Title : Repetitive Transcranial Magnetic Stimulation for Dementia

Approval Period: 01/31/2020 - 11/12/2020

Modification

1. **Summarize your proposed changes.**

   This investigator received email from ART@va.gov, stating that there is "Clinical Trial Results Due in ClinicalTrials.gov for E1889-P at RR&D (Palo Alto)". This PI corresponded with Jolie Bergman, ART Database Coordinator (206.277.4163), and was instructed to prepare a document named "Statistical Analysis Plan". and submit it to IRB before uploading to ClinicalTrials.gov.
   Please see attached. Thank you.

2. **Indicate Level of Risk**

   No Change

3. **Update the Conflict of Interest (COI) section if any changes in COI have been made since the last protocol submission.**

   N Is there a change in the conflicting interest status for any existing personnel on this protocol?

Protocol Director

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Jauhtai Joseph Cheng		MD		Clinical Assistant Professor (Affiliated) [VAPAHCS]
Department	**Mail Code**	**Phone**	**Fax**	**E-mail**
Psychiatry and Behavioral Sciences	151Y	650-493-5000 x63617		jauhtai.cheng2@va.gov
CITI Training current				Y

Admin Contact

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Beatriz Hernandez		BA		Data Analyst
Department	**Mail Code**	**Phone**	**Fax**	**E-mail**
Psych/Public Mental Health & Population Sciences	5550	(650) 852-3287		bhernandez@stanford.edu
CITI Training current				Y

Investigator

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department	**Mail Code**	**Phone**	**Fax**	**E-mail**
CITI Training current				

Other Contact

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department	**Mail Code**	**Phone**	**Fax**	**E-mail**

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CITI Training current				

Academic Sponsor

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department	**Mail Code**	**Phone**	**Fax**	**E-mail**
CITI Training current				

Other Personnel

Name Jerome A Yesavage		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.** Professor
Department Psych/Public Mental Health & Population Sciences	**Mail Code** 5550	**Phone** (650) 852-3287	**Fax** (650) 852-3297	**E-mail** yesavage@stanford.edu
CITI Training current				Y

Name John Wesson Ashford		**Degree (Program/year if student)** M.D., Ph.D. (VA)		**Position, e.g. Assistant Professor, Resident, etc.** Clinical Professor (Affiliated) [VAPAHCS]
Department Psychiatry and Behavioral Sciences	**Mail Code** 5550	**Phone** (650) 493-5000	**Fax** (650) 852-3297	**E-mail** ashford@stanford.edu
CITI Training current				Y

Name Laura Lazzeroni		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.** Professor
Department Psych/General Psychiatry and Psychology (Adult)	**Mail Code** 5717	**Phone** (650) 723-0947	**Fax**	**E-mail** Lazzeroni@stanford.edu
CITI Training current				Y

Name Margaret Windy Mcnerney		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department Psychiatry and Behavioral Sciences	**Mail Code**	**Phone** 650-493-5000	**Fax**	**E-mail** windymc@stanford.edu
CITI Training current				Y

Name Lisa Marie Kinoshita		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.** Soc Sci Res Assoc
Department	**Mail Code**	**Phone**	**Fax**	**E-mail**

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Psych/Public Mental Health & Population Sciences	5550	(650) 852-3287		lisakino@stanford.edu
CITI Training current				Y

Name Jyoti Bhat		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department Psychiatry and Behavioral Sciences	**Mail Code**	**Phone**	**Fax**	**E-mail** jyoti.bhat2@va.gov
CITI Training current				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 — Y
- Cancer Subjects — N
- Laboratory Personnel — N
- Healthy Volunteers — Y
- Students — N
- Employees — N
- Prisoners — N
- Other (i.e., any population that is not specified above) — Y

Study Location(s) Checklist — Yes/No

- Stanford University
- Clinical & Translational Research Unit (CTRU)
- Stanford Hospital and Clinics
- Lucile Packard Children's Hospital (LPCH)
- VAPAHCS (Specify PI at VA) — Y

  Jauhtai Joseph Cheng, MD
- 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 — N

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medical or research institutions in which one site takes a lead role.(e.g., multi-site clinical trial)

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
• Is Stanford responsible for ClinicalTrials.gov registration? (See Stanford decision tree) NCT# 02621424	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	N

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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.

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

Payment	**Yes/No**
• Subjects will be paid/reimbursed for participation? See payment considerations.	Y

Funding	**Yes/No**
• Training Grant?	N
• Program Project Grant?	N
• Federally Sponsored Project?	Y
• Industry Sponsored Clinical Trial?	N

Funding

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Funding - Grants/Contracts

Funding Administered By : VA
SPO # (if available) :
Grant # (if available) :
Funded By (include pending) : VA
Principal Investigator : Jauhtai Joseph Cheng

Grant/Contract Title if different from Protocol Title :
same (Repetitive Transcranial Magnetic Stimulation for Dementia)

Y For Federal projects, are contents of this protocol consistent with the Federal proposal?
Is this a Multiple Project Protocol (MPP)?
Is this protocol under a MPP?

Funding - Fellowships

Gift Funding

Dept. Funding

Other Funding

Resources :

a) Qualified staff.

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

Jauhtai Joseph Cheng, MD (PI). The PI is a licensed, board certified neurologist, and specialty board-certified in sleep medicine. He performs neurological consultation on patients with mild cognitive impairment and dementia. He also sees patients with complex, disabling medical/neurological conditions that prior diagnostic work up had failed to yield a clear diagnosis. He conducts and supervises neurological and neurophysiological testing. His research interest is developing new treatment modalities for patients with disorders of the nervous system. He is the Site Investigator of the VA cooperative study CSP#556 (effectiveness of rTMS in depressed VA Patients).

Jerome Yesavage, MD (Co-investigator). Dr. Yesavage is Associate Chief of Staff for Mental Health at the VA Palo Alto Health Care System, and Professor of Psychiatry at Stanford University. Over the past 20 years, he has conducted several studies developing and validating novel treatment modalities, such as transcranial magnetic stimulation. He is also Director of the VA Mental Illness Research, Education, and Clinical Center (MIRECC) at VA Palo Alto Health Care System, and Professor of Psychiatry at Stanford University School of Medicine. Dr. Yesavage has tremendous experience in the design and conduct of similar studies. He will be involved in the design, execution, and analysis of this study, and will have the resources of the MIRECC, ACRC, WRIISC to draw upon as needed. Dr. Yesavage will provide guidance and assist in matters pertaining to design and execution of this study.

Allyson Rosen, PhD (Co-investigator). Dr. Rosen is the Director of Dementia Education, MIRECC, Clinical Associate Professor (Affiliated) Department of Psychiatry and Behavioral Sciences, Stanford University. She conducts aging and cognitive research at VAPAHCS. She is an expert in neuropsychology and will assist in the design of the study as well as analysis of the study results.

Maheen Adamson, PhD (Co-investigator). Dr. Adamson is the Director for Research at the War Related Illness and Injury Study Center, California (WRIISC CA). She conducts research to explore new treatment

options for veterans with chronic multiple illness. Her current research involves providing nonpharmacological interventions for treatment of cognitive deficits in Veterans with TBI. She is the PI for VA Rehab SPIRE award for using repetitive transcranial magnetic stimulation (rTMs) to improve executive function in Veterans with mild and moderate Traumatic Brain Injury (TBI). She is also a Co-protocol Director and Co-I for a VA Rehab Merit award for rTMs for treatment of pain in Gulf War 1 Veterans. Dr. Adamson will assist in matters pertaining to study design and execution.

Wes Ashford, MD, PhD (Collaborator) Dr. Ashford is PI on a recently-funded clinical trial (VA Merit Award) entitled "Repetitive Transcranial Magnetic Stimulation for the Treatment of Chronic Pain in GW1 Veterans". He is the Director of War-Related Injury and Illness Study Center at VAPAHCS. Dr. Ashford will provide guidance and assist in matters pertaining to design and execution of this study.

Ahmad Salehi, MD (Consultant). Dr. Salehi is Director of WRIISC Translational Laboratory, VAPAHCS and Clinical Associate Professor, Department of Psychiatry and Behavioral Sciences, Stanford University Medical School. He is a world expert in neuropathology in neurodegenerative disorder, well experience in collecting measuring, and analyzing the significance of biomarkers such as nerve growth factor (NGF), BDNF, amyloid precursor protein (App). In his current research, he is using extensive proteomic and genomic methods to verify the effects of certain neurotransmission in individuals with dementia. Dr. Salehi agrees to serve as consultant in matters pertaining to biomarker collection and analysis.

Art Noda (Data Manager) has 25 years of experience of doing data management and analysis for clinical studies. He has used Statistical Analysis System (SAS, Cary N.C.) software for database management, programming and data analysis for 18 years. He has developed advanced skills using SAS in database construction and management as well as proficiency in a variety of complex statistical analyses. Currently he is supporting various investigators on issues related to data management, security, analysis and presentation at VAPAHCS. In the current project, he will design and implement a database for the secure storage of all study-related data, consult on all statistical examinations of the data set, and assist with presentations and manuscript preparation.

Megan Reif, R.N. (nurse) is the current member of CSP556 VA Cooperative study Palo Alto Site. She has ample experience in conducting clinical research and will be consulted on matters pertaining to current study design and execution. She is currently the treater for CSP556 study, delivering rTMS treatment to study participant. She will be the backup treater for this proposed study.

Study Coordinator (TBD) A full-time Study Coordinator (SC), preferably one who is experienced in health science (mental health) and clinical trials, will be recruited for the study and will be under the direct supervision of the principal investigator/protocol director. The SC will recruit and randomize patients into the study, perform assessments including the quality of life assessments. The SC will perform other administrative tasks including completion of case report forms, correction of edits and data clarification. The SC will also contact study participants with appointment reminders and for follow-up as needed. If needed, study coordinator or research assistants will assist in the bio-specimen collection and/or processing.

Laura C. Lazzeroni, PhD (Consultant). Dr. Lazzeroni has collaborated with Dr. Yesavage for the past five years, with a research focus on statistical genetics and other biostatistical issues, such as multiple hypothesis testing and simultaneous inference. Dr. Lazzeroni will provide bio-statistical consultation as needed.

Mark George, MD (Consultant). Dr. George is one of the world's leading experts in the use of brain imaging and stimulation to understand depression and to devise new treatments for depression. He is also one of the first scientists to expand the study of brain imaging technology for psychiatric disorders. He pioneered the use of a noninvasive brain stimulation method, transcranial magnetic stimulation (TMS), for depression. He is currently leading the VA cooperative study CSP556, the effectiveness of rTMS in depressed VA patients, as the co-PI. Dr. George agrees to serve as a consultant in matters pertaining to rTMS study design, execution and analysis.

Brian Yochim, PhD (Consultant). Dr. Yochim has published extensively on the neuropsychological

assessment of dementia, with a focus on the development and validity of state-of-the-art measures of cognitive functions affected by Alzheimer's disease. He is Clinical Assistant Professor (Affiliated) in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. He has evaluated hundreds of patients with Mild Cognitive Impairment (MCI) or Dementia due to various cognitive/neurological disorders. Dr. Yochim agrees to be consulted on matters pertaining to neuropsychological measures.

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 have completed all VA- and Stanford-required training in Human Subjects, Good Clinical Practice, Privacy, and HIPAA, and any required training for specific procedures. All staff have been trained in this protocol by the Protocol Director. Some staff have also worked with similar protocols, and all staff members are very familiar with procedures for this study. Any new staff who join the project will take all required training before beginning work on the project, and will be carefully trained on all necessary aspects of the protocol by the Protocol Director, who supervises staff for this project. Data privacy and proper specimen collection procedures will be stressed before subject contact is allowed.

c) Facilities.

Please describe and justify.

The project will take place at the MIRECC (Mental Illness Research, Education, and Clinical Center), located at VA Palo Alto Health Care System, Palo Alto Division. Private interview rooms and a large conference room are available for this project, as well as office space for staff.
The MIRECC is a major clinical research center that is operated through the Department of Veterans Affairs where Dr. Cheng (PI) and Drs. Yesavage, Adamson, and Ashford (Co-Investigators) have the needed laboratory space, computer access, data analytic software, data storage, and personnel with statistical expertise to conduct the proposed study. Dr. Yesavage is the Director of the MIRECC as well as the Associate Chief of Staff for Mental Health and can assign additional space for research if needed.
The Stanford-VA Alzheimer Research Study Center is a major clinical research center for the improvement of diagnostic accuracy of varieties of cognitive dysfunction, that is operated through the Department of Veterans Affairs and funded by the States of California, where Dr. Yesavage (Co- Investigator) is the co-director and Dr. Jauhtai Cheng is the senior neurology consultant.
The PI has access to two repetitive transcranial magnetic stimulation (rTMS) machines that are also being used in two other funded studies. There are also five quiet interview rooms in the MIRECC building, each furnished with a table and three chairs. The rooms are shared with other researchers and are reserved on an as-needed basis. Office supplies (clipboard, stopwatch, etc.) are readily available. A receptionist is available to inform research staff of the arrival of participants and guide them to their appointments. Two treatment rooms are dedicated solely to house the two TMS systems with the nurse station, and the other three are available on an as needed basis.

d) Sufficient time.

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

We will have sufficient time to conduct and complete the research. Each of the investigators has sufficient time available to conduct their part of the research.
Each participant will spend a maximum of 6 weeks in the project (active treatment phase).
We expect to begin recruitment in January, 2016.
The project will be completed by December, 2018.

e) Access to target population.

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

VAPAHCS has several services which will be sources of research participants: the Stanford- VA Alzheimer Research Study Center (a California State funded project), Geriatric Memory Clinics, Neurology clinics, the Geriatric Research, Education, and Clinical Center (GRECC), and the General Outpatient Clinics.
The investigator conducts and supervises outpatient neurocognitive evaluations for veterans and adult volunteers at Stanford-VA Alzheimer Research Study Center. Approximately 90% of patients seen have some degree of cognitive impairment, ranging from Mild Cognitive Impairment (MCI) to dementia. The clinic evaluates approximately 20 patients per month. It is estimated that as many as 3 patients per month will be willing and able to participate in this research project.
The Geriatric Research, Education, and Clinical Center (GRECC) consists of three services. The Geriatrics Primary Care Clinic provides primary care to veterans age 65 or older. The patient panel consists of approximately 184 active patients. Approximately 11% of patients in this clinic have a current diagnosis of dementia, 7% with mild cognitive impairment or cognitive disorder NOS, and 16% of patients have other neurologic conditions that may impair cognition. The Geriatrics Interdisciplinary Team Continuity Clinic is an interdisciplinary team clinic providing primary care for approximately 65 frail, often medically complex older veterans. Approximately 48% of patients have a diagnosis of dementia, 31% with mild cognitive impairment or cognitive disorder NOS, and 28% of patients have other neurologic conditions that may impair cognition. The Geriatric Consult Clinic provides interdisciplinary geriatrics team consultative evaluation and management direction for patients who receive their primary care within the VA system. The consultative team includes a geriatrician, clinical nurse specialist, and geriatric social worker. Patients are referred to this clinic for geriatric conditions and/or syndromes, including cognitive disorders and dementia, poly-pharmacy, and falls. In the past 6 months the Clinic was referred 59 patients, and of these patients 61% had dementia and 27% had cognitive disorder NOS or mild cognitive impairment.
Another ongoing research project, PTSD-Sleep Apnea longitudinal study, has accumulated a large cohort of veterans (about 250) with average of about 65 year-old. The participants of this study has had their baseline cognitive function assessed. Their cognitive functions are monitored longitudinally. It is estimated that as high as a quarter of the participants meet diagnostic criteria of mild cognitive impairment sometime during the study period. The PI (J. Cheng) is a consultant of the study and has access to this pool of patients.
Lastly, the Primary Care Outpatient clinics will serve as a source of participants. These clinics serve thousands of patients annually and have a history of referring patients to the MIRECC for research participation.

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 Principal Investigator is the study physician who is available for consultation with participants if an adverse event should occur. Dr. Yesavage and Ashford (Co-Investigators) are psychiatrists, and Dr. Adamson is a psychologist; all are available to participants if needed. The Protocol Director or a senior research associate will provide psychological resources to participants, if necessary. Appropriate referrals will be made when necessary in the judgment of the physician and/or psychologist. As the study takes place at the VA Palo Alto medical center, medical assistance is readily available if needed.

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

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

The purpose of this study is to is to evaluate the effectiveness of repetitive transcranial magnetic stimulation (rTMS) as a treatment for cognitive impairment due to conditions such as Alzheimer's disease (AD).

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

The primary hypothesis is that rTMS applied to the dorsolateral prefrontal cortex will lead to improved memory, language and executive function compared to patients who receive a sham, control treatment. The improvement is defined as having higher performance on the California Verbal Learning Test (CVLT-II). Secondary Hypothesis are that 1)rTMS- will lead to higher performance on secondary cognitive measures relating to executive function and naming compared to performance by participants in the sham treatment group at the termination of treatment; and that 2) rTMS-induced memory improvement parallels changes in BDNF levels after treatment.

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 behavioral traits in humans in classroom or other environment)

This is a study of aging and cognition 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.

Prescreening: We will review medical records of veterans who have learned about this study and expressed their interest in participating, and veterans who have consented to receive information about other studies when they entered a VA study previously. Additionally, study staff will review charts of veterans being seen in the VA healthcare system. Veterans will not receive blind phone calls from study staff. For charts that are flagged in the prescreening phase as potentially meeting eligibility criteria, these veterans will be contacted by their health care provider initially, and basic study information provided. If the veteran is interested and contacts the study team, a formal screening process will follow.

Screening: The veteran will meet with principal investigator and study coordinator. Detailed study information will be provided and veteran given opportunities to ask questions and clarify any issues. When the veteran clearly expresses understanding and decides to participate a consent form will be presented to the veteran and signature obtained to complete the informed consent. An optional consent form for lumbar puncture will also be signed by the veteran if he (she) decides to participate in that portion of the study. Since we have the Palo Alto VA MRI Center, an optional consent for a MRI will also be signed by the veteran if he (she) decides to

participate in that portion of the study.
The research participant will be scheduled to have baseline cognitive function evaluated and recorded . Medical history will be verified and physical exam performed. Motor threshold will be obtained. When all eligibility criteria are met, randomization phase is begun.

Randomization:
This is a double-blind, randomized clinical trial. Eligible participants will be randomly assigned to one of two groups: Group 1) rTMS treatment group, one to three treatments daily, 3 to 5 days a week, for about 2 weeks to achieve a total of 20 sessions (similar to another ongoing protocol at this site) and Group 2) sham treatment (same frequency and duration as treatment group). The location of each patient's dorsolateral prefrontal cortex will be estimated by measuring 6 centimeters from the location where the motor threshold is found; this placement method is commonly used in rTMS research. In the case of the optional MRI, the MRI will be used to guide TMS stimulation.
rTMS will then be applied to each participant's left dorsolateral prefrontal cortex.

Participants will complete the California Verbal Learning Test, second edition (CVLT-II) at three time points: initial baseline evaluation, immediately after treatment, and 4 months after cessation of treatment. Adverse effects of rTMS will be recorded carefully. Participants will also complete other measures including but not limited to, word-finding (Boston Naming Test), category fluency test (animal), speed and executive functioning (Trail Making Test part A and B), Brief Visuospatial Momory Test (BVMT-R)Mini Mental State Examination (MMSE) and a depression assessment. To minimize practice effects of repeated testing, alternate forms of neuropsychological tests will be counterbalanced and administered when available.

Intervention Phase:
Units of 5-10 sessions will normally be delivered over one week's time. The entire treatment phase (20 sessions) will normally occur in 2-4 weeks, depending on scheduling constraints, though some consideration of scheduling flexibility must be made to accommodate holidays and other events. At the end of every fifth session, study staff will enter progress notes for each participant in the Computerized Patient Record System (CPRS). Patients will be tested on the outcome measures after the 20th session and at a 4 month follow-up for comparison to the sham control group.

Follow-up Phase:
After the acute treatment phase ends, patients will enter a 4 month follow-up period, and a total of one year monitoring period for possible increased risk of seizure. If a participant in the active treatment group continues to decline at the same rate as participants in the control group at the end of 20 sessions of treatment, or drops out during treatment, the participant will be considered a treatment failure for the purpose of the primary analyses.

At the end of the 4 month follow-up visit after all study measures

have been completed the Veteran will be notified of whether they received sham or active treatment. If they received sham, they will be offered the option to repeat the intervention and follow-up phases of the study and receive active rTMS treatment. Assessments including the neuropsych testing and sample collection will only be repeated as described previously in the intervention and follow-up phase descriptions if administering personnel is available. All unblinded data will be stored in a separate section of the database to be used for exploratory analysis. To assess the risk of seizure, there will be a one year post-treatment monitoring period. We will collect information about events or symptoms suspicious for seizure.

Intervention Regimen:
Selection of rTMS Stimulation Parameters: We will be using the parameters that are known as "intermittent theta burst protocol". The proposed parameters are the most likely, based on current knowledge, to be potentially effective in the VA population. The specifics are:

Location: left dorsolateral prefrontal cortex;
Power: 80 % of motor threshold as separately determined for each patient prior to treatment/sham sessions;
Pulse frequency: triplet pulses repeating at 5 Hz
Length of each pulse train: 2 seconds;
Time between pulse trains: 8 seconds;
Length of treatment: about 5 minutes;
Total 600 pulses per session;
5 days/week, 20 sessions (completed in 2-4 weeks depending on scheduling constraints). Depending on schedule, and at physician's discretion, up to three rTMS sessions can be scheduled per day with at least a one hour interval between sessions.

Location & Intensity: rTMS studies in this area have used dosage levels ranging from 90% of motor threshold to 120% of motor threshold depending on the site selected for treatment stimulation. Older studies used lower intensity stimulation because of safety concerns at the time which have now been alleviated with greater experience. In several recent studies, 120% of motor threshold has been necessary and sufficient to stimulate the prefrontal cortex in older participants, even those with prefrontal atrophy. This threshold is both tolerable and safe. The reason we have chosen the DLPFC is that in a review of 8 studies of rTMS in dementia, all studies used this target area, although two studies also treated other brain areas in the same treatment period.

Sham (Control) treatment: This system, or something quite similar, has been used in the CSP-556 OPT-TMS depression clinical trial and several other smaller studies and the blind has been maintained. Sham (Control) treatment will be accomplished by using the Cool-B65-A/P coil that functions both as an active (A) and placebo (P) coil. It has a symmetrical mechanical design and no labeling on the coil indicates the active or placebo side. Consequently it is not possible for the operator to see or hear which side is used. Additionally, for each treatment session, whether sham or active,

each patient shall wear scalp electrodes through which, in the case of sham treatments, a low-voltage, low electric current (2 – 20ma at no more than 100V) will be passed in order to provide cutaneous stimulation that mimics the sensation of actual rTMS. At the same time, the Sham 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 all participants (active or placebo).

Biomarker collection and genetic testing:
We plan to collect indicators of the possible effects of rTMS of brain derived nerve growth factors (BDNF). It has been shown that val66met polymorphism in BDNF can affect the response to rTMS. For this reason, the val66met polymorphism will be determined in each subject. Furthermore, the amounts of BDNF in plasma and CSF will be quantified. DNA samples will be purified from blood collection.

Blood samples will be obtained at the baseline visit and after completion of the treatment. A venipuncture will be performed. A maximum of 10 ml of blood will be withdrawn for analysis at any one time. Subjects need not be fasting. DNA and proteins will be extracted from the blood sample.

Optional CSF sample collection: Lumbar puncture (LP) will be done at the baseline visit and after completion of the treatment. Risks will be explained and consent obtained from the participant. The procedure will be performed by a physician per standard proceedures in a treatment room.

BDNF genotype will be determined through one-step amplified refractory mutation system polymerase chain reaction (ARMS-PCR), and subsequent gel electrophoresis. BDNF, Val66Met will be determined the analysis of amplicons according to Sheikha and colleagues (2010). PCR amplicons will be analyzed on 2% agarose gel. Genotyping will be repeated on samples to ensure accuracy. Plasma levels of BDNF will be determined using Quantakine ELISA kits (R & D Systems).

Rises in BDNF levels would be an indication of the rTMS effect if this occurred only in the active treatment group. Apo-E and BDNF genotypes will be used as moderator of the response. Consultant Dr. Ahmad Salehi at VAPAHCS is experienced with collecting relevant measures.

Optional structural MRI scanning: For MRI Guided TMS, participants will undergo written informed consent, neurophsycological testing, and then TMS. In an MRI guided TMS protocols that there will be 2-3 sessions where behavioral testing and MRI will precede TMS. The MRI will be used to guide the TMS stimulation. This approach is a structural MRI target (Talairach coordinates –45, 45, 35) based on an MRI guided TMS clinical trial that showed an advantage over a non-image guided approach (5 cm rule) (Fitzgerald et al., 2009). Thus we will examine two approaches to target location: The 6 cm Rule, and a structural MRI target location approach.

b) Explain how the above research procedures are the least risky that can be performed consistent with

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sound research design.

There is little risk to the proposed procedures. Seizure occurred in rare occasions during high frequency stimulation (>10 Hz). Seizure risk is minimized by careful patient selection (by excluding patients with history of seizure or other conditions that increase risks of seizure). A seizure protocol is in place to avoid participant injury in the event that seizure does occur.

TMS is considered fairly safe procedure.

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).

No deception will 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.

No audio or video recordings will be used.

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).

No standard treatments will be withheld.
There are 5 drugs approved for the treatment of Alzheimer's disease (tacrine, also known by the brand name Cognex; donepezil, also known by the brand name Aricept; galantamine, also known by the brand name Reminyl; rivastigmine, also known by the brand name Exelon; and memantine, also known by the brand name Namenda). Thus, alternatives to participation in this study include the continued use of tacrine, donepezil, galantamine, rivastigmine, or memantine.All approved anti-dementia therapies are permitted provided doses are stable for at least 4 weeks prior to randomization and there is agreement to maintain the dose throughout the study. Supplements and nutraceuticals at stable doses are allowed at the discretion of the investigator.

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

The therapy under investigation is not available except during study participation at this time.
This study does not require participant to stop any anti-dementia therapy prior to or during the study.

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?

The study is expected to continue until all participants have completed
the procedures.

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3. Background

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

Clinical Background. Alzheimer's disease (AD) is extremely common among older Veterans, and is the most frequent cause of dementia in the general population. Current treatments for AD are of limited effectiveness and do not halt the progression of the disease.
Recently, repetitive transcranial magnetic stimulation (rTMS) has emerged as a possible treatment for AD. It also has been asserted that rTMS enhanced performance in cognitive functions in patients with AD or mild cognitive impairment. Finally, rTMS has been found to be effective to improve auditory comprehension in Alzheimer's disease. Bentwich et al. (2011) found that rTMS improved performance on the Alzheimer Disease Assessment Scale – Cognitive (ADAS-cog) in patients with dementia due to AD. Thus there appears to be some evidence for clinical benefit to rTMS treatments in patients with cognitive impairment possibly related to AD pathology.
Mechanism of Action. Studies show that rTMS may modify neuronal networking functions beyond the site of stimulation. There are also data indicating that externally applied electromagnetic field (rTMS) not only changes the bioelectrical milieu locally, but also may effect cerebral metabolism in sites distant to the local stimulus. Such changes have been hypothesized to increase synaptic plasticity and long-term potentiation (LTP) in areas important for cognitive functioning in AD. In addition, rTMS has reversed a decline in brain-derived neurotrophic factor (BDNF) in mice, and caused increased level of BDNF in chronic pain patients. More recently, it was found that response to TMS is affected by BDNF Polymorphism (Chang 2014) and the Apo-e status modulates the changes in network connectivity induced by brain stimulation in non-demented elders (Pena-Gomez 2015). Thus there is increasing knowledge about potential mechanisms of action of rTMS in AD.
While not yet utilized in dementia research on a large scale, rTMS is well suited for this pilot project given the clinical and research expertise in rTMS trials at this site for various other disorders common among Veterans. rTMS is currently being used at the VA Palo Alto Health Care System (VAPAHCS) and Stanford University in the treatment of: executive dysfunction in Veterans with traumatic brain injuries (VA Rehabilitation grant with notification of funding received: PI: Dr. Adamson), pain (VA Rehabilitation grant funded with 7 participants enrolled: PI: Dr. Ashford & Co-I/Co-Protocol Director: Dr. Adamson), and depression (VA Co-op studies funded CSP 556 with 65 participants enrolled, PI: Dr. Yesavage). The PI in the CSP 556 Site Investigator and as such is fully trained in the use of rTMS and has applied it to Veterans in the CSP 556 Protocol. This PI is also staff neurologist in the VA/Stanford State of California Alzheimer's Disease Study Center where he consults on 2-4 new AD evaluations per week.

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

Not applicable.

4. Radioisotopes or Radiation Machines

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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

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

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

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

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

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

For well-established radiographic procedures describe the exam.

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

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

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

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's medical condition or whether it is being performed because the research participant is participating in this project.

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.

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 : Venture Stimulator

Describe the device to be used.

Repetitive Transcranial Magnetic Stimulation

Manufacturer : MagVenture

Risk : Non-significant

Y I confirm the above are true.

Rationale for the device being non-significant risk:

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rTMS is an FDA approved treatment modality. The device to be used for this study is the same type of device that is being used by a similar study (Protocol #29889 - Repetitive Transcranial Magnetic Stimulation to Improve Cognitive Function in TBI)

Sponsor of Project

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

Y The sponsor is the STANFORD (SU, SHC, LPCH, VA) investigator.

Please read the following:

Sponsor-Investigator Research Requirements

If you would like further information on this process and/or assistance prior to submitting your protocol contact: The Stanford Center for Clinical and Translational Education and Research (Spectrum) at clinicaltrials@med.stanford.edu or for cancer research contact: ccto-regulatory@stanford.edu

Y I have read and understand the above guidance.

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?

5. 2 Device Name : MRI Coil

Describe the device to be used.

MRI Compatible TMS coil. 70mm Double

Manufacturer : **Magstim**

Risk : **Non-significant**

Y I confirm the above are true.

Rationale for the device being non-significant risk:

The FDA considers this device to be of non-significant risk if used following the guidelines of Wasserman, 1998. Theta burst rTMS is a new protocol that has been safely used but which follows different safety limits from simple rTMS. We will follow what has been previously used (Huang and Rothwell, 2004; Huang et al., 2005; Silvanto et al., 2007;Oberman and Pascual-Leone, 2009.))

Sponsor of Project

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

Y The sponsor is the STANFORD (SU, SHC, LPCH, VA) investigator.

Please read the following:

Sponsor-Investigator Research Requirements

If you would like further information on this process and/or assistance prior to submitting your protocol contact: The Stanford Center for Clinical and Translational Education and Research (Spectrum) at clinicaltrials@med.stanford.edu or for cancer research contact: ccto-regulatory@stanford.edu

Y I have read and understand the above guidance.

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

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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.

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.

This equipment is not 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) We plan to enroll 62 participants at the VA Palo Alto Health Care Systems, a Stanford-affiliated site.
(ii) This is the only site for this project.
(iii) Patients will be subjects with an established diagnosis of Mild Cognitive Impairment (MCI), or dementia likely due to Alzheimer's disease.

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

Age Range: 55 years of age and older
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, and homeless people will not be recruited for this protocol.
Some participants may be decisionally challenged, due to having dementia. All potential participants who meet the diagnostic criteria for dementia will have an appropriate surrogate provide consent. If a potential subject's competency is in question, a trained clinician will make the competency evaluation based on a brief clinical interview, according to VA guidelines. In most cases, the participant with the diagnosis of mild

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cognitive impairment is competent to give consent for research. If the person lacks capacity, then a proxy (legally authorized representative) will need to sign the consnet form. The patient's assent will be obtained & documented by also including their signature on the ICF form. We will follow the recommendations set out in the Alzheimer's Association position paper, "Research Consent for Cognitively Impaired Individuals" (AD & Assoc Disorders 2004 (vol 18, pp 171-175) (attached).

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. The research topic to be studied is irrelevant to children because we are studying the effects of aging in subjects over the age of 55. Alzheimer's disease does not occur in children.

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.

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 to good physical health.

g) How will you identify and recruit potential participants about the research study? (E.g., by: chart review; notified by treating physician; response to ad). 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.

Participants will be recruited through Veteran healthcare centers, the Stanford-VA Alzheimer Research Center, clinics throughout the VA Palo Alto Health Care System, the Mental Illness Research, Education, and Clinical Center (MIRECC), and the Geriatric Research, Education, and Clinical Center (GRECC). Participants will also be informed of the study through IRB-approved flyers posted throughout the VA Palo Alto Health Care System (VAPAHCS) campus and local community. IRB-approved recruitment content will be posted online using sites such as craigslist, VA facebook, and online registries such as the Brain Health Registry. These methods have been successful in recruiting research participants at VAPAHCS.

Prior to the in-person screening evaluation, potential participants may be identified by the investigator through routine clinical contact, through a chart review of existing Center participants, chart review of VA patients, or as a result of a telephone screen. Prospective participants will be known to meet as many of the inclusion/exclusion criteria as possible. Prospective participants will attend an in-clinic screening.

For prospective participants who had signed consents to be contacted for other studies, their charts will be reviewed. If deemed eligible, the study coordinator or PI for the earlier study will send a letter to the veteran to provide introduction of this study. If the prospective participant agrees to continue and calls the study team, phone screen process may proceed. For prospective participants who are referred by their health care providers, and who contact the study team, study coordinator will proceed with a phone screen. Other prospective participants who learned of this study by other means, will initiate the contact themselves. Advertising materials and phone script are attached.

h) Inclusion and Exclusion Criteria.

Identify inclusion criteria.

-Veterans aged 55 years or older

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-Diagnosed with Mild Cognitive Impairment (MCI) or dementia likely due to Alzheimer's disease.
-Ability to obtain a Motor Threshold, determined during the screening process.
-With an adequately stable condition and living environment to enable attendance at scheduled clinic visits.
-If on a prescription medication for cognition that medication dose will be stable for at least 4 weeks prior to randomization in to the study and participant will be willing to remain on a stable regimen during the acute treatment phase.
-Able to read, verbalize understanding, and voluntarily sign the Informed Consent Form (to be signed by the participant, or a designated legal representative when the participant lacks decision making capacity) prior to participating in any study- specific procedures or assessments.

Identify exclusion criteria.

-Patients with prior exposure to rTMS or ECT
-Unable to safely withdraw, 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
-Current substance abuse (not including caffeine or nicotine) as determined by patient report or chart review.
-Active current suicidal intent or plan as determined by patient report or chart review.
-Current or Prior history of a seizure disorder as determined by patient report or chart review
-Traumatic brain injury within the last two months
-Participation in another concurrent interventional clinical trial
-Known current psychosis as determined by patient report or chart review.
-Current or prior history of a mass lesion, cerebral infarct or other non-cogitative, active CNS disease that would increase the risk for seizure.
-Not fluent in English or a hearing impairment severe enough to impair comprehension

-Participants cannot participate in the optional LP if they are taking anticoagulants such as warfarin, dabigatran, or FxA inhibitors, such as endoxaban, apixaban, and rivaroxaban.
-Participants cannot participate in the optional LP if they are on dual antiplatelet therapy--with aspirin and an antiplatelet, such as ticragelor, prasugrel, or clopidogrel.
-Participants on a single antiplatelet agent, like ASA, will be individually assessed to rule out factors that might increase bleeding risks.
-Participants on a P2Y12 inhibitor, such as tricragelor, prasugrel, or clopogrel, will be individually assessed to rule out factors that might increase bleeding risks.

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).

The study staff may conduct a short phone screen based on eligibility criteria. Please see attached phone screen and limited waiver of authorization

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, and document this on the consent form. 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.

Participants may be members of the Stanford/VA Alzheimer's Disease Center, and may be participating in other protocols in the Center. Great care is taken to ensure that participants do not participate in protocols that may interfere with each other in any way.

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

Compensation of $300 will be offered to participants who complete the study. If a participant withdraws or stops early in any of the three phases they will be paid according to what phase they are in. $40 for Screening phase, $200 for intervention phase, $60 for follow-up phase. If a veteran returns for the unblinded treatment sessions they will be offered an additional $200 for the repeat of the intervention phase and $60 if they for the repeat of the follow-up phase. We feel this is a reasonable amount in light of the time and effort the participant will spend in the study. The amount of this payment is similar to that paid for other, similar studies by this lab and others conducting similar studies. Travel reimbursement will be provided based on the driving mileage at government rate.

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

No costs to the subject will arise as a result of participation in this study, other than transportation to and from the Center, and the time involved.

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.

The entire study should take 2 years.
(i) Screening for each participant will take approximately 2 days.
(ii) Each participant will actively participate in the study for about 3-5 weeks, with a 4 month follow-up visit. If they received sham treatments and choose to return for active treatments the study participation could extend an additional 4 months. To assess the possible increased risk of seizure, there is a total of one year post-treatment monitoring period. During this monitoring period we will be informed if participants experience events or symptoms suspicious for seizure.
(iii) Analysis of participant data is estimated to take about 6 months.

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.

Previously it was thought that RTMS studies carry little risk beyond occasionally causing a vascular headache in participants susceptible to migraine. Safety studies in human participants have been concerned with the theoretical possibility of magnetic injury to the brain, alteration in the baseline EEG, change in cardiovascular stability, hormonal aberrations and persistent changes in cognitive or perceptual function. No short or long-term sequelae have been described in these safety studies. A study in rabbits suggested that transcranial magnetic stimulation has an auditory click that may raise the hearing threshold. Studies in humans have found no evidence of hearing loss in humans due to TMS As a precaution ear plugs are used. In 1995 the Food and Drug Administration determined that transcranial magnetic stimulators, delivering less than one pulse a second, "does not now present a potential for serious risk to health."

However, one of our study participant developed seizure six months after he received RTMS treatment. We are in the process of assessing if RTMS treatment contributed to this new onset of seizure. Before that issue is clarified, we consider seizure is a potential risk for patients receiving RTMS.

MRI
There are no known physical, social, or legal risks associated with MRI. One possible psychological risk is that some people experience claustrophobia during an MRI, or lesser degrees of anxiety. Subjects scanned

using the new 3.0 Tesla magnet may experience localized non-painful twitching sensations due to the radiowave changes during the scan. Peripheral nerve stimulation is much more common at higher field strengths(3.0 Tesla)although not completely unavoidable at 1.5 Tesla.

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

Not applicable.

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

Not applicable.

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

Venipuncture.
There is mild local discomfort associated with venipuncture, along with a risk of bruising or bleeding. On very rare occasions there may be mild bleeding or bruising at the sampling site. Removal of blood by a needle and syringe poses a small risk of pain or bruising at the site of the needle stick, but this is temporary. Some people may experience fainting or dizziness, and there is also a slight risk of infection at the site of the needle stick.

Cognitive testing.
Cognitive testing and psychosocial measurements can cause anxiety similar to what might be be associated with any test. Repeated evaluations of mood and mental status may be slightly frustrating or produce fatigue and boredom.

Lumbar puncture.
LP is a standard neurodiagnostic procedure for collection of CSF but may be associated with pain during the performance of the procedure. This is usually temporary and confined to the lower back. A persistent low-pressure headache may develop after lumbar puncture, probably due to leakage of CSF. Although frequency of post-LP headache as high as 10% has been reported using standard 20 gauge spinal needles, rates of less than 2% have been reported in elderly participants when atraumatic (Sprotte) needles are used (Peskind et al, 2005). If a post-LP headache persists it may need additional treatment, e.g. with fluids and analgesics. Uncommonly a blood patch (injection of some of the subject's blood to patch the CSF leak) may be needed. Potential but rare risks of lumbar puncture include infection, damage to nerves in the back, bleeding into the CSF space, and death. The risk of these is much less than 1%.

Participants cannot participate in the optional LP if they are taking anticoagulants such as warfarin, dabigatran, or FxA inhibitors, such as endoxaban, apixaban, and rivaroxaban. Participants cannot participate in the optional LP if they are on dual antiplatelet therapy-- with aspirin and an antiplatelet, such as ticragelor, prasugrel, or clopidogrel. Participants on a single antiplatelet agent, like ASA, will be individually assessed to rule out factors that might increase bleeding risks. Participants on a P2Y12 inhibitor, such as tricragelor, prasugrel, or clopogrel, will be individually assessed to rule out factors that might increase bleeding risks. Assessments will include lab reviews, such as PT, PTT, platelet count, etc.

MRI scans.
See above

Genetic and Biomarker testing.
Genetic testing is done on the collected blood and CSF samples. Blood and CSF samples are to be brought to a designated lab for biomarkers levels and genotyping processes, under the supervision of consultant, Dr. Salahi.

TMS.
Previously it was thought that RTMS studies carry little risk beyond occasionally causing a vascular headache in participants susceptible to migraine. Safety studies in human participants have been concerned

with the theoretical possibility of magnetic injury to the brain, alteration in the baseline EEG, change in cardiovascular stability, hormonal aberrations and persistent changes in cognitive or perceptual function. No short or long-term sequelae have been described in these safety studies. A study in rabbits suggested that transcranial magnetic stimulation has an auditory click that may raise the hearing threshold. Studies in humans have found no evidence of hearing loss in humans due to TMS As a precaution ear plugs are used. In 1995 the Food and Drug Administration determined that transcranial magnetic stimulators, delivering less than one pulse a second, "does not now present a potential for serious risk to health."

However, one of our study participant developed seizure six months after he received RTMS treatment. We are in the process of assessing if RTMS treatment contributed to this new onset of seizure. Before that issue is clarified, we consider seizure is a potential risk for patients receiving RTMS.

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

Not applicable.

The risks of the Physical well-being.

See above procedures. No other risks to physical well-being are anticipated.

The risks of the Psychological well-being.

A 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.

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.

Biomarker and Genetic testing.
It is possible that bioassay and genetic testing could cause some psychological stress. However, all participants are informed that only members of the research staff will see results of the biomarker and genetic testing which will be in a coded format with no individual identification. We will not release results of the genetic testing to anyone outside of the research project (including participants, family, physician, or any other third party).

The risks of the Economic well-being.

No risks to economic well-being are anticipated.

The risks of the Social well-being.

No risks to social well-being are anticipated.

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. Provide an explanation as to why the research must be completed at this location and complete the [LINKFORINTERNATIONALREASEARCHFORM] International Research Form. 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.

Data. All data will be stored in locked filing cabinets or on secure servers.

Venipuncture.
Experienced medical personnel will handle all the blood drawing procedures and clean conditions will be maintained.

Cognitive testing.
If the participant is fatigued or uncomfortable with testing, a break can be taken to rest. If a participant is unwilling to continue a testing session, they will be given the option of continuing at a later time, ending the current session, or ending all participation.

Lumbar puncture.
Although frequency of post-LP headache as high as 10% has been reported using standard 20 gauge spinal needles, rates of less than 2% have been reported in elderly participants when atraumatic (Sprotte) needles are used (Peskind et al, 2005). If a post-LP headache persists it may need additional treatment, e.g. with fluids and analgesics. Uncommonly a blood patch (injection of some of the subject's blood to patch the CSF leak) may be needed. Trained and licensed medical personal will perform the lumbar puncture under sterile conditions.

MRI.
For MRI, participants are told to wear ear plugs to protect hearing, they are carefully screened for non-removable metal and other risks that could interfere with a safe and comfortable scan. They are excluded and warned about claustrophobia, and warned to tell the investigator if the experience twitches or hearing or any other symptom that concerns them (see above for more detail.

All participants will rest for at least 30 minutes after the procedure, and will be asked to avoid strenuous physical activity for the next 48 hours. They will be advised to drink more liquids than usual and to avoid alcohol during this time. All precautions are taken to anticipate potential problems and minimize these risks.

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, participants will be closely monitored and treated for any medical or psychological consequences. The facility where the rTMS studies are performed is fully equipped to safely handle a seizure. A seizure safety protocol is attached.

However, one of our study participant developed seizure six months after he received RTMS treatment. We are in the process of assessing if RTMS treatment contributed to this new onset of seizure. Before that issue is clarified, we consider seizure is a potential risk for patients receiving RTMS. We ask that the participants of the study inform the study team of any symptoms or event suspicious for seizure during the study and the one year post-treatment monitoring period, so that proper evaluation and management can be provided. At the end of that one year, the study team will contact the participants by phone and inquire about the presence of any symptoms or event suspicious for seizure.

rTMS treatment can result in mild to moderate headaches in as many as 30 out of 100 patients. Some people also report discomfort at the site of rTMS stimulation. This occurs in around 15 out of 100 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 treatment. If this occurs, patients should let the doctor or nurse know and they may be able to move the rTMS coil position or provide patients with a bite block to reduce the pain.

rTMS treatment may produce movement, discomfort, or tingling of the arm, leg, face, or scalp. They may also experience temporary numbness in the face. The procedure will be stopped if a participant complains of these symptoms.

There is a possible risk of hearing loss due to the light clicking sounds made by the device. However, studies in humans have found no evidence of hearing loss in humans due to TMS. In 1995 the Food and Drug Administration determined that transcranial magnetic stimulators, delivering less than one pulse a second, "does not now present a potential for serious risk to health." As a precaution ear plugs are used in this study. Patients will wear soft earplugs with NRR of 30 dB or higher. Earphones that cover the ears (and thus, also the ear plugs) will be used during rTMS sessions to provide sham noise. This setup should greatly reduce the possibility of hearing loss. For patients who have subjective hearing changes during or after the treatment, an audiology consultation will be requested on their behalf for further evaluation.

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 experiment will end at either the normal termination or whenever the subject decides to withdraw from the study.
In the event that an interim analysis demonstrates futility, the ME determines unacceptable level of risk, regulatory agencies mandate discontinuation of the study, or a product recall occurs that necessitates stopping the study, any planned treatments will be immediately discontinued. Subjects will will be asked to complete the end-of-study assessments as described in the 4 month follow-up visit. At the end of one year post-treatment monitoring period, study team will contact the participant the study team will contact the participants by phone and inquire about the presence of any symptoms or event suspicious for seizure.

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?

At each visit, participants will be asked about any adverse events that may have occurred since the last visit. Information about adverse events (including any injuries, illnesses, hospitalizations, deaths, or suicides; this would include any adverse effects on sleep caused by study procedures) is collected at each visit by the interviewer. Any potentially serious problem is brought immediately to the Principal Investigator for review. In addition, sleep quality will be evaluated as part of the treatment protocol. Note that in this elderly population a wide variety of unrelated adverse events, such as falls, hospitalizations, illness, and even death, are not unexpected. The Principal Investigator will review all reported Adverse Events and Serious Adverse Events as soon as possible after the occurrence. SAEs are reported to IRB within 72 hours after the Principal Investigator is notified, as required by local IRB rules. All data entered into the database is monitored by the database manager. A formal review of the accumulating data and any data integrity issues is conducted at a meeting of the Principal Investigator

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and the data manager every 3 months during the active data collection period.

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 monitoring entity (ME) is a group of experts in the area of rTMS, clinical trials, and biostatistics that will review the progress of the study and monitor 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 annually to review data reports prepared by our staff. At the six-month interval between the annual meetings, the ME will receive a data report for their review. 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. This group will receive outcome data during the course of the study.

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.

Steven Chao, MD – Neurologist, expertise in clinical trials and Dementia. Wes Ashford, MD – Psychiatrist, expertise in clinical trials, dementia, and rTMS. Patricia Suppes, MD - Physician experienced mental health and research.

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.

All Adverse Events and Serious Adverse Events will be reviewed by the Protocol Director as soon as possible after the occurance.

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?

Information about adverse events is collected at each visit by the interviewer. Any potentially serious problem is brought immediately to the Protocol Director. All data entered into the database is monitored by the Protocol Director and the database manager. The board will meet every 6 months.

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'.

see 2g.

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.

The Protocol Director and the IRB.

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.

rTMS could potentially generate substantial health benefits for VHA patients. Repetitive TMS may offer a viable treatment option for Veterans with Alzheimer's disease. Moreover, it could be disseminated and delivered to both urban as well as to rural facilities, and in VA Hospitals as well as Community Based Outpatient Clinics (CBOC's). In sum, rTMS has the potential to dramatically improve access to effective mental and cognitive health and rehabilitation for a large number of severely ill VA patients. For these reasons, the anticipated risks are reasonable in relation to the anticipated benefits to research participants and others.

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).

During screening, participants will meet in a private interview room with a member of the study team to sign the consent form, discuss the protocol, and determine suitability for enrollment. All 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 identifiable information or PHI:
- full name,
- social security number (for VA hospital registration and payment),
- telephone number (for communication),
- mailing address (for appointment notices and to mail payment),
- date of birth (study metric),
- date of visit,
- VA CPRS medical record
- Medical history and physical examination information,
- Demographic information (gender, ethnicity, education)
- Medications
- Progress notes,
- Biological specimens (e.g. blood, spinal fluid),
- Diagnostic/Laboratory test results,
- Discharge summary,
- Survey/Questionnaire responses,
- Cognitive and Psychological test results.

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.

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Provide any additional information on ALL data security measures you are taking. You must use secure databases such as https://researchcompliance.stanford.edu/panels/hs/redcap RedCap. 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 for more information for securing mobile computing devices. Additionally,any PHI data on paper must be secured in an locked environment.

By checking this box, You affirm the aforementioned. Y

Paper data with PHI will be kept in locked file cabinets and electronic files are maintained on a secure VA network, on a server located in a secure server room accessible only by authorized personnel. Electronic records are maintained in secure, password-protected databases. Only staff listed for a given protocol are granted access to appropriate server folders.

Computers will be password protected. Laptops and removable drives will be encrypted. Computer data backups will be stored in locked cabinets.The MIRECC is located in a locked area of Building 5 at the VAPAHCS, and locked doors control access to the area. Offices are locked when not occupied.

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. REDCap data are transmitted from behind the VA firewall (on the VA intranet) and REDCap servers are housed at the VA Informatics and Computing Infrastructure (VINCI). VINCI servers are physically located at the VA Austin Information Technology Center (AITC), located in Austin, Texas. REDCap is only available to VA researchers through a web URL that requires a VA generated login and email address. 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). All personnel involved in this study will have successfully completed 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.

Biomarker/genetic information is stored in a separate password-protected file, , which can only be accessed by the PI ,the data manager, and appropriately delegated staff. Only the PI can match genetic information with the subject ID number. The genetic data is only used for analysis of data conducted by the PI or data manager in this study unless the subject or legally authorized representative consents to future use and sharing of genetic data and samples as documented on the informed consent document.

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.

Data and specimens will be given a code and information linking code

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and PHI will be kept on a secure, password protected computer behind a firewall. The Data Manager is responsible for de-identification. The PI has the code key and is ultimately responsible for de-identification of samples.

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).

Members of the research team will have access to all non-genetic data. The data manager has no access to any subject names or contact information.

If the subject requests it explicitly (in writing), we will send information about neuropsychological assessments and clinical results to his/her personal physician.

De-identified study data may be shared with collaborating researchers at Stanford University and at other institutions. De-identified data may also be shared with collaborating researchers at other institutions in the future. No names, social security numbers, genetic and biomarker samples, or other identifying data will be shared with anyone outside of this research study unless the subject or legally authorized representative consents to future use and sharing of genetic data and samples as documented on the informed consent document.

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 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 of the established 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 .

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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
Jauhtai Joseph Cheng	PD	jauhtai.cheng2@va.gov	N	10/10/2019		
Laura Lazzeroni	OP	Lazzeroni@stanford.edu	N	10/10/2019		
Jerome A Yesavage	OP	yesavage@stanford.edu	N	10/11/2019		

13. Consent Background

13. 1 Consent 2017-2018 - 1604 rTMS and Dementia Consent

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) The persons obtaining consent will be one of the investigators, the study coordinator, or a research assistant, who have been trained to give informed consents. (ii) The consenting interview is always done after the potential research subject (and, if required, the legally authorized representative) has been presented with a description of the study and indicated interest in participating, and before any information is collected, or any questionnaires answered. The consenting interview typically takes place in one of the private interview rooms in the MIRECC. (iii) Enough time will be allowed for the consent discussion for the potential participant or LAR to make an informed decision, and to ask any and all questions they may have and discuss the study with the researchers. We estimate this will take between 30 minutes and one hour. (iv) The potential participant and LAR may take the consent home to discuss with family or others, and return later to sign it if they so desire. (v) Every attempt will be made to ensure the participant and LAR does not feel coerced. Participants are allowed as much time as needed to discuss the project with the research staff. If desired by the participant, the signing of the consent is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others. We believe that the payment offered for participation is not great enough to entice a person to participate if they do not want to do so. (vi) Not applicable. Re-Consenting process: One of the participant developed seizure six months after the RTMS treatment, which is beyond the four months follow up period of the original protocol. The study team is proposing to extend the post-treatment monitoring period from four months to one full year to assess the risk of seizure associated with RTMS treatment. This re-consenting process will allow the study team to have eight additional months (i.e., one full year counting from the last day of active RTMS treatment) to monitor the occurrence of any events or symptoms the participants might have that may be suspicious for

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seizure. The re-consent process will be done in the following manner: Study team will prepare the re-consent form and a letter to the participant to explain the reason for re-consenting and the process involved. Once approved, the study team will mail the participants the letter and updated consent, asking the participant to sign and return. The study team will follow up by phone. Once the study team receives the signed re-consent from, the team member will countersign the document and send a copy back to the veteran.

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.

The potential participant or LAR will be asked questions about the study to make sure they understand. All participants will have a good understanding of English, since the standardized forms, questionnaires, and tests used are not currently available in other languages. Hearing impairment severe enough to impair comprehension is an exclusion criteria for a similar reason.

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.

We expect all persons with the diagnosis of mild cognitive impairment who meet inclusion criteria will have capacity to give informed consent. When in doubt, a trained clinician will make the competency evaluation based on a brief clinical interview, according to VA guidelines. In most cases, the participant with the diagnosis of mild cognitive impairment is competent to give consent for research. If the person lacks capacity, then a proxy (legally authorized representative) will need to sign the consent form. The patient's assent will be obtained & documented by also including their signature on the ICF. Prospective participants who meet diagnostic criteria of dementia will be deemed unable to give consent and a surrogate decision maker has to give the consent. Cognitive impairment is not always associated with the lack of capacity for informed consent to research. The majority of potential participants this study will have mild Alzheimer's disease, and thus are expected to be capable of giving informed consent to participate in research. We will first screen all potential participants using a telephone interview with the participant and/or caregiver, chart review, or referral from treating physicians so that we have a rough idea of the participants general cognitive status. When the participant and caregiver arrive study staff will first engage in conversation designed to give a rough idea of the potential participant's general cognitive status. If there is any question about a potential subject's capacity to give informed consent, they will be evaluated by the study physician prior to consent for competency, and appropriate VA protocol will be followed, including, if indicated, evaluation by two physicians. If the person lacks capacity (but is still eligible for the study), then the patient's assent will be obtained & documented, and a proxy (legally authorized representative, as specified by VA regulations) will need to sign the consent form. In any case, we will always go over the consent form with both the participant and the caregiver/study partner. We feel a separate assent form is not needed for this reason. We will follow the recommendations set out in the Alzheimer's Association position paper, "Research Consent for Cognitively Impaired Individuals" (AD & Assoc Disorders 2004 (vol 18, pp 171-175) (attached).

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.

The persons obtaining consent will be one of the investigators, (Dr. Cheng) the study coordinator (TBN), or a research assistant(TBN), all of whom have been trained to give informed consents. All staff have completed the required training in Human Subjects, Good Clinical Practice, and HIPAA.

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?

Consent will be obtained from the participant. All participants involved in the study will be able to participate in the decision-making process by providing assent or consent as we will exclude individuals with severe dementia and/or mental illness. If a potential subject's competency is in question, a trained clinician will make the competency evaluation based on a brief clinical interview, according to VA guidelines. In most cases, the participant is competent to give consent for research. If the person lacks capacity, then the patient's assent will be obtained and documented, and a proxy (informed legally authorized representative) will be asked to sign the consent form. The LAR is usually the study partner (a spouse or adult child of the participant).

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?

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Participants are allowed as much time as needed to discuss the project with the research staff. If desired by the participant, the signing of the consent is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others.

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

Participants are allowed as much time as needed to discuss the project with the research staff. If desired by the participant, the signing of the consent is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others.

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)?

All information presented to the participant, including anything they must sign, has been approved by the IRB.

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.

13. 2 Waiver of Documentation 1604 Telephone Screen rTMS for Dementia

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) The person conducting the phone screen will be one of the investigators, the study coordinator, phone screens and consents. (ii) The phone screen is always done after the potential participant indicated interest in participating, and before any information is collected, or any questionnaires answered. (iii) Enough time will be allowed for the consent discussion for the potential participant to make an informed decision, and to ask any and all questions they may have and discuss the study with the researchers. We estimate this will take around 30 minutes. (iv) The potential participant may stop the phone interview to discuss with family or others, and call back later to complete it if they so desire. (v) Every attempt will be made to ensure the participant does not feel coerced. Participants are allowed as much time as needed to discuss the project with the research staff. The potential participant is free to stop the interview or hang up the phone at any time. (vi) Not applicable.

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.

The potential subject will be asked questions about the study to make sure they understand. All participants will have a good understanding of English, since the standardized forms, questionnaires, and tests used are not currently available in other languages. Hearing impairment severe enough to impair comprehension is an exclusion criteria for a similar reason.

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.

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We expect all persons with the diagnosis of mild cognitive impairment who meet inclusion criteria will have capacity to give informed consent to a telephone interview. Cognitive impairment is not always associated with the lack of capacity for informed consent to research. The majority of potential participants this study will have mild cognitive impairment or mild Alzheimer's disease, and thus are expected to be capable of giving informed consent to participate in research. We will first screen all potential participants using our standard telephone interview We will follow the recommendations set out in the Alzheimer's Association position paper, "Research Consent for Cognitively Impaired Individuals" (AD & Assoc Disorders 2004 (vol 18, pp 171-175) (attached).

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.

The persons conducting the phone interview will be one of the investigators, (Dr. Cheng) the study coordinator (TBN), or a research assistant(TBN), all of whom have been trained to give informed consents. All staff have completed the required training in Human Subjects, Good Clinical Practice, and HIPAA.

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?

Consent will be obtained from the participant. All participants involved in the study will be competent to participate in the decision-making process as we are excluding individuals with serious dementia and/or mental illness. If a potential subject's competency is in question, the phone interview will be ended.

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?

Participants are allowed as much time as needed to discuss the project with the research staff. If desired by the participant, completion of the phone interview is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others.

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

Participants are allowed as much time as needed to discuss the project with the research staff. If desired by the participant, completion of the phone interview is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others.

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)?

All information presented to the participant, including anything they must sign, has been approved by the IRB.

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

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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 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:

The phone interview presents minimal risk.

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

15. HIPAA Background

15. 1 Authorization **4.7.16 hipaa ftms and dementia**

15. 2 Waiver of Authorization for Recruitment **chart review**

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.**

We will do chart reviews and use CPRS to identify potential participants. We are collecting the following identifiable information or PHI: • full name, • social security number (for VA hospital registration and payment), • telephone number (for communication), • mailing address (for appointment notices and to mail payment), • date of birth (study metric), • date of visit, • VA CPRS medical record • Medical history and physical examination information, • Demographic information (gender, ethnicity, education) • Medications • Progress notes, • Biological specimens (e.g. blood, spinal fluid), • Diagnostic/Laboratory test results, • Discharge summary, • Survey/Questionnaire responses, • Cognitive and Psychological test results.

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.**

All data will remain inside the VA firewall or on REDCap as described previously (section 11).

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.**

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All data will remain inside the VA firewall, and will be retained or destroyed according to VA requirements.

15. 3 Waiver of Authorization phone screen

a) Describe the Protected Health Information (PHI) needed to conduct the research. PHI is health information linked to HIPAA identifiers. List BOTH health information AND HIPAA identifiers. If you are using STRIDE, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol.

Names, phone numbers and addresses will be collected at the phone screen in order to be able to contact the participants for initial visit and the follow-up visits. The participants' birth date will be required, as age is an exclusion criteria.

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.

All data is entered into a password-protected electronic database. Contact data (names, phone numbers) is kept separate from all other data about a subject. Only subject IDs, , are entered into the electronic database containing research data. Additionally, genetic information is stored in a separate password-protected file, in a separate location, which can only be accessed by the PI or authorized personnel. Only the PI can match genetic information with the subject ID number. The genetic data is only used for analysis of data conducted by the PI alone. All other data is entered into the master electronic database. Once entered into the electronic database, the raw data is then filed away. All hardcopy data files are housed in locked storage with accessibility only by the PI and approved members of the research team. Confidentiality is assured and no information is released to persons other than the subject without permission.

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.

Data will be kept in a secure location until the research has concluded and appropriate waiting periods have ended, as mandated by applicable regulations. At that time, paper data will be shredded and electronic data will be erased using the best available methods.

16. Attachments

Attachment Name	Attached Date	Attached By	Submitted Date
Cheng 3800956	08/13/2015	emilyg	
AlzAssocResConsentIRB	08/13/2015	emilyg	
Cheng VARQs_APP1m(1)	08/20/2015	emilyg	
CITI Kinoshita 2015-11	11/24/2015	emilyg	

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CITI Lazzaroni 2015-03	11/24/2015	emilyg	
1511 Cheng Assent rTMS Dementia	12/07/2015	kdphung	
1604 ad Brochure rTMS and dementia	04/12/2016	emilyg	
1604 CRF AE Form	04/12/2016	emilyg	
1604 CRF Baseline Form	04/12/2016	emilyg	
1604 CRF Contact Information	04/12/2016	emilyg	
1604 CRF Medical History	04/12/2016	emilyg	
1604 CRF Medication	04/12/2016	emilyg	
1604 CRF Physical Exam	04/12/2016	emilyg	
1604 Prospective Participant Letter	04/12/2016	emilyg	
1604 rTMS Treatment Log	04/12/2016	emilyg	
Having a Lumbar Puncture	04/12/2016	emilyg	
1604 Seizure Protocol	04/12/2016	emilyg	
1604 ad Study Flyer rTMS and Dementia	04/13/2016	emilyg	
1604 ad Info card.rTMS dementia	04/13/2016	emilyg	
1605SummaryBrainRegistry	05/31/2016	emilyg	
1605TellMeMoreBrainRegistry	05/31/2016	emilyg	
MoCA-Test	05/31/2016	emilyg	
CITI McNerney 2015-08	06/29/2016	emilyg	
CITI Reif 2014-09 Human Subjects	06/29/2016	emilyg	
Recruitment messaging_rTMS&Dementia_2016.08.15v3	08/19/2016	emilyg	
1701 ad Flyer rTMS and Dementia	02/02/2017	labibas	
1701 ad Brochure rTMS and Dementia	02/02/2017	labibas	
2017.02.15 Monitoring Entity Meeting Minutes	10/10/2017	jauhtaic	
2017.06.12 Monitoring Entity	10/10/2017	jauhtaic	

Meeting Minutes			
rMTS_ME_Report 1	10/10/2017	jauhtaic	
rTMS_ME_Report_2	10/10/2017	jauhtaic	
ME Report 3	09/28/2018	labibas	
ME Report 4	09/28/2018	labibas	
2017.12 Report 3 Minutes	09/28/2018	labibas	
2018.08 Report 4 Minutes	09/28/2018	labibas	
letter to veterans for one year extension	11/05/2018	sheenad	
2019.10.10 Monitoring Entity Meeting Minutes	10/10/2019	jauhtaic	
Data Monitoring Meeting 10_10_2019	10/10/2019	jauhtaic	
AuditReport	10/11/2019	jauhtaic	
Statistical Analysis Plan	01/27/2020	jauhtaic	

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

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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)

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.

A document named "Statistical Analysis Plan" is being submitted for IRB's review. Per ClinicalTrials.gov, this is required for reporting clinical trial results to ClinicalTrials.gov. This document reads:
==========
RTMS for Dementia Statistical analyses Plan:
Primary Hypothesis 1 (Primary Memory Outcome): rTMS will lead to higher performance on the California Verbal Learning Test (CVLT-II) compared to performance by participants in the sham treatment group at the termination of treatment.
Secondary Hypothesis 2 (Secondary Cognitive Outcomes): rTMS- will lead to higher performance on secondary cognitive measures relating to language (Animal Fluency and Boston Naming Test, BNT), visual memory (Brief Visual Memory Test, BVMT) and executive functioning and processing speed (Trail making A&B), compared to performance by participants in the sham treatment group at the termination of treatment.
Secondary Hypothesis 3 (Exploration of Mechanism of Action): rTMS-induced memory improvement parallels changes in BDNF levels after treatment.

Mixed model analysis will be used to compare performance on the primary neuropsychological measures (CVLT-II Long-Delay Free Recall and Cued Recall and CVLT Short-Delay Free Recall and Cued Recall) by the treatment and control group at the cessation of treatment and at 4 months after cessation of treatment. Secondary analyses will also be conducted to compare performance between the groups at the same time points on Animal Fluency, Boston Naming Test, Brief Visual Memory Test (BVMT) and Trail making A&B.

We expect that changes in BDNF measures relating to neuronal plasticity over the course of treatment may account for some of the observed effects of rTMS on memory. Therefore, mixed model analysis will also be used to compare BDNF levels at baseline and after the RTMS treatment.

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.