This randomized controlled trial involved 301 medication-free patients with TRMD and excluded patients dual-diagnosed with co-morbid substance abuse (past year) or PTSD. Response and remission rates were significantly better in rTMS than in controls at the end of 6 weeks treatment, but results were smaller and not

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significantly better after 4 weeks treatment. Because the 4 week outcome was the a priori defined primary end point, the FDA Advisory panel reviewing this study did not accept this result as adequate support of this new indication for rTMS. However, the most recent data concerning the 12 month durability of a TMS antidepressant effect are quite good, with over 90% retention of remission 12 months later in a treatment resistant group (Demitrack, 2013). This compares to a 50% relapse rate in similar populations who are treated with ECT, or even worse outcomes in patients treated with medications (STAR\*D). We are now rediscovering how exercise, practice, and stimulation can cause plastic changes in the brain (Colcombe et al, 2006). In sum, the only way to discover whether there are acute or more durable effects with rTMS treatment for TBI is to do the proposed study.)

(Rationale for rTMS use in EF improvement: Repetitive TMS treatment can induce neuronal long-term potentiation (Wang et al 2011) involving brain-derived neurotrophic factor (BDNF) resulting in synaptic repair (Cheeran et al., 2008; Lu et al., 2013). Pape et al (2006) reviewed the evidence for rTMS as a possible intervention for TBI-induced cognitive dysfunction in patients with Parkinson's disease and strokes. So far, improvements after rTMS treatments (stimulation site: DLPFC in neurobehavioral outcomes (Pape et al., 2009) and executive function (Pachalska et al., 2011) have only been reported in severe TBI patients. Case studies (Bonni et al., 2013) have found rTMS to lead to improved cognitive functioning in patients with TBI. A recent review of rTMS studies across various mental illnesses strongly suggests its use in TBI to promote recovery and minimize disabilities (Demirtas-Tatlided et al., 2012). Stimulation of the left dorsolateral prefrontal cortex (DLPFC) has led to improvements in major depressive disorder. This brain area has also been shown to be involved in executive

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functioning (Yochim et al., 2007), and we thus hypothesize that stimulation of this area will lead to concomitant improvement in executive functioning).

The proposed pilot study is an advance and necessary for the VA because: 1) It will incorporate dual-diagnosis TBI (mild and moderate) patients including patients with PTSD. These dual-diagnosis patients are usually excluded from industry and National Institute of Health trials and as such the proposed study is unique in that it will address the patient that providers encounter in the VA system specifically. 2) It will focus on improvements in cognitive dysfunction - a major complaint for many Veterans who may not seek medical care and which will impact their cognitive health and independence as they grow older. 3) Furthermore, unlike industry trials, the proposed study will use a sham rTMS procedure that will be more difficult to distinguish from the actual rTMS.

**b) Describe any animal experimentation and findings leading to the formulation of the study.**

Animal analogues, primarily rats, have been used in the testing of rTMS. Results from these studies have been crucial in establishing the safety parameters for use with humans.

**4. Radioisotopes or Radiation Machines**

**a) List all standard of care procedures using ionizing radiation (radiation dose received by a subject that is considered part of their normal medical care). List all research procedures using ionizing radiation (procedures performed due to participation in this study that is not considered part of their normal medical care). List each potential procedure in the sequence that it would normally occur during the entire study. More Info**

Identify Week/Month of study	Name of Exam	Identify if SOC or Research
	X-ray (for MRI)	Research

**b) For research radioisotope projects, provide the following radiation-related information:**

**Identify the radionuclide(s) and chemical form(s).**

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N/A

**For the typical subject, provide the total number of times the radioisotope and activity will be administered (mCi) and the route of administration.**

N/A

**If not FDA approved provide dosimetry information and reference the source documents (package insert, MIRD calculation, peer reviewed literature).**

N/A

**c) For research radiation machine projects, provide the following diagnostic procedures:**

**For well-established radiographic procedures describe the exam.**

For MRI screening, a skull x-ray or other radiologic procedure might be obtained if the subject reports the possibility that there is metal in the body. This will be done at the radiologist's discretion, and is likely to be infrequent.

**For the typical subject, identify the total number of times each will be performed on a single research subject.**

If an MRI X-ray screen is indicated, for a typical subject only one X-ray would be performed.

**For each radiographic procedure, provide the setup and technique sufficient to permit research subject dose modeling. The chief technologist can usually provide this information.**

These infrequent procedures will be at the radiologist's discretion. The radiation exposure from such x-rays is equivalent to that occurring from natural sources over two months, and increases the risk of cancer by 1/250,000.

**For radiographic procedures not well-established, provide FDA status of the machine, and information sufficient to permit research subject dose modeling.**

N/A

**d) For research radiation machine projects, provide the following therapeutic procedures:**

**For a well-established therapeutic procedure, identify the area treated, dose per fraction and number of fractions. State whether the therapeutic procedure is being performed as a normal part of clinical management for the research participants' medical condition or whether it is being performed because the research participant is participating in this project.**

N/A

**For a therapeutic procedure that is not well-established, provide FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions.**

N/A

**5. Devices**

**a) Please list in the table below all Investigational Devices (including Commercial Devices used off-label) to be used on participants.**

**5.1 Device Name : rTMS Device**

**Describe the device to be used.**

The MagPro X100 is an advanced, high performance magnetic stimulator.  
**Applications:**  
--Is often used within Transcranial Magnetic Stimulation (TMS) and

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**repetitive Transcranial Magnetic Stimulation (rTMS) research**  
**--Examination of human cortical physiology**  
**--Examination of the physiology of the motor pathways in the central and peripheral nervous system**  
**--Examination of functional aspects of motor nerve stimulation**  
**Features:**  
**--3 waveforms: Biphasic, Biphasic Burst and Monophasic**  
**--Selectable current direction**  
**--Stimulation rates up to 100 pulses per second**  
**--Programmable input/output triggers**  
**--System operation control via a built-in computer, eliminating the need for an external computer to set up and control the timing of stimulus sequences**  
**--Flexible protocol storage in built-in computer**

**Manufacturer :** Magventure

**Risk :** Non-significant

Y I confirm the above are true.

**Rationale for the device being non-significant risk:**

After a decade of research, rTMS is generally regarded as safe and without lasting side effects if established guidelines are followed (Janicak et al., 2008; Machii et al., 2006). There have been no significant cognitive (Triggs et al., 1999; Little et al., 2000), neurological (Nahas et al., 2000) or cardiovascular sequelae reported as a result of rTMS. See answer to 9 A.

**Sponsor of Project**

**Indicate who is responsible for submitting safety reports to the FDA:**

Y The sponsor is a non-STANFORD investigator or group.

**Ordering, Storage and Control**

**To prevent the device being used by a person other than the investigator, and in someone other than a research participant: Confirm that the device will be handled according to the SHC/LPCH policy for Investigational New Devices or as appropriate. If no, please provide an explanation. :**

Y Confirm?  
\_\_\_\_\_

b) Please list in the table below all IDE Exempt Devices (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices) to be used on participants.

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## 6. Drugs, Reagents, or Chemicals

- a) Please list in the table below all investigational drugs, reagents or chemicals to be administered to participants.
- b) Please list in the table below all commercial drugs, reagents or chemicals to be administered to participants.

## 7. Medical Equipment for Human Subjects and Laboratory Animals

**If medical equipment used for human patients/participants is also used on animals, describe such equipment and disinfection procedures.**

No equipment that is used on humans is also used on animals.

## 8. Participant Population

- a) **State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii) the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons for using such participants.**

(i) 100 participants are expected to be enrolled  
(ii) 100 participants at VAPAHCS  
(iii) all participants will be Veterans, Military personnel and Civilians.

- b) **State the age range, gender, and ethnic background of the participant population being recruited.**

Age range: 20-65 years  
Note: We may include participants between 65-70 if they contact us and pass the screening (and are not showing cognitive decline related to dementia)  
Gender: Males and Females  
Ethnic Background: Any race or ethnic origin

- c) **State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects and the additional safeguards that have been included in the protocol to protect their rights and welfare.**

Children, pregnant women, economically and educationally disadvantaged, decisionally impaired, and homeless people will not be recruited for this protocol.

- d) **If women, minorities, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).**

There will be no participation of children in this study.

- e) **State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receive it. Please see Stanford University policy.**

It is unlikely that any laboratory personnel, employees, or students will qualify for participation in this study. If any do qualify and wish to participate, they will be treated the same as any other participant.

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- f) **State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rights and welfare.**

Participants should all be in fair physical health though may be cognitively impaired as seen in the chronic symptoms of mild/moderate TBI (note we have removed the 1 SD or more below the mean score on Trail Making Test B (TMT B) criteria from our inclusion criteria). All procedures are considered low risk or standard of care.

- g) **How will you identify participants for recruitment? (E.g., by: chart review; referral from treating physician; response to ad). Attach recruitment materials in Section #16 (Attachments). All Final or revised recruitment materials, flyers, etc. must be submitted to the IRB for review and approval before use. You may not contact potential participants prior to IRB approval. See Advertisements: Appropriate Language for Recruitment Material.**

Based on the team established, we will recruit from: War Related Illness and Injury study Center (WRIISC) at VAPA (one of the three in the nation tasked to address complex problems faced by Veterans of the recent wars; PI: Adamson, PhD, Deputy Director Research), Polytrauma VAPA (Co-I: Maya Yutsis, PhD; one of the 5 polytrauma network sites the country and a participating DVBIC site), Memory clinics at VAPA as well as from the surrounding VA clinics. Letters will be sent to patients and providers with information about the study, and a pre-paid response postcard. Phone calls will be made to these Veterans as followup within two weeks. Flyers will be posted in relevant clinic settings and on the Stanford University Marguerite Shuttle, and study information will be advertised on social media, including facebook. (We plan to recruit an average of 2.2 patients/month to meet our target enrollment of 40 participants in 18 months).

- h) **Inclusion and Exclusion Criteria.**

**Identify inclusion criteria.**

**Inclusion Criteria**

- Age 20-65 years (we may accept participants who pass the screening between 65-70)
- History of (Post Traumatic Amnesia < 1 day for mild TBI; 1 day > x < 7days for moderate TBI)
- Ability to obtain a Motor Threshold (MT) will be determined during the screening process.
- If on a psychotropic medication regimen, that regimen will be stable for at least 4 weeks prior to entry to the study and patient will be willing to remain on a stable regimen during the acute treatment phase.
- Has an adequately stable condition and environment to enable attendance at scheduled clinic visits.
- For female participants, agrees to use one of the following acceptable methods of birth control: abstinence, oral contraceptive; Norplant etc.
- Able to read, verbalize understanding, and voluntarily sign the Informed Consent Form prior to participating in any study-specific procedures or assessments.

**Identify exclusion criteria.**

**Exclusion Criteria**

- Pregnant or lactating female.
- Unable to be safely withdrawn, at least two-weeks prior to treatment commencement, from medications that substantially increase the risk of having seizures
- Have a cardiac pacemaker or a cochlear implant
- Have an implanted device (deep brain stimulation) or metal in the brain (see standard MRI exclusion criteria including metal screening section in telephone screen, Appendix A).
- Have a mass lesion, cerebral infarct or other active CNS disease, including a seizure disorder.
- Known current psychosis as determined by DSM-IV coding in chart (Axis I, psychotic disorder, schizophrenia) or a history of a non-mood psychotic disorder.
- Diagnosis of Bipolar Affective Disorder I (as determined by chart review and intake interview)
- Current amnesic disorders, dementia, MOCA ≤ 16, or delirium.
- Current substance abuse (not including caffeine or nicotine) as determined by positive toxicology screen, or by history via AUDIT, within 3 months prior to screening
- Prior history of seizures



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- Severe TBI or open head injury
- TBI within last two months or in acute stage
- Participation in another concurrent clinical trial
- Patients with prior exposure to rTMS (NOTE: TMS is allowed)
- Active current suicidal intent or plan. Patient at risk for suicide will be required to establish a written safety plan involving their primary psychiatrist and the treatment team before entering the clinical trial

**i) Describe your screening procedures, including how qualifying laboratory values will be obtained. If you are collecting personal health information prior to enrollment (e.g., telephone screening), please request a waiver of authorization for recruitment (in section 15).**

Research Assistants will assess for participant eligibility in a telephone screen. Telephone screening will assess a potential participant's background, demographics, health questions, and psychiatric stability. Study Personnel will meet once per week to review, discuss, and make determinations about the appropriateness of potential participants for the study.

If by study midpoint (approximately end of year one) we are unable to get 20 participants per year, we will reconsider inclusion/exclusion criteria.

Patients who are screened over the telephone for possible eligibility for the study will be listed on the Patient Screening Log. Note: we will make all our efforts to screen patients for both rTMS and MRI exclusions but as our primary aim is to test rTMS for use in TBI population, we will enroll participants in the study who are ineligible to be in the MRI scanner but eligible for rTMS treatment. After the patient signs the Informed Consent Form, the on-site screening procedures and assessments can be initiated.

Data will be collected on paper forms and questionnaires, and entered into encrypted, password-protected databases located on physically secure VA servers behind a firewall. All types of data collected will be de-identified according to the VHA Privacy Handbook 1200.12. Each subject will be assigned a subject ID (SUBID). The SUBID codebook will be maintained by the PI, and will be available to appropriate members of the research team but kept in a locked file cabinet or in an encrypted, password-protected file on a physically secure, password protected computer at VAPA.

All research personnel involved in this study will have successfully completed all applicable VA, and Stanford training. All subject-level identifiable data will be treated as Protected Health Information (PHI) unless that data does NOT contain any of the data elements that HIPAA considers protected. No sensitive data or PHI will be stored on any device other than the secure server. Paper forms will be stored in locked file cabinets in locked offices.

Data from the rTMS study will be entered into a designed ACCESS database and maintained on a VA server located at VAPA, password protected, encrypted and no PHI will be present.

**j) Describe how you will be cognizant of other protocols in which participants might be enrolled. Please explain if participants will be enrolled in more than one study.**

We will ask the potential subject if they are participating in any other protocols. They will be instructed not to participate in any other protocols during their involvement with our study without first getting prior authorization from both our research team and that of the other study. Overlapping participation will be handled on a case-by-case basis.

**k) Payment/reimbursement. Explain the amount and schedule of payment or reimbursement, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations**

There will no longer be payment for participation in this study.

**l) Costs. Please explain any costs that will be charged to the participant.**

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There are no costs to participants other than time and inconvenience.

**m) Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.**

Duration of the study: 2 years

Total time per participant for all screening: 7-8 hours.

For active participation in the study -

- Baseline: approximately 8 hours on-site with MRI, labs, clinical exams
- Intervention: approx. 30-60 minutes/session, 20 sessions over 2 -6 weeks, depending on scheduling
- Follow-up: one follow-up visits over 6 months, each visit lasting approx. 8.5 hrs

Analysis of participant data immediately post treatment and at 6 month follow-up

**9. Risks**

- a) For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the participant it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

**The risks of the Investigational devices.**

MagVenture MagPro X100 - see rTMS risks under "procedures" below.

**The risks of the Investigational drugs. Information about risks can often be found in the Investigator's brochure.**

n/a

**The risks of the Commercially available drugs, reagents or chemicals. Information about risks can often be found in the package insert.**

n/a

**The risks of the Procedures to be performed. Include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).**

rTMS - rTMS Safety especially for Mild and Moderate TBI Veterans

After a decade of research, rTMS is generally regarded as safe and without lasting side effects if established guidelines are followed (Janicak et al., 2008; Machii et al., 2006). There have been no significant cognitive (Triggs et al., 1999; Little et al., 2000), neurological (Nahas et al., 2000) or cardiovascular sequelae reported as a result of rTMS.

The primary safety concern with rTMS, in any population, has been the risk of seizure induction. Eight seizures have been reported secondary to rTMS (Wassermann, 1998). These have occurred in a sample size estimated to be over several thousand rTMS treatment sessions. The rTMS community has adopted and widely used the guidelines prescribing a safe interval between pulse trains (Gerloff et al., 1997) and the safety guidelines from a National Institute of Neurological Disorders and Stroke (NINDS) workshop on rTMS. To our knowledge there have been two publications since 1997 describing events during rTMS that might be considered seizures. Conca and colleagues reported a patient who experienced a 'pseudoabsence seizure'. It is unclear if this was a true seizure (Conca et al., 2000). Bernabeu and colleagues reported on a patient who had a seizure during rTMS. In this case, there was a brief interstimulus interval (Bernabeu et al., 2004). The risk of seizures for rTMS treatment is less than 1%.

How does this impact our study: The current safety guidelines have not been tested for mild and moderate TBI population which is precisely the purpose of this pilot grant. In TBI population, posttraumatic epilepsy

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is the most common delayed sequelae of TBI. But this incidence is very low (about 5%) in TBI patients with closed head injury (Ropper et al., 2005) who are most likely our mild and moderate TBI patients. In a clinical setting, for example in Polytrauma Transitional Rehabilitation Program (PTRP – VAPA) the expected recovery trajectory for persons with mTBI is full cognitive recovery in 3-6 months following injury. Persisting or worsening cognitive status is often related to other co-morbid psychiatric issues, such as depression and PTSD, chronic pain, sleep apnea (all will be) used as covariates in our analysis). Including persons with moderate TBI in our study would likely allow for examination of rehabilitation treatment effects on cognitive functioning for those who tend to have persisting cognitive difficulties following injury. On PTRP, patients are often admitted from the acute inpatient rehab unit on anticonvulsant medications if they had a seizure 1 day or more following the injury. Typically, if the patient experienced a seizure immediately at the scene of the incident, they are not considered at a greater risk for subsequent seizures. For those who do not have a history of seizures following injury, they are not considered at a greater risk of subsequent seizures and are not placed on anticonvulsant medications. Importantly, the interval between the head injury and the first seizure varies greatly (Demirtas-Tatlidede et al., 2012) and must be considered as a variable for recruitment in this study. Currently PTRP houses patients 2 months to 2 years post TBI. Note, that there is only one case study which performed detailed safety assessments and reported a lack of adverse events in a patient with severe TBI following application of a specific rTMS protocol over 5 consecutive days through 6 weeks (Pape et al., 2009). Our protocol will be highly stringent and will exclude any severe TBI patients (including those with any fractures, metal plates or open head injuries), acute patients or those who have had a concussion within the last 2 months, and those who have a history of seizures of any type.

Neuropsychology testing - The risks posed by neuropsychological testing are mild frustration and mild fatigue that will not persist.

MRI - The study participant may get a metal taste in their mouth or some tingling in their hands or feet during the MRI scan. Occasionally, individuals experience claustrophobia (fear of confinement in a small space) during the MRI scan.

**The risks of the Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.**

X-ray - x-ray involves exposure to an FDA-approved low dose of radiation. The radiation exposure from such x-rays is equivalent to that occurring from natural sources over two months, and increases the risk of cancer by 1/250,000.

**The risks of the Physical well-being.**

See above, Procedures to be performed.

**The risks of the Psychological well-being.**

A psychiatric screening will be performed to determine whether the participant meets inclusion and exclusion criteria for the study. From past experience, potential risk to participants is expected to be minimal. Specifically, questions asked may be potentially distressing to the participants or may cause them to think about problems relating to them that may be anxiety-provoking or upsetting. We have created and attached a suicidality protocol in the event that such a protocol is needed.

Cognitive Testing. There do not appear to be any risks associated with cognitive testing other than the commitment of significant time for participation. Some participants may experience anxiety during and after the cognitive testing.

Questionnaires. There are virtually no risks involved in filling out the questionnaires, sleep-wake cycle questionnaires and sleep logs other than the time involved.

MRI. One possible psychological risk is that some people experience claustrophobia during an MRI, or lesser degrees of anxiety.

**The risks of the Economic well-being.**

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n/a

**The risks of the Social well-being.**

Loss of confidentiality

**Overall evaluation of Risk.**

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

- b) If you are conducting international research, describe the qualifications/preparations that enable you to both estimate and minimize risks to participants. Also complete the International Research Form and attach it in the Attachments section. If not applicable, enter N/A.**

n/a

- c) Describe the planned procedures for protecting against and minimizing all potential risks. Include the means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable). Include steps to minimize risks to the confidentiality of identifiable information.**

- Loss of confidentiality.

o Every precaution will be taken to minimize loss of confidentiality. A double lock system will be maintained: within a locked office and locked file cabinet. All electronic data will be secured on an encrypted, password-protected database behind a VA firewall.

**MRI**

- There are no expected risks associated with the MR imaging of brain function, other than the possibility of some mild frustration and mild fatigue. The study participant may get a metal taste in their mouth or some tingling in their hands or feet during the MRI scan. Occasionally, individuals experience claustrophobia (fear of confinement in a small space) during the MRI scan.

o Breaks will be provided in order to reduce the possibility of frustration and fatigue.

o The metal taste sensations go away after the scan is complete.

o The MRI scanners have built-in communication systems, so study participants will have constant contact with staff during the scan. If the participant experiences severe claustrophobia, they will be asked to discontinue participation in the imaging measures in this study.

- Study personnel will verbally review the currently approved and required VA MRI scan checklist at the time of the telephone screen, and before every scheduled MR scan.

**rTMS**

In the unlikely event that a seizure does occur, the participant will be closely monitored and treated for any medical or psychological consequences. Lab tests will be drawn and the participant will be seen by a neurologist as soon as possible. The facility where the rTMS studies are performed is fully equipped to safely handle a seizure. The participant will be given a letter regarding the seizure to share with his or her primary health care provider. The letter will indicate that the seizure during rTMS does not increase risk for future seizures.

rTMS treatment can result in mild to moderate headaches in as many as 30 out of 100 of patients. Some people also report discomfort at the site of rTMS stimulation. This occurs in around 15 out of 100 of patients. Headaches and site discomfort usually readily respond to acetaminophen or ibuprofen. Painfulness improves over time or goes away. Often patients fall asleep in the second week while receiving the same treatment that on the first day was reported as very painful.

There is a small risk of dental pain with rTMS, during or immediately after the treatment. If this occurs, study staff may be able to move the rTMS coil position or provide a bite block to reduce this pain or make it not happen.

rTMS treatment may produce movement or tingling of the arm, leg, face or scalp. Participants may also experience a temporary feeling of numbness in the face.

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There is a possible risk of hearing loss due to the light clicking sounds made by the device. Participants will wear earphones during rTMS sessions. This should greatly reduce the possibility of hearing loss. Hearing will be tested at baseline, after the intervention phase, and after follow-up to see if any hearing loss has occurred.

The rTMS operator will monitor all participants for ear protection, coil placement, and seizure activity during all sessions.

- d) Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.**

The clinical trial will terminate after 2 years or when 40 participants have been through the protocol.

rTMS treatment will be done only by trained medical personnel (MD, Nurse, or Nurse Practitioner) who can provide necessary medical or professional intervention in the event of adverse effects to the participants.

- e) Data Safety and Monitoring Plan (DSMP). See guidance on Data Safety and Monitoring.**

**A Data and Safety Monitoring Plan (DSMP) is required for studies that present Medium or High risk to participants. (See Overall Evaluation of Risk above). If Low Risk, a DSMP may not be necessary. Multi-site Phase III clinical trials funded by NIH require the DSM Plan to have a Data Safety Monitoring Board or Committee (DSMC or DSMB). The FDA recommends that all multi-site clinical trials that involve interventions that have potential for greater than minimal risk to study participants also have a DSMB or DSMC.**

**The role of the DSMC or DSMB is to ensure the safety of participants by analyzing pooled data from all sites, and to oversee the validity and integrity of the data. Depending on the degree of risk and the complexity of the protocol, monitoring may be performed by an independent committee, a board (DSMC/DSMB), a sponsor's Data Safety Committee (DSC), a Medical Monitor, a sponsor's safety officer, or by the Protocol Director (PD).**

**Describe the following:**

**What type of data and/or events will be reviewed under the monitoring plan, e.g. adverse events, protocol deviations, aggregate data?**

--Primary and secondary outcome measures --Safety/drug use measures --Adverse events (AE), Serious adverse events (SAE), Unanticipated Problem (UP), & Unanticipated Adverse Device Effect (UADE)  
Inclusion/exclusion criteria

**Identify who will be responsible for Data and Safety Monitoring for this study, e.g. Stanford Cancer Institute DSMC, an independent monitoring committee, the sponsor, Stanford investigators independent of the study, the PD, or other person(s).**

The ME is a group of outside and inside experts that includes the PD in the areas clinical trials and biostatistics that reviews the progress of the study and monitors patient enrollment, outcomes, adverse events, and other issues related to patient safety. The ME makes recommendations to the PI as to whether the study should continue or be modified or terminated. The ME can consider patient safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or infeasibility of addressing the study hypotheses (e.g., poor patient intake, poor adherence to the protocol). The ME will meet for every patient to review data reports prepared by our staff. There is continuous communication between the two members of ME and PI and study staff. Any member of the ME can ask for a meeting of the group if he/she feels that it is necessary, based upon the data. The VA SPIRE REHAB committee did not assign an outside DMC for this study as it is a smaller pilot study. The VA SPIRE committee in Rehab is the main regulatory body and monitors it via annual progress reports.

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**Provide the scope and composition of the monitoring board, committee, or safety monitor, e.g., information about each member's relevant experience or area of expertise. If the Monitor is the Stanford Cancer Center DSMC or the PD, enter N/A.**

Jauhtai Joseph Cheung, MD – Neurologist, expertise in clinical trials and rTMS Steven Chao, MD – Neurologist, expertise in TBI

**Confirm that you will report Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the person or committee monitoring the study in accordance with Sponsor requirements and FDA regulations.**

AE - within 48 hours; SAE - within 48 hours; UP - within 5 days

**If applicable, how frequently will the Monitoring Committee meet? Will the Monitoring Committee provide written recommendations about continuing the study to the Sponsor and IRB?**

There is no outside DMC assigned by the VA for this grant. All monitoring is done by PI and ME and the VA Rehab SPIRE progress reports.

**Specify triggers or stopping rules that will dictate when the study will end, or when some action is required. If you specified this in Section 2g [Study Endpoints], earlier in this application enter 'See 2g'.**

We will suspend enrollment if 10 participants experience a seizure (not including syncope) during study participation, and request that the ME evaluate the data, to determine if enrollment of new patients should be resumed without protocol changes, if protocol modifications should be made before resuming enrollment, or if the study should be terminated. We recognize that study termination or modification based on serious adverse events, such as seizures, ultimately rests with the DMC and the study PI and that more stringent stopping points may be initiated during the study. If a patient is determined to be suicidal, either based on the CSSRS, HRSD, clinical evaluation, or by statements made by the patient, a clinical evaluation will be immediately conducted by the Principal Investigator, by the patient's individual mental health provider, or a mental health emergency clinician. The patient will not be left alone until the evaluation has been completed and a decision made about disposition in conjunction with the Chief of Mental Health Outpatient Clinic or the Mental Health Emergency clinician. For alcohol/drug use, stopping criteria for treatment will include: 1. Alcohol use greater than one glass of wine/day or equivalent. Use of alcohol when patient has been warned of serious medication/alcohol interactions, will also fit these criteria. If patients are found to be noncompliant with this, the Principal Investigator will decide whether to administer treatment and evaluate the patient's appropriateness for continued participation. 2. Abuse of illegal drugs. If patients are found to be noncompliant with this, the Principal Investigator will decide whether to administer treatment and evaluate the patient's appropriateness for continued participation. 3. Abuse or misuse of prescribed medications will also result in either withdrawal from the study or inclusion as a noncompliant patient.

**Indicate to whom the data and safety monitoring person, board, or committee will disseminate the outcome of the review(s), e.g., to the IRB, the study sponsor, the investigator, or other officials, as appropriate.**

ME review of all events will be communicated to the IRB when appropriate, via recommended protocol changes or a submitted report through the eProtocol system.

**Select One:**

- The Protocol Director will be the only monitoring entity for this study.  
 Y This protocol will utilize a board, committee, or safety monitor as identified in question #2 above.

**10. Benefits**

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- a) **Describe the potential benefit(s) to be gained by the participants or by the acquisition of important knowledge which may benefit future participants, etc.**

Potential benefits are improvement in executive function and better quality of life by participating in this trial.

## 11. Privacy and Confidentiality

### Privacy Protections

- a) **Describe how the conditions under which interactions will occur are adequate to protect the privacy interests of participants (e.g., privacy of physical setting for interviews or data collection, protections for follow-up interactions such as telephone, email and mail communications).**

Participants will meet in a private interview room with a member of the study team to sign the consent form and discuss the protocol for the study. All treatment and interviews will be done in a private setting. Samples will be obtained in a private setting.

### Confidentiality Protections

- b) **Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.**

We are collecting the following PHI:  
Full name  
Social Security Number (for VA hospital registration and payment)  
Mailing address (for appointment notices and to mail payment)  
Email address (backup communication)  
Telephone number (for communication)  
Date of birth (study metric)  
Date of visit  
Demographics  
Account numbers  
Diagnostic/Laboratory test results  
fMRI images  
Biological specimens  
Medical history and physical examination information  
Survey/questionnaire responses  
Psychological test results  
Alcohol and substance use information  
VA CPRS medical records

- c) **You are required to comply with University Policy that states that ALL electronic devices: computers (laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted. See <http://med.stanford.edu/datasecurity/> for more information on the Data Security Policy and links to encrypt your devices.**

**Provide any additional information on ALL data security measures you are taking. You must use secure databases such as RedCap <https://med.stanford.edu/researchit/infrastructure/redcap.html>. If you are unsure of the security of the system, check with your Department IT representative. Please see <http://med.stanford.edu/irt/security/> for more information on IRT Information Security Services and [http://www.stanford.edu/group/security/securecomputing/mobile\\_devices.html](http://www.stanford.edu/group/security/securecomputing/mobile_devices.html) for more information for securing mobile computing devices. Additionally, any PHI data on paper must be secured in an**

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**locked environment.**

**By checking this box, You affirm the aforementioned. Y**

Data will be collected on paper forms and questionnaires, and entered into encrypted, password-protected databases located on physically secure VA servers behind a firewall. All types of data collected will be de-identified according to the VHA Privacy Handbook 1200.12. Each subject will be assigned a subject ID (SUBID). The SUBID will be maintained by the PI, and will be available to appropriate members of the research team but kept in a locked file cabinet or in an encrypted, password-protected file on a physically secure, password protected computer at VA Palo Alto. MRI images collected at the VA Palo Alto will be kept on secure VA server and will adhere to all the OI&T and privacy rules. If MRI is to be transferred to Stanford for analysis, it will be done via a HIPAA agreement and consent of the participant. The PI together with the Study coordinator (SC) are responsible for maintaining accurate, complete and up-to-date records for each participant. The PI is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

Every attempt will be made to randomize a participant so that he/she will receive his/her first rTMS treatment as soon as possible after randomization. Nonsequential treatment numbers will be assigned to help ensure the confidentiality of veteran participants (see Human Subjects also).

All personnel involved in this study will have successfully completed all applicable VA, and Stanford training. All subject-level identifiable data will be treated as Protected Health Information (PHI) unless that data does NOT contain any of the data elements that HIPAA considers protected. No sensitive data or PHI will be stored on any device other than the secure server. Paper forms will be stored in locked file cabinets in locked offices.

Data from the rTMS study will be on a VA server located at VA Palo Alto, password protected, encrypted and no PHI will be present. Specifically, data in the ACCESS database will be on the secure VA server.

- d) Describe how data or specimens will be labeled (e.g. name, medical record number, study number, linked coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and by whom the images will be de-identified.**

All types of data collected will be de-identified according to the VHA



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Privacy Handbook  
1200.12. Each subject will be assigned a subject ID (SUBID).

**e) Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data or specimens).**

The research team will have access to data.

**f) If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.**

A study code is assigned to a subject after they sign a consent form.  
This code is independent of any identifying information.

**g) If data or specimens will be coded, indicate who will maintain the key to the code and describe how it will be protected against unauthorized access.**

The code will be maintained by the PI, and will be available to appropriate members of the research team but kept in a locked file cabinet or in an encrypted, password-protected file on a physically secure, password protected computer at VA Palo Alto.

**h) If you will be sharing data with others, describe how data will be transferred (e.g., courier, mail) or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, describe how you will secure the data while in transit. See <http://www.stanford.edu/group/security/securecomputing/> <http://www.stanford.edu/group/security/securecomputing/>. Additionally, if you will be using or sharing PHI see <https://uit.stanford.edu/security/hipaa> <https://uit.stanford.edu/security/hipaa>.**

No PHI will be transferred to anyone outside the established rTMS research team.

**i) How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected (e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data)?**

All research staff will complete and remain current with all required VA and Stanford training prior to working with human subjects. The Protocol Director will also reinforce the importance of maintaining confidentiality.

**12. Potential Conflict of Interest**

Investigators are required to disclose any financial interests that reasonably appear to be related to this protocol.

Financial Interest Tasks

Investigators	Role	Email	Has Financial Interest?	Date Financial Interest Answered	Date OPACS Disclosure Submitted	Date OPACS Review Completed

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Maheen Mausooof Adamson	PD	madamson@stanford.edu	Y	07/23/2018	07/23/2018	08/03/2018
Jerome A Yesavage	FS	yesavage@stanford.edu	N	01/12/2018		
Amit Etkin	OP	amitetkin@stanford.edu	N	01/12/2018		
David J. Clark	OP	djclark@stanford.edu	N	01/12/2018		
Odette Althea Harris	OP	odette@stanford.edu	N	01/12/2018		

**13. Consent Background**

**13.1 Waiver of Documentation rTMS\_TBI\_telephonescreen**

Check if VA related Y

a) Describe the informed consent process. Include the following.

- i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)
- ii) When and where will consent be obtained?
- iii) How much time will be devoted to consent discussion?
- iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?
- v) What steps are you taking to minimize the possibility of coercion and undue influence?
- vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

i. Trained study personnel will be conducting telephone screening. All will be trained and knowledgeable about the study. ii. Screening will happen on VA office phones, in a secure and private office setting, and every effort will be made to ensure that the potential research participant is in a private and comfortable environment at the time of screening. iii. 45 minutes is allotted for telephone screening, but it is possible that it could take additional time in order to answer participant questions, as needed. iv & v. First, the information contained in the telephone screen is explained in language they can understand. Repetition is required during any learning process and is incorporated into the telephone screening procedures. Additionally, throughout the screening process participants are encouraged to ask questions, and screeners repeatedly check in to make sure everything is understood so far and ask if there are any questions. Special care is taken to repeatedly inform prospective participants that their participation is entirely voluntary and that they may withdraw at any time and for any reason without penalty or loss of currently existing benefits. The emphasis on the voluntary nature of participation is designed to minimize the possibility of coercion or undue influence on participation. vi. N/A

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter 12.2 for guidance.

Prospective participants are then asked to carefully read the written informed consent form, and any questions are answered. Next, the prospective participant is asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they are asked to sign and date the last page. Understanding English is a requirement for this study.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent, (iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

All participants in this study must be able to independently consent to participate.

Additional VA questions:

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- i) **List the people to whom you have formally delegated responsibility to obtain informed consent, and state whether they have the appropriate training to perform this activity.**

All study personnel (PI, study coordinator, research assistants, RN/RNP/PA) will be appropriately trained to obtain informed consent.

- ii) **Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?**

Legally effective informed consent will be obtained. Use of an LAR would exclude a participant from eligibility.

- iii) **Will the circumstances of the consent process minimize the possibility of coercion or undue influence and provide the prospective participant or their representative sufficient opportunity to consider whether to participate?**

Minimization of the possibility of coercion or undue influence will be done by having prospective participants carefully read the written informed consent form, and any questions are answered. Next, the prospective participant is asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they are asked to sign and date the last page. The emphasis on the voluntary nature of participation is designed to minimize the possibility of coercion or undue influence on participation.

- iv) **Will the circumstances of the consent process minimize the possibility of coercion or undue influence?**

Minimization of the possibility of coercion or undue influence will be done by having prospective participants carefully read the written informed consent form, and any questions are answered. Next, the prospective participant is asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they are asked to sign and date the last page. The emphasis on the voluntary nature of participation is designed to minimize the possibility of coercion or undue influence on participation.

- v) **Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?**

No exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence is included.

- vi) **Please confirm the following:**

- a. **A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.**
- b. **If the sponsor or the IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person is needed to serve both capacities, a note to that effect is placed under the witness's signature line.**
- c. **A copy of the signed and dated consent document will be given to the person signing the consent document.**
- d. **The consent form is on the VA Form 10-1086.**

**Select one of the following regulatory criteria for a waiver of documentation (signature) and provide a protocol-specific justification:**

- 1) **45 CFR 46.117(c)(i). For research that is not subject to FDA regulation, the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.**
- 2) **45 CFR 46.117(c)(ii). For research that is not subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**
- 3) **45 CFR 46.117(c)(iii). For research not subject to FDA regulation, if subjects or legally authorized representatives (LAR) are members of a distinct cultural group in which signing forms is not the norm, the research presents no more than minimal risk and there is an appropriate alternative mechanism for documenting that informed consent was obtained.**
- 4) **Y 21 CFR 56.109(c)(1). For research that is subject to FDA regulation, presents no more than**

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**minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**

**Rationale for above selection:**

Information from the telephone screening will be protected from breach of confidentiality through several safeguards including password protected computers, locked offices, doors, and file cabinets, and secure VA computer networks.

**13.2 Consent** **rTMS TBI Consent\_2018-2019**

Check if VA related Y

**a) Describe the informed consent process. Include the following.**

- i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)**
- ii) When and where will consent be obtained?**
- iii) How much time will be devoted to consent discussion?**
- iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?**
- v) What steps are you taking to minimize the possibility of coercion and undue influence?**
- vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.**

i. Trained study personnel will be obtaining consent. All will be trained and knowledgeable about the study.  
ii. Consent will be obtained in a private room at the study center. Consent will be the first component of participation in this study. iii. 30 minutes is allotted to consent discussion, but it is possible that consent could take up to 60 minutes if needed. iv & v. First, the information contained in the written informed consent document is explained verbally to prospective participant in a language they can understand. Repetition is required during any learning process and is incorporated into the informed consent procedures. Special care is taken to repeatedly inform prospective participants that their participation is entirely voluntary and that they may withdraw at any time and for any reason without penalty or loss of currently existing benefits. Prospective participants are then asked to carefully read the written informed consent form, and any questions are answered. Next, the prospective participant is asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they are asked to sign and date the last page. The Study Staff and a witness also sign and date informed consent document, and the participant is given a copy for their records. The emphasis on the voluntary nature of participation is designed to minimize the possibility of coercion or undue influence on participation. vi. n/a

**b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.**

Prospective participants are then asked to carefully read the written informed consent form, and any questions are answered. Next, the prospective participant is asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they are asked to sign and date the last page. Understanding English is a requirement for this study.

**c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent, (iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.**

All participants in this study must be able to independently consent to participate.

**Additional VA questions:**

**i) List the people to whom you have formally delegated responsibility to obtain informed consent, and state whether they have the appropriate training to perform this activity.**

All study personnel (the PI, study coordinator, research assistants, and RN/RNP/PA) will be appropriately trained to obtain informed consent.

**ii) Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?**

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Legally effective informed consent will be obtained. Use of an LAR would exclude a participant from eligibility.

**iii) Will the circumstances of the consent process minimize the possibility of coercion or undue influence and provide the prospective participant or their representative sufficient opportunity to consider whether to participate?**

Minimization of the possibility of coercion or undue influence will be done by having prospective participants carefully read the written informed consent form, and any questions are answered. Next, the prospective participant is asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they are asked to sign and date the last page. The emphasis on the voluntary nature of participation is designed to minimize the possibility of coercion or undue influence on participation.

**iv) Will the circumstances of the consent process minimize the possibility of coercion or undue influence?**

Minimization of the possibility of coercion or undue influence will be done by having prospective participants carefully read the written informed consent form, and any questions are answered. Next, the prospective participant is asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they are asked to sign and date the last page. The emphasis on the voluntary nature of participation is designed to minimize the possibility of coercion or undue influence on participation.

**v) Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?**

No exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence is included.

**vi) Please confirm the following:**

- a. A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.
- b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person is needed to serve both capacities, a note to that effect is placed under the witness's signature line.
- c. A copy of the signed and dated consent document will be given to the person signing the consent document.
- d. The consent form is on the VA Form 10-1086.

**14. Assent Background (less than 18 years of age)**

**15. HIPAA Background**

**15.1 Authorization** **rtms\_tbi\_hipaa**

**15.2 Waiver of Authorization for** **rmti\_tbi\_recruitment**

**Recruitment**

- a) Describe the protected health information (PHI) needed to conduct screening or recruitment. PHI is health information linked to HIPAA identifiers. List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol.

Full name Mailing address Telephone number Demographics Education Date of Birth Date of visit Medical
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history Survey/questionnaire responses (e.g.; TBI & memory related questions) Psychological test results (for exclusion criteria purposes) Alcohol/substance use

b) Please Answer:

- Y **Do you certify that the use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals?**
- Y **Do you certify that the research could not practically be conducted with out the waiver?**
- Y **Do you certify that you have adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted?**
- Y **Do you certify that the research could not practically be conducted with out access to and use of the protected health information?**

c) **Please describe an adequate plan to protect any identifiers from improper use and disclosure.**

Information from the telephone screening will be protected from breach of confidentiality through several safeguards including password protected computers, locked offices, doors, and file cabinets, and secure computer networks as described previously.

d) **Please describe an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.**

If potential participants are found to be ineligible for or uninterested in participation in the study, records will be securely maintained until such time as their destruction is allowed by an approved and published VA schedule of record retention.

**16. Attachments**

Attachment Name	Attached Date	Attached By	Submitted Date
rtms_device_userguide	02/21/2014	madamson	
rtms_device	02/21/2014	madamson	
Magventure_sham	02/21/2014	madamson	
magventure_technicaldata	02/21/2014	madamson	
medical history	02/21/2014	madamson	
MAST	02/21/2014	madamson	
DAST	02/21/2014	madamson	
Columbia Suicide	02/21/2014	madamson	
OSU TBI Questionnaire	02/21/2014	madamson	
Trauma History Questionnaire	02/21/2014	madamson	
safety_Protocol	02/21/2014	madamson	
Seizure Protocol	02/21/2014	madamson	
Brief Pain Inventory	02/21/2014	madamson	

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Pittsburgh Sleep Quality Index	02/21/2014	madamson	
Demographics	02/21/2014	madamson	
Flinders Fatigue Scale (FFS) with instructions	02/21/2014	madamson	
MAPI	02/21/2014	madamson	
Handedness questionnaire	02/21/2014	madamson	
Physical Exam	02/21/2014	madamson	
rTMS Treatment Log 2-21-14	02/21/2014	madamson	
WAIS Digit Span	02/21/2014	madamson	
Pure Tone Audiometry form	02/21/2014	madamson	
DKEFS - Fluency	02/21/2014	madamson	
Rey AVLT Word List	02/21/2014	madamson	
DKEFS - Color-word interference	02/21/2014	madamson	
VA_Rehab_rTMS_TBI_grant	03/13/2014	madamson	
VA required questions_revised	03/24/2014	madamson	
MOCA	01/27/2015	madamson	
Cognitive test battery list	01/27/2015	madamson	
HAM-D 17	01/27/2015	madamson	
Epworth Sleepiness Scale	02/23/2015	jb29	
VR-36	02/23/2015	jb29	
PCL-M	02/23/2015	jb29	
CAPS-V	02/23/2015	jb29	
Life Event Checklist - V	02/23/2015	jb29	
TMT A&B	02/23/2015	jb29	
HIT-6	02/23/2015	jb29	
Response form	02/27/2015	jb29	
Welcome letter	02/27/2015	jb29	
VA rTMS_TBI Flyer	03/04/2015	madamson	
B.R.I.E.F.	03/24/2015	jb29	
Planning - Camping Trip	03/24/2015	jb29	
Planning - Game Night	03/24/2015	jb29	

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Planning - Party	03/24/2015	jb29	
Planning - Sporting Event	03/24/2015	jb29	
Webneuro	03/24/2015	jb29	
Cognitive and non-cognitive assessments	03/24/2015	jb29	
provider letter to Veteran	04/12/2015	madamson	
letter to provider	04/12/2015	madamson	

**Obligations**

The Protocol Director agrees to:

- Adhere to principles of sound scientific research designed to yield valid results
- Conduct the study according to the protocol approved by the IRB
- Be appropriately qualified to conduct the research and be trained in Human Research protection, ethical principles, regulations, policies and procedures
- Ensure all Stanford research personnel are adequately trained and supervised
- Ensure that the rights and welfare of participants are protected including privacy and confidentiality of data
- Ensure that, when de-identified materials are obtained for research purposes, no attempt will be made to re-identify them.
- Disclose to the appropriate entities any potential conflict of interest
- Report promptly any new information, modification, or unanticipated problems that raise risks to participants or others
- Apply relevant professional standards.

Any change in the research protocol must be submitted to the IRB for review prior to the implementation of such change. Any complications in participants or evidence of increase in the original estimate of risk should be reported at once to the IRB before continuing with the project. Inasmuch as the Institutional Review Board (IRB) includes faculty, staff, legal counsel, public members, and students, protocols should be written in language that can be understood by all Panel members. The investigators must inform the participants of any significant new knowledge obtained during the course of the research.

IRB approval of any project is for a maximum period of one year. For continuing projects and activities, it is the responsibility of the investigator(s) to resubmit the project to the IRB for review and re-approval prior to the end of the approval period. A Notice to Renew Protocol is sent to the Protocol Director 7 weeks prior to the expiration date of the protocol.

Department Chair must approve faculty and staff research that is not part of a sponsored project. VA applicants must have Division Chief or Ward Supervisor approval. E-mail the Department Chair approval to IRBCoordinator@lists.stanford.edu.

All data including signed consent form documents must be retained for a minimum of three years past the completion of the research. Additional requirements may be imposed by your funding agency, your department, or other entities. (Policy on Retention of and Access to Research Data, Research Policy Handbook, <http://doresearch.stanford.edu/policies/research-policy-handbook/conduct-research/retention-and-access-research-data>)



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PLEASE NOTE: List all items (verbatim) that you want to be reflected in your approval letter (e.g., Amendment, Investigator's Brochure, consent form(s), advertisement, etc.) in the box below. Include number and date when appropriate.

Y By checking this box, I verify that I, as the Protocol Director (PD) responsible for this research protocol, have read and agree to abide by the above obligations, or that I have been delegated authority by the PD to certify that the PD has read and agrees to abide by the above obligations.