Study Protocol and Analysis Plan
Title: Transcranial Magnetic Stimulation for the Treatment of Veterans With Alcohol Use Disorders
NTC: 03191266
Date: 06/27/2025

Title : Transcranial Magnetic Stimulation for the Treatment of Veterans With Alcohol Use Disorders
Approval Period: 02/28/2025 - 02/28/2026

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Protocol Director

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
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CITI Training current				Y

Admin Contact

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Timothy Durazzo				Professor-Univ Med Line
Department	5717	**Phone**		**E-mail**
Psych/Public Mental Health & Population Sciences		4156867609		tdurazzo@stanford.edu
CITI Training current				Y

Investigator

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

Other Contact

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Claudia Beatriz Padula		PhD		Instructor (Affiliated) [VAPAHCS]
Department		**Phone**		**E-mail**
Psychiatry VA Research		650-493-5000		padula@stanford.edu
CITI Training current				Y

Academic Sponsor

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

Other Personnel

Name	**Degree (Program/year if student)**	**Position, e.g. Assistant Professor, Resident, etc.**

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Jerome A Yesavage		MD		Professor
Department		**Phone** (650) 852-3287	(650) 852-3297	**E-mail** yesavage@stanford.edu
CITI Training current				Y

Name Keith Humphreys		**Degree (Program/year if student)** PhD		**Position, e.g. Assistant Professor, Resident, etc.** Professor
Department Psych/Public Mental Health & Population Sciences	5717	**Phone** (650) 723-9067	(650) 617-2736	**E-mail** knh@stanford.edu
CITI Training current				Y

Name Laura Lazzeroni		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.** Professor
Department		**Phone** (650) 723-0947		**E-mail** Lazzeroni@stanford.edu
CITI Training current				Y

Name Meng Gu		**Degree (Program/year if student)** PhD		**Position, e.g. Assistant Professor, Resident, etc.** Sr Res Scientist-Physical
Department Rad/Radiological Sciences Laboratory	5488	**Phone**		**E-mail** mgu@stanford.edu
CITI Training current				Y

Name Margaret Windy Mcnerney		**Degree (Program/year if student)** PhD		**Position, e.g. Assistant Professor, Resident, etc.**
Department Psychiatry VA Research		**Phone**		**E-mail** windymc@stanford.edu
CITI Training current				Y

Name Arthur Noda		**Degree (Program/year if student)** MS		**Position, e.g. Assistant Professor, Resident, etc.** Research Data Analyst
Department Psych/Public Mental Health & Population Sciences		**Phone** (650) 493-5000	(650) 852-3297	**E-mail** artnoda@stanford.edu
CITI Training current				Y

Participant Population(s) Checklist **Yes/No**

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• Children (under 18)	N
• Pregnant Women and Fetuses	N
• Neonates (0 - 28 days)	N
• Abortuses	N
• Prisoners	N
• International Participants	N
Please enter the countries separated by comma	
• Impaired Decision Making Capacity	N
• Cancer Subjects	N
• Laboratory Personnel	N
• Healthy Volunteers	N
• Students	N
Stanford students N Other students N	
• Employees	N
• Other (i.e., any population that is not specified above)	Y

Study Location(s) Checklist

	Yes/No
• Stanford University	Y
• Clinical & Translational Research Unit (CTRU)	
• Stanford Medicine Health Care	
Tri-Valley	
• Stanford Medicine Children's Health	
• VAPAHCS (Specify PI at VA)	Y
Timothy C. Durazzo, PhD	
• Other (Click ADD to specify details)	

General Checklist

1. Multi-site

	Yes/No
• Is this a multi-site study? A multi-site study uses the same protocol to conduct human subjects research at more than one site.	N

2. Cooperative/Collaborative Study?

	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

3. Cancer Institute

Yes/No

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• 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

4. Clinical Trials	**Yes/No**
• Investigational drugs, biologics, reagents, or chemicals?	N
• Commercially available drugs, reagents, or other chemicals administered to subjects that are being studied?	N
• Investigational Medical Device / Commercial Medical Device used off-label or if being studied?	Y
• IDE Exempt Device (Commercial Medical Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Medical Devices)	N
• Will this study be registered on clinicaltrials.gov? (See Stanford decision tree)	Y
• Who will register for ClinicalTrials.gov? NCT# 03191266	N

5. 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 Material Transfer Agreements	N

6. Biosafety (APB)	**Yes/No**
• Are you submitting a Human Gene Transfer investigation using a biological agent or recombinant DNA vector? If yes, please complete the Gene Transfer Protocol Application Supplemental Questions and upload in Attachments section.	N
• Are you submitting a Human study using biohazardous/infectious agents? If yes, refer to the https://ehs.stanford.edu/forms-tools/genome-editing-and-gene-drives-stanford Administrative Panel on BioSafety website prior to performing studies.	N
• Are you submitting a Human study using samples from subjects that are known or likely to contain biohazardous/infectious agents? If yes, refer to the https://ehs.stanford.edu/forms-tools/genome-editing-and-gene-drives-stanford Administrative Panel on BioSafety website prior to performing studies.	N

7. Human Embryos or Stem Cells	**Yes/No**
• Human Embryos or Gametes?	N
• Human Stem Cells (including hESC, iPSC, cancer stem cells, progenitor cells)	N

8. Veterans Affairs (VA)	**Yes/No**

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• 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

9. Equipment **Yes/No**

• Use of Patient related equipment? If Yes, equipment must meet the standards established by Biomedical Engineering (BME) (650-725-5000)	N
• Medical equipment used for human patients/subjects also used on animals?	N
• Radioisotopes/radiation-producing machines, even if standard of care? ; More Info	N

10. Payment **Yes/No**

• Subjects will be paid/reimbursed for participation? See payment considerations.	Y

11. Funding **Yes/No**

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

Funding

Funding - Grants/Contracts/Agreements

Funding Administered By :	VA	**SPO/RRA # (if available) :**	pending
Grant # (if available) :	RX002303-01A2	**Funded By/Partner (include pending) :**	Department of Veterans Affairs RR&D
Principal Investigator :	Timothy C. Durazzo		

Grant/Contract Title if different from Protocol Title :

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

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Funding - Fellowships

Gift Funding

Dept. Funding

Other Funding

Resources :

a) Qualified staff.

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

Qualification of PI:
Timothy C. Durazzo, PhD (PI/PD): Dr. Durazzo is a licensed Clinical Psychologist in CA, with specialization in Clinical Neuropsychology and formal training in neuroscience and magnetic resonance neuroimaging. He is the attending Clinical Neuropsychologist for the War Related Injury and Illness Study Center (WRIISC) and Research Scientist for the Mental Illness Research and Education Clinical Center (MIRECC) at the VA Palo Alto Health Care System (VAPAHCS). He concurrently holds a faculty appointment as an Associate Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. He conducts psychoeducational/therapy groups at the VAPAHCS Addiction Treatment Services. He has have served as PI, Co-Investigator on multiple NIH and DoD grants. A major component of his research program focuses on the neurobiological and neurocognitive consequences of alcohol and substance use disorders, the factors that influence recovery from these conditions, and the mechanisms promoting the relapse/remit cycle in addictive disorders. He has extensive experience in the recruitment, screening, longitudinal cohort maintenance, fiduciary management, supervision of students, technicians and fellows, and the day-to-day administration of federally funded grants. He has expertise in the administration and interpretation of all proposed psychiatric, neuropsychological, and psychosocial measures, as well as in the acquisition and processing of data from all the magnetic resonance methods proposed in this project. The PI has received extensive training in TMS safety and administration, is certified to administer TMS in clinical and research settings, and will deliver all TMS procedures in conjunction with this study. He will direct the day-to-day conduct of the study, train and supervise project personnel, consult with Drs. Yesavage and N. Williams and Ashford (as needed)to determine eligibility of prospective participants, oversee data collection, entry and management, and conduct or supervise all statistical analyses.

Qualifications of Other Personnel:
Jerome Yesavage, MD: Dr. Yesavage is a Psychiatrist, ACOS Mental Health, and Director of VISN 21 MIRECC at the VAPAHCS and Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. Dr. Yesavage has extensive experience as PI and Co-Investigator in clinical trials of rTMS treatment in multiple populations and in the diagnoses and treatment of mental disorders. Dr. Yesavage will serve as a study physician for the rTMS treatment component of this application (i.e., be available for medical emergencies and consultation) and will directly assist the PI on supervising rTMS safety, protocol adherence, and assessment for adverse events. Dr. Yesavage will also be involved in data interpretation, manuscript preparation, and dissemination of findings via Posters or Presentations at professional conferences.

Keith Humphreys, PhD: Dr. Humphreys is a Career Research Scientist at the Center for Healthcare Evaluation, VAPAHCS and Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. Dr. Humphreys also co-directs the Neurochoice Initiative at Stanford Neuroscience Institute which among other projects is using fMRI and other MR technology to

predict the outcome of alcohol and methamphetamine dependent Veterans in psychosocial addiction treatment. He will assist the PI in statistical analyses, manuscript preparation and provide additional guidance and advice on cohort maintenance and follow-up data collection. Dr. Humphreys will also be involved in data interpretation, manuscript preparation, and dissemination of findings via Posters or Presentations at professional conferences.

Claudia B. Padula, PhD: Dr. Padula has experience with and continues her training in behavioral and cognitive testing, functional MRI, study design, execution and analysis via her VA Career Development Award. She is a Research Health Scientist Specialist at the VAPAHCS and Clinical Instructor at the Stanford University School of Medicine. Dr. Padula has extensive experience in the recruitment, screening, longitudinal cohort maintenance, fiduciary management, supervision of students, technicians and fellow's expertise in the administration and interpretation of all proposed psychiatric, neuropsychological, and psychosocial measures, as well as in the acquisition and processing of data from all the magnetic resonance methods proposed in this project.

Laura Lazzeroni, PhD: Dr. Lazzeroni is an Associate Professor and Biostatistician in the Department of Psychiatry and Behavioral Sciences at the Stanford University School of Medicine. She will act as the primary biostatistician and assist the PI in conducting standard and advanced survival analysis modeling, and provide any assistance needed for the successful execution of the project's data collection and analysis. Dr. Lazzeroni will also be involved in data interpretation, manuscript preparation, and dissemination of findings (via Posters or Presentations) at professional conferences.

Meng Gu, PhD: Dr. Gu is an electrical engineer, magnetic resonance (MR) physicist, and research associate at Lucas Center for Imaging and Spectroscopy in the Department of Radiology at Stanford University. He is an expert in MR spectroscopy implementation, testing, acquisition, processing. Dr. Gu has developed novel pulse sequences, reconstruction and quantification methods for better metabolite detection, which have been extensively used by investigators at Stanford University and other institutions. He will be responsible for maintaining the integrity of MR spectroscopy pulse sequences on VA scanners, and directly assist the PI in spectroscopy volume localization, spectroscopy data quality evaluation and quality assurance, and data processing. He will assist Dr. Furst in maintaining the integrity of structural and perfusion MR pulse sequences on the VA 3T GE scanner. Dr. Gu will also be involved in data interpretation, manuscript preparation, and dissemination of findings (via Posters or Presentations) at professional conferences.

Daniel Spielman, PhD: Dr. Spielman is an electrical engineer, senior magnetic resonance (MR) physicist and Professor of Radiology at Lucas Center for Imaging and Spectroscopy in the Department of Radiology at Stanford University. He has over 25 years of experience as a medical imaging researcher in the field of vivo MR imaging and spectroscopy and the development of new methods of imaging metabolism within the body. Dr. Spielman has multiple years of experience in spectroscopy studies of individuals with different neuropsychiatric disorders. He will directly support the PI and Dr. Gu on spectroscopy data acquisition and processing, and provide relevant updates on advancements in the acquisition and processing methods utilized in this project.

Margaret Windy McNerney, PhD: Dr. McNearney is a postdoctoral scholar in the Stanford/VA WRIISC Fellowship and has a submitted application for a VA Career Development Award. She has extensive experience and current certification in the processing, genotyping and quantitation of genetic biomarkers associated with this study.

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 study personnel involved in this protocol, as well as those that may join at a later point, will be given all protocol materials, including background materials and the IRB proposal. The core study personnel, Drs. Durazzo, Padula, Yesavage, and Research Assistants (RAs) will meet weekly to discuss the ongoing

research and ensure that all personnel are appraised of any updates in the protocol. Study personnel will also communicate regularly with each other as to the progress of each person's roles and responsibilities within the protocol. Study personnel that will be performing magnetic resonance scans at the VAPAHCS are trained MRI technicians and will complete appropriate safety training courses required for users of those facilities prior to scanning participants. All core study personnel will also be trained on the necessary procedures and forms for informed consent form and participant compensation. Further, study personnel operating at the VA will be approved by the VA to conduct research on VA premises.

c) Facilities.

Provide the location(s) where the research will be conducted, including physical address if not conducted on site at Stanford University, Stanford Hospital on Pasteur Dr., Lucile Packard Children's Hospital on Welch Rd. or VAPAHCS. Describe the facilities and resources available to conduct the research at these sites.

The facilities are available to support each component of the protocol:

Recruitment and screening: The VAPAHCS substance abuse treatment clinics and providers are available to support recruitment and screening of patient participants. These activities will be carried-out at the VAPAHCS MIRECC, Building 5, 4th floor or at participants' substance abuse treatment clinic at the VAPAHCS, depending on which location is most convenient for the participant. Private interview/exam rooms are available for this purpose at both locations.

Consent: Conducted at the VAPAHCS MIRECC, Building 5, 4th floor and/or at participants substance abuse treatment clinic at the VAPAHCS, depending on which location is most convenient for the participant. Private interview/exam rooms are available for this purpose at both locations.

Clinical interview, neuropsychological and behavioral testing: Conducted at the VAPAHCS MIRECC, Building 5, 4th floor. Private interview rooms are available for this purpose. Neuropsychological and behavioral testing will be undertaken using computerized and paper-and-pencil measures.

Transcranial Magnetic Stimulation: Conducted at the VAPAHCS MIRECC, Building 5, 4th floor. Private treatment rooms are available for this purpose.

Neuroimaging:
Magnetic resonance scans will be conducted at the VAPAHCS. A 3 Tesla GE Discovery 750 MRI scanner with a 32-channel head coil is available at the VAPAHCS Diagnostic Radiology Center (Bldg. 102) directly adjacent to Building 5 (where MIRECC offices are located). Equipment is available for measurement of patient's vital signs and other parameters for monitoring patient safety. All MRI data will be securely transferred via the network to Dr. Durazzo's lab space.

Genetics: The MIRECC Genetics and Translational Laboratories are in Building 7, in Dr. McNerney's Lab.

d) Sufficient time.

Explain the time that you and your research team will allocate to perform the research activities, including data analysis.

We expect to begin participant recruiting participants from 11/2017-06/2023 with an end date of 09/2024. We anticipate running 100 total participants over 4 years 50 active TMS, 50 sham rTMS. With the addition of two RAs in 11/2017, we will have sufficient personnel and physical resources to successfully execute all Aims of this protocol.

e) Access to target population.

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

required number of participants.

Subjects for the study will be identified via the VAPAHCS Addiction Treatment Services ATS for recruitment of individuals with alcohol use disorder. Access to this population is provided via the support of the Director of the Foundations of Recovery (FOR; the primary recruitment site), Dr. Marina Urman-Yotam, MD (see attached letter of support). The census for ATS programs, particularly the FOR over the past 12 months indicates it is very feasible to meet the required target number of participants. The majority of participants will be recruited from the FOR, which is a residential treatment program; therefore, 24 hour monitoring for any adverse events will be in place as an additional layer of participant safety.

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.

If a medical adverse event should occur, study staff includes two VA physicians who are board-certified in psychiatry (Drs. Yesavage and Ashford). Additional medical assistance will be available through the VA TMS clinical roll-out staff RN's and physicians trained in TMS safety and adverse event management, and VAPAHCS Emergency Department service is readily available, if needed. Immediate psychiatric/psychological consultation will available for participants if required via Dr. Durazzo (Licensed Clinical Psychologist) and/or Drs. Yesavage and Ashford (Board Certified Psychiatrists. Appropriate referrals will be made when necessary in the judgment of the PI or study physicians.

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

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

1. Purpose

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

The purpose of this study is to evaluate the efficacy of intermittent theta burst (iTBS) transcranial magnetic stimulation (TMS) as a treatment for Veterans with an alcohol use disorder (AUD) to decrease the exceedingly high rate of relapse associated with this condition.

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

At least 60% of those with AUD will experience a major relapse period within 6 months of treatment, irrespective of the intervention (psychosocial and/or pharmacological) employed. Consequently, the high prevalence of AUD and relapse following treatment in Veterans is associated with substantial resource allocation and costs for the DVA Health Care System. Current pharmacological and psychosocial interventions demonstrate only a moderate level of efficacy, which is reflected in the high rate of relapse in AUD.

iTBS-TMS is a neurostimulation method that is at the forefront of innovative, non-invasive, and safe treatments for AUD, and the disorders that commonly co-occur with AUD. To reduce the high rate of relapse in Veterans with AUD, it is necessary for interventions to more effectively address the associated neurobiological dysfunction

and salient co-occurring conditions. Accordingly, additional rigorously controlled studies are required to determine if iTBS-TMS is an effective treatment for Veterans with AUD.

This double-blind placebo controlled project will deliver completely novel data on the efficacy of iTBS-TMS to promote sustained abstinence for Veterans with AUD during the first 6 months following treatment. Monthly monitoring over the entire first 6 months following treatment is crucial, given relapse within the first 6 months of treatment is robustly related to poor psychosocial functioning over the ensuing 1-3 years. The ultimate goal of this proposal is provide treatment that more effectively promotes sustained abstinence in the Veteran with AUD, as extended abstinence is robustly associated with optimum biomedical, neuropsychological,psychiatric, and psychosocial recovery and functioning.

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)

The goal of this study evaluate the efficacy of iTBS-TMS as a treatment for Veterans with an AUD; therefore, humans must be studied.

2. Study Procedures

a) Please SUMMARIZE the research procedures, screening through closeout, which the research participant will undergo. Sections in the protocol attached in section 16 can be referenced, 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. For research involving collaborators, please specify the respective roles of Stanford and each collaborator on the protocol.

PROTOCOL SUMMARY:

Please note: Stanford Co-Investigators who are currently not WOC/Staff at the VA (i.e., Drs. Meng Gu, Daniel Spielman, N. Williams) will not personally execute any study procedure at the VA Palo Alto. Stanford Co-investigators will only be involved in processing and statistical analysis of de-identified neuroimaging, neuropsychological and genetic data.

1. Recruitment and screening: Participants will be recruited via VA Palo Alto Addiction Treatment Services.

2. Informed Consent: Prior to consent, The PI, or Co-I or qualified RA, will recheck inclusion/exclusion criteria.

3. Baseline/Pretreatment Assessment:

- Psychiatric Assessment
- Alcohol and Substance use
- Neurocognitive Assessment
- 3 Tesla Magnetic Resonance Neuroimaging: The study will use the 3T UHP system at the Cognitive and Neurobiological Imaging (CNI) facility. The UHP shares a common software and hardware architecture to GE's FDA-approved Premier system but uses a higher-performance gradient coil and is not FDA approved for diagnostic use and is subject to the 21 CFR 812 investigational device(IDE) regulations as well as 21 CFR 50 and 56. The system has been tested by GE according to UL606001-1 and also for compliance with IEC 60601-

2-33 (ed 3.1) -- meeting limits and guidelines for peripheral nerve stimulation, patient thermal, SAR limit, acoustic noise, flammability rating UL94-5VA for safety covers, hydrostatic pressure, electrical hazards, dielectric strength and pinch point. The MRI scans in this study will also utilize operational parameters within FDA guidelines for Nonsignificant Risk thus an Investigational Device Exemption (IDE) from FDA should not be necessary.
- Saliva sample as described in DETAILS OF RECRUITMENT, DESIGN AND TREATMENT below)

4. Treatment Phase: iTBS-TMS . Active iTBS-TMS Treatment Group – will receive a total of 20 treatments delivered 5-6 days/week, two (2) to

(3)treatments per day,
over 2 consecutive weeks. Sham Treatment group will receive the same frequency and duration of treatment, without actual administration of iTBS-TMS. The majority
of participants will be recruited from Palo Alto VA residential treatment programs; therefore, 24 hour monitoring for any adverse events will be in place as an additional layer of participant safety.

5. Post-Treatment Phase: Within 3-4 days of completion of the Treatment Phase, all participants will repeat neurocognitive assessment, select psychiatric assessment measures, select alcohol and substance questionnaires, 3 Tesla Magnetic Resonance Neuroimaging and blood draw. During this time, all participants will be receiving treatment-as-usual at the VA clinics, and scheduling of iTBS-TMS will be arranged as not to interfere with their daily treatment curriculum.

6. Monthly Follow-ups: For 1 year following completion of

active/sham iTBS-TMS treatment, participants will be contacted monthly,via telephone or in person, to complete brief standardized measures of alcohol and substance use, as well as craving to assess for changes in these variables over the preceding 30 days. These brief contacts will be 15-20 min in duration and tracking sobriety is the primary outcome measure of this study.

DETAILS OF RECRUITMENT, DESIGN AND TREATMENT
Recruitment and screening: Potential participants from the VAPAHCS treatment programs will be identified based on VA medical/clinical staff diagnoses of an alcohol use disorder without any comorbid condition any conditions that be contraindicated for study (e.g., taking medications that lower seizure threshold, magnetic resonance neuroimaging contraindications, medically confirmed seizure disorder). Specifically, medical/clinical staff of the programs listed above will identify potential participants who meet eligibility criteria and inform the patient that a research opportunity is available to them and offer contact information to study personnel or the participant may request that study personnel contact them. The study has been explained to clinicians via treatment team meetings, so they are familiar with eligibility criteria. The PI, Co-PI or qualified RA will check inclusion/exclusion criteria based on initial eligibility and sociodemographic data via in person screen at the treatment program or at the MIRECC, Building 5, 4th floor. Private interview rooms are available for this purpose at both locations.

Baseline/Pretreatment Assessment see section 2.a.3.b. of grant application:
a) Psychiatric Assessment: will use standardized measures employed in clinical practice and research.
b) Alcohol and Substance use: will use standardized measures employed in clinical practice and research. Participants will be asked to submit a urine sample to screen for illegal/non-prescribed drug use and/or complete a breathalyzer to screen for alcohol use.
c) Neurocognitive Assessment: will use standardized measures employed in clinical practice and research
d) 3 Tesla Magnetic Resonance Neuroimaging: will be conducted at the VAPAHCS.
e) Saliva samples: The PI, Co-PI or research assistant will collect saliva samples at Building 5. These samples will initially be stored in a locked cabinet in the PI or Co-Is office at VAPAHCS, Bldg. 5. Dr. McNerney will then take possession of the participants' saliva samples and take them to the VA-MIRECC Genetics Laboratory for DNA extraction, genotyping and biomarker quantitation

at the VA-MIRECC Translational Laboratory. These labs are located in Building 7 at VAPAHCS.

Design, Treatment Phase and Treatment Arms: This is a double-blind randomized group design, which will enroll 100 participants. After screening and baseline procedures, participants will be randomized to active or sham rTMS conditions (50 active, 50 sham); thus participants will have a 50% probability of receiving active treatment. Participants will receive 20 iTBS-TMS sessions over the course of 2 weeks. Participants will be required to be abstinent from alcohol and illicit substances for 5 days and demonstrate no clinically significant withdrawal symptoms prior to the first iTBS-TMS session.

Rationale for Brain Region Site: The left dorsolateral prefrontal cortex DLPFC) was chosen as the rTMS stimulation site given excitatory transcranial magnetic stimulation to this region has been demonstrated to decrease cravings in non-Veterans with AUD. Additional stimulation of this site has been robustly shown to be associated with decreased unipolar depressive symptomatology; depressive disorders are highly comorbid in Veterans with AUD.

Duration of Treatment Phase: Active iTBS-TMS Treatment Group – will receive a total of 20 treatments delivered 5-6 days/week. Participants will typically receive two treatments per day (Monday-Friday), over 2 consecutive weeks; inter-treatment interval will be at least 2 hours. However, in the event the participant is unable to complete the typical two iTBS-TMS sessions per day due to participant or research personnel illness, scheduling issues, or other unforeseen circumstances. There have been no adverse events reported in the literature implementing multiple iTBS sessions per day in any population. Sham Treatment group will receive the same frequency and duration of treatment, without actual administration of iTBS-TMS. For both the active and sham iTBS-TMS groups, sessions will typically be conducted prior to the beginning to the participants treatment day, and at lunch, as to not interfere with their treatment-as-usual in the VA substance treatment clinics.

Procedures for Delivery of rTMS Sessions:

1. Anatomical localization of the left DLPFC for the stimulation coil will be individualized for each participant and achieved through standardized procedures for EEG electrode placement, optimized for transcranial magnetic stimulation.

2. Motor Threshold MT Elicitation: Inherent to the safe and accurate dosing of iTBS-TMS stimulation, resting MT elicitation will be performed according to established protocols, which have been in use since 1994. This protocol is well- established as an effective method for MT Elicitation, widely implemented within both sham-controlled

transcranial magnetic stimulation research with demonstrated safety.
MT will be calculated for all participants prior to randomization.

3. iTBS-TMS Dosing: Dosing of iTBS-TMS will be delivered at 120% of the participants active MT adjusted to the skull to cortex distance (via
each participants structural MRI), as this is documented to modulate the desired cortical target, and is not associated with any adverse events. Six hundred (1200) pulses of iTBS-TMS
at 50 Hz will be utilized, consistent with standard parameters. There
will be 10 trains of 3 pulses at 50Hz every 200ms (50Hz over 5Hz), which is 30 pulses per theta burst train. Twenty (40) trains will be delivered to achieve 1200 pulses over approximately 6 minutes.

4. Sham Control and Blinding Methods: The sham-control and blinding methods will be the same as used in TMS trials in which investigator and participant blinding to group assignment was carefully documented and achieved in previous clinical trials conducted with Veterans at VA medical centers. These methods involve:

(a) the Cool-B65-Active/Placebo Coil, which functions as both an active and sham coil; (b) scalp electrodes; and (c) a white-noise generator. The scalp electrodes are used to pass a low-voltage, low-electric current (2–20mA at no more than 100V) to mimic the sensation of receiving actual iTBS. The white-noise generator is used to send low-volume white noise to the subject's ears when magnetic stimulation pulses are initiated to hide the click noise the iTBS-TMS produces.

Post-Treatment Phase: Within 3-4 days of completion of the Treatment Phase, all participants will repeat neurocognitive assessment, select psychiatric assessment measures, select alcohol and substance questionnaires, random urine substance screen and alcohol breathalyzer, 3 Tesla Magnetic Resonance Neuroimaging and saliva sampleas described above in Baseline/Pretreatment Assessment.

Monthly Follow-ups: For 1 year following completion of the treatment phase, participants will be contacted monthly, via telephone or in person,
to complete a brief standardized measures of alcohol and substance use, as well as craving to assess for changes in these variables over the preceding 30 days. These brief contacts will be 15-20 min and tracking sobriety is the primary outcome measure of this study.

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

All procedures will be performed by staff trained specifically for the
tasks for which

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they are responsible. All procedures, including the iTBS-TMS, and are considered low-risk procedures. iTBS-TMS is regarded as safe and without lasting side effects when established
guidelines are followed. The primary serious adverse event associated with transcranial magnetic stimulation procedures are seizures, however, the estimated prevalence is very low at < 1%. In the case of transcranial magnetic stimulation-seizures, all have occurred during stimulation, there was no recurrence of seizures, and no incidences of status epilepticus. There have been no significant adverse cognitive, brain structural, neurologic or cardiovascular sequelae reported as a result of rTMS. Seizure risk will be minimized by careful patient selection by rigorously screening and exclusion of participants with history of seizure disorders or other conditions and medication use that increases risks of seizure. A seizure protocol is in place to avoid participant injury in the unlikely event that a seizure does occur attached. Overall, the risks to participants in this proposal are reasonable in relation to anticipated benefits, if any, to the participants, and the importance of the knowledge that may be expected to result.

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).

N/A

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

N/A

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).

The participants in this study will concurrently receive standard-of-care cognitive-behavioral and pharmacological interventions from the VAPAHCS substance treatment clinics they are enrolled in. There are no potential risks to the participants who receive concurrent cognitive-behavioral and any procedure associated with the proposed research protocol. No participant will be enrolled who is taking a medication that lowers seizure threshold. Risks to confidentiality will be minimized by following all procedures dictated by HIPAA. Of course, potential participants may decline to be involved in the study and receive only the

available standard-of-care cognitive-behavioral and pharmacological interventions.

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

This study will not impose any restrictions on treatment/therapy after conclusion. At
this point, the rTMS treatment under investigation will only be available during the
treatment phase of 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?

In order to have sufficient power to evaluate the primary hypotheses of this study, it is expected to continue until all participants have completed the procedures and follow-up assessments.

3. Background

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

To date, there have been nine transcranial magnetic stimulation studies for the treatment of AUD. Results suggest TMS may serve as a novel treatment intervention for AUD. However, the generalizability of the published clinical trials to Veterans is severely limited because of several design limitations:

• All were international studies with modest sample sizes, did not include Veterans, and consisted primarily of inpatients; AUD treatment at most VA and civilian facilities delivered via outpatient clinics

• Six of nine studies were single blind designs, only five utilized a true sham
control condition; double blind, sham/placebo controlled designs are the standard in evaluation of the efficacy of an intervention.

• Six studies excluded participants for conditions e.g., major depressive disorder that commonly co-occur with AUD, and the effects of concurrent smoking on TMS efficacy were not rigorously evaluated. Consequently, the results do not generalize to the typical Veteran seeking treatment for AUD.

• Two studies employed single TMS sessions and four had 10 total sessions; this number of treatments may have not been sufficient to promote sustained abstinence, particularly in Veterans.

• The primary outcome measure in most studies was craving. Higher baseline craving is moderately associated with relapse risk during the first few
weeks of treatment, but is a poor predictor of relapse several months after treatment. Therefore, it is necessary to obtain baseline measures of impulse control and risk taking, which are substantially more robust predictors of relapse after treatment.

• The primary follow-up period was 1 month; such a short follow-up interval did not permit evaluation of the long-term efficacy of TMS

treatment. Regular monitoring over the entire first 1 year following treatment is imperative, given relapse during the first 6 months-1 year following treatment is strongly related to clinically significant impairments in psychosocial functioning over the ensuing 1-3 years in Veterans and civilians with an AUD.

• Only one placebo controlled study employed biomarkers for the mechanism(s) of therapeutic action or treatment response, so objective biomarkers of TMS treatment response in AUD have yet to be firmly established. Identification of biomarkers of mechanism(s))and level of treatment response are necessary to more effectively tailor TMS treatment to the individual Veteran.

The efficacy of iTBS-TMS for the treatment of Veterans with AUD is unknown until the foregoing limitations are addressed and a representative sample of Veterans is studied. The proposed project will rigorously address the above limitations and provide completely novel information on the efficacy of TMS to decrease the high rate of relapse in Veterans with AUD. It is imperative to conduct the proposed study over the next 4 years since TMS will be rolled-out as a clinical service to each VISN in 2018, organized and lead by our VISN 21 MIRECC TMS treatment team)for treatment of major depression, and it will likely be applied to Veterans with AUD or comorbid AUD and depression without sufficient support and direction from clinical trials with Veterans. We believe this proposed work will provide preliminary data to allow VA clinicians to make decisions about the utility of iTBS-TMStreatment for AUD.

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

N/A

4. Radioisotopes or Radiation Machines

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

Identify Week/Month of study	Name of Exam	Identify if SOC or Research

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) if they are being studied.

5. 1 Device Name : MagPro X100

Describe the device and how it will be used.

The MagPro X100 and similar transcranial magnetic stimulation devices are FDA approved for treatment for major depressive disorder. It is considered to be non-significant risk medical device when all standard safety protocols are followed.

Manufacturer : **MagVenture**

Risk : **Non-significant**

Y I confirm the above are true.

Rationale for the device being non-significant risk:

Transcranial magnetic stimulation is an FDA approved treatment modality for major depressive disorder. Although the MagPro X100 and similar transcranial magnetic stimulation devices are not currently FDA approved for alcohol use disorders, the MagPro X100 to be used in the present study is an FDA-cleared device.

Sponsor of Project

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

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

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 : 3T UHP

Describe the device and how it will be used.

3T G.E. Healthcare MR system is an upgrade to the 3T MR750 which was a commercial FDA-approved system.

Manufacturer : **GE**

Risk : **Non-significant**

Y I confirm the above are true.

Rationale for the device being non-significant risk:

The 3T Ultra-High Performance (UHP) MRI scanner from GE is an upgrade to the 3T MR750 which was a commercial FDA-approved system. The UHP system utilizes many components from GE's 3T Signa Premier, including gradient drivers, power supply, transmit and receive system electronics, but uses a higher-performance gradient coil. The 3T UHP system is not FDA approved, and is subject to the 21 CFR 812 investigational device (IDE)
regulations as well as 21 CFR 50 and 56. The system has been tested by GE according to UL606001-1 and also for compliance with IEC 60601-2-33 (ed 3.1) -- meeting limits and guidelines for peripheral nerve stimulation, patient thermal, SAR limit, acoustic noise, flammability rating UL94-5VA for safety covers, hydrostatic pressure, electrical hazards, dielectric strength and pinch point. The MRI scans in this study will also utilize operational parameters within FDA guidelines for Nonsignificant Risk thus an Investigational Device Exemption (IDE) from FDA should not be necessary. In addition, the MR research being conducted requires highly specialized software that does not exist in the clinical MR market so it is designed and implemented by researchers at the CNI. Any such software will be considered investigational, will function as a non-significant risk device, and is subject to the 21 CFR 812 investigational device(IDE) regulations as well as 21 CFR 50 and 56. The investigational image acquisition software will conform to FDA guidelines for MR safety related to heating (SAR), peripheral nerve stimulation

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(dB/dt), and acoustic noise.

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?

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 and Devices

a) Please list in the table below all investigational drugs, reagents or chemicals if they are being studied.

b) Please list in the table below all commercial drugs, reagents or chemicals if they are being studied.

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.

N/A

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),(ii) & (iii): One hundred 100 participants are expected to be enrolled (50 active rTMS and 50 sham rTMS) from all substance abuse clinics at the VAPAHCS, but primarily from the Foundations of Recovery (FOR),a 30 day residential program.

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

The study will be open to males and females, regardless of race and ethnic origin, 21-65 years of age, who are in active treatment for an AUD at the VAPAHCS. The 21-65 age range was chosen given the vast majority of information on iTBS-TMS efficacy and safety has been obtained from this range and this is the typical age range of Veterans seeking treatment for AUD at the VAPAHCS.

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.

Individuals with the following conditions that are associated with decisional impairment will be excluded: History of Schizophrenia Spectrum Disorders, Bipolar Disorders, neurodegenerative diseases (e.g., Alzheimer disease, Parkinson's disease) active current suicidal intent or plan (patients with a previous clinical flag for risk for suicide will be required to have an established safety plan involving their primary psychiatrist and the treatment team before entering the clinical trial. Individuals with a lack of fluency in English, Wechsler Adult Reading Test below the 7th percentile (i.e., moderate or greater impairment in estimated general intelligence), females who are pregnant or actively attempting pregnancy (conservative exclusion for magnetic resonance researchwill also be excluded from the study. Children and homeless people will not be included. It is common for Veteran AUD and substance use samples to contain economically and educationally disadvantaged; however, no undue influence will be exerted on these individual and level of compensation for study participation will not be coercive. Additionally, the treatment phase of this study will occur while participants are receiving standard-of-care treatment at the VAPAHCS, which will permit additional on-going monitoring for any adverse events.

d) If women, minorities, non-English speaking individuals, 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.).

No children will be involved in this project as they are not in the age range of US Armed Services Veterans. The study will be open to male and females, regardless of race, ethnic origin, and sexual preference and identity, 21-70 years of age, who are in active treatment for an AUD at the VAPAHCS. Approximately 5% females and 40%racial and ethnic minorities were observed among the Veteran participants in PI's previous studies at the VA San Francisco. Given the similar demographics of Veterans at the VAPAHCS, we anticipate a similar distribution of females and racial and ethnic minorities.

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 possible that up to 15%of our participants may be current VA laboratory personnel or employees. We do not anticipate that any Veteran participants will be current Stanford employees or students.

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.

No healthy volunteers will be included in this study.

g) Describe your plan to identify and recruit potential participants including who will inform them about the study and how they will be initially contacted by the researchers (e.g., Research Engagement services; chart review; treating physician; ads including social media posts). All final or revised recruitment materials must be approved by the IRB before use. Contacting potential participants is not permitted prior to IRB approval. See https://stanfordmedicine.box.com/shared/static/8uebsdjrrqjyauanjp9i9d0gm1i480co.pdf Recruitment Guidance for additional information.

Potential participants from the VAPAHCS treatment programs (Foundations of Recovery and ACT Intensive Outpatient programs)will be identified based on VA medical/clinical staff diagnoses of an alcohol use disorder without any comorbid condition any conditions that be contraindicated for study e.g., taking medications that lower seizure threshold, magnetic resonance neuroimaging contraindications, medically confirmed seizure disorder. The study protocol has been explained to medical/clinical via treatment team meetings, and they are fully cognizant of study procedures and eligibility criteria. Medical/clinical staff of the programs listed above will identify potential participants who meet eligibility criteria and will verbally inform them that there is a VA-sponsored treatment they may be interested in; the medical/clinical staff offer contact information for study personnel or the participant may request to the medical/clinical staff that study personnel contact them. In this way, the participant is self-referred to the study. The PI, VA-based Co-Is or qualified RA will check inclusion/exclusion criteria based on initial eligibility and sociodemographic data via in person screen at the treatment program or at the MIRECC, Building 5, 4th floor. Private interview rooms are available for this purpose at both locations.

h) Inclusion and Exclusion Criteria.

Identify inclusion criteria.

The study will be open to male and females, regardless of race and ethnic origin, 21-70 years of age, whoare in active treatment for an AUD at the VAPAHCS. The 21-65 age range was chosen given the vast majority of information on rTMS efficacy and safety has been obtained from this range and this is the typical age range of Veterans seeking treatment for AUD at the VAPAHCS. At time of enrollment, 21-65 years of age, meet Diagnostic and Statistical Manual of Mental Disorders, 5th Edition DSM-5)criteria for AUD, and alcohol is self-identified as primary substance of misuse. Actively in treatment at VAPAHCS Addiction Treatment Service, and able to read, verbalize understanding, and voluntarily sign the Informed Consent Form prior to participation in study procedures. Participants will be accepted if taking medications specifically for the treatment of major depressive disorders, cigarette smoking, or for other psychiatric conditions as long as the medications are not documented to lower seizure threshold; must be stable on any psychotropic medication for at least 1 month prior to enrollment; it would be clinically contraindicated to require participants to discontinue such medications for research. iTBS-TMS is safely administered to individuals who are taking psychotropic medications that do not lower seizure threshold. Participants will be abstinent from alcohol and non-prescribed substances for at least 5 consecutive days prior to active or sham rTMS to ensure no participant is experiencing active acute withdrawal.

Identify exclusion criteria.

Psychiatric: History of Schizophrenia Spectrum Disorders, Bipolar Disorders, a current substance use disorder that exceeds the severity of the AUD (based on DSM-5 diagnostic criteria), active current suicidal intent or plan (patients with a previous clinical flag for risk for suicide will be required to have an established safety plan involving their primary psychiatrist and the treatment team before entering the clinical trial, any form of previous rTMS or electroconvulsive treatment. Biomedical: Including, but not limited to uncontrolled thyroid disease, unstable congestive heart failure, angina, other severe cardiac illness as defined by treatment regimen changes in the prior 3 months, cerebrovascular accident, cancer if < 1 year since end of treatment; unstable diabetes, COPD requiring oxygen supplementation, Alzheimer's disease, Parkinson's disease, any biomedical implants with ferromagnetic content, neurostimulation devices, cardiac pacemakers or any magnetic resonance contraindications, traumatic brain injury with self-reported or observed loss of consciousness > 30 minutes, any primary or traumatically induced seizure disorder, and alcohol-related seizure(s) in the past 30 days. General: Lack of fluency in English, Wechsler Adult Reading Test below the 7th percentile (i.e., moderate or greater impairment in estimated general intelligence), females who are pregnant or actively attemptingpregnancy (conservative exclusion for magnetic resonance research), current use of any medication or substance that is documented to lower seizure threshold or has been identified as a contraindication for rTMS treatment.

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).

1) Initial screen for alcohol use disorder undertaken by the treatment program clinical staff at intake, with the support of the

director. The clinical staff will offer each incoming patient with a diagnosis of AUD the opportunity to participate in the study, and refer to the potential participant to the PI, Co-I or trained RA's study contact number, and the PI, Co-I or trained RA's will answer/return the potential participant's call; alternately, the potential participant can request to the clinical staff that PI, Co-I or trained RA's contact in-person at the VAPAHCS treatment program them to further explain the study.

2) If the potential participant is interested in the study, the PI, Co-I or trained RA will then conduct an in-person or telephone screen for study specific inclusion and exclusion criteria. We are requesting a waiver of authorization for this recruitment process. Eligible participants will be invited to complete Informed Consent document and enroll in the study. Ineligible participants will be immediately informed that they do not satisfy inclusion/exclusion criteria. Ineligible participants will not be given the specific reasons why they are not eligible in order to maintain the integrity
and security of the study inclusion/exclusion criteria. Rather, ineligible participants will be informed that they have a current or past history of medical, physical or psychological conditions that does not permit safeapplication of the rTMS protocol used in this study.

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.

Subjects may be part of other protocols, including neuroimaging protocols, and this would not be expected to interfere with our protocol. However, we plan to specifically inquire with subjects as to their involvement in other research protocols as to best safeguard the both the subject's welfare and the integrity of data collected by us and other research groups.

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

Participants will not be compensated for study screening. Participants will receive a maximum of $240 for all baseline and treatment phase and week 5 follow-up study procedures. If participants do not complete all baseline or post-treatment visit procedures, they will receive a pro-rated amount that is lower than $200, based on how many procedures you completed. Participants will receive an additional $50 if all monthly contact from week 9 – 25 are completed. Total possible compensation over 1 yearis approximately $290. The mechanism of payment will adhere to the VA mandated procedure: payment form, which the participant can obtain cash or check at the VA Palo Alto upon completion of Baseline and Post-treatment Visit. This rate of compensation is commensurate with other AUD research being conducted at the VAPAHCS and the payment mechanism is used by other alcohol/substance abuse research currently conducted at the VA Palo Alto. The total amount of payment is proportional to the participant's time and effort and is intended to facilitate participation without adding undue influence.

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

No costs will be incurred by any participant.

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.

(i) Probable duration of study = 7 years. End date is 30 September 24. Participant recruitment will likely end 30 September 23. Final fiscal year 2024 will be devoted to data processing and analyses.

(ii)Total time per participant:

Study Phase	Estimated Participation Time
Screening:	20-30 min
Baseline:	6.5 hours, 2-4 hours/day over 1 week.
Treatment:	6.5 hours, 40 min/day,over 2 weeks
Follow-up:	Week 5, 4 hours typically over 2 days

Follow-up Weeks 9 – 61: 4 hours

Total Active Participation Time = approx. 22 hours over 1 year.
All procedures will be conducted before or after normal ATS clinic hours, or during lunch break, to not interfere with the patient's treatment schedule. The project will be conducted at the VAPAHCS MIRECC Palo Alto Division, which is on the same campus as the FOR program.

(iii).)Analysis of participant data will be ongoing for baseline data and after breaking of blind in year 6.

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.)

i. The risks of the Investigational devices.

Transcranial magnetic stimulation (TMS) device: TMS is regarded as safe and without lasting side effects when established guidelines are followed. The primary safety concern associated with any form of transcranial magnetic stimulation procedures are seizures, however, the estimated prevalence is very low at < 1%. In the case of transcranial magnetic stimulation-seizures, all have occurred during stimulation, there was no recurrence ofseizures, and no incidences of status epilepticus. All the reported seizures resolved promptly after removalof stimulation, without medical intervention and were not associated with lasting adverse effects. In those rare seizure cases, the motor cortex was typically being stimulated; in the proposed study a non-primary
motor region of the cortex left DLPFC)is the stimulation site. There have been no significant adverse cognitive, brain structural, neurologic or cardiovascular sequelae reported because of TMS. Participants treated with rTMS may experience temporary discomfort at the site of stimulation due to depolarization of sensory and motor neurons in the scalp under the point of stimulation. Muscle tension headache may result in some participants estimated to occur in less than 10%%of sessions, and can persist for 1-2 hours post stimulation. rTMS treatment can result in mild to moderate headaches in approximately 15% of participants. These headaches are never disabling or persistent and usually respond to ibuprofen or acetaminophen. The incidence of headaches in those with serial transcranial magnetic stimulation typically diminishes with increasing number of sessions. In some people, particularly those with a history of a history of Bipolar Disorder I or II, daily transcranial magnetic stimulation caused them to experience mania increased energy, no need for sleep, and racing thoughts; this study will exclude for a history of cyclothymia and Bipolar Disorders.

Magnetic Resonance Neuroimaging: The magnetic resonance scanning devices (3 Tesla, General Electric MR750) used in scanning at the Stanford Center for Cognitive (CNI)and Neurobiological Imaging poses a non-significant risk to subjects in line with the criteria for exception from an IDE, and routinely used by many other investigators at Stanford. There have been no serious adverse events incurred during scanning at the Stanford CNI.

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

N/A

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

N/A

iv. The risks of the Procedures to be performed. Include all investigational, non-investigational and

non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

Saliva collection. There are no known risks to the participant associated with saliva collection.

Cognitive, Psychiatric and Alcohol/drug Assessments and Questionnaires. Memory and cognitive testing can cause anxiety or frustration. The level of psychological stress is similar to what would be associated with a clinical neuropsychological assessment.

Genetic and Biomarker testing. Genetic testing will be conducted on the collected blood samples. Samples will be brought to our research center's lab at VAPAHCS Dr. Windy McNerney, who will conduct all biomarker and genotyping analyses/assays,

iTBS-TMS risks are described above in 9.i. Investigational devices. Magnetic Resonance Neuroimaging risks are described above in 9. i. Investigational device.

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

N/A

vi. The risks of the Physical well-being.

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

vii. The risks of the Psychological well-being.

Screening, neuropsychological, psychiatric interviews and questionnaires: The screening interview, neuropsychological and psychiatric assessments, as well as self-report questionnaires may be fatiguing and/or distressing for some individuals. Study participants will be informed that they are free to decline to answer any questions or to stop the assessments at any time. Neurocognitive and psychiatric interview sessions will include breaks. In the event that a study participant appears to be under undue strain, the test or interview session will be discontinued.

Genetic Biomarker and Genetic testing: It is possible that biomarker and genetic testing could cause minor psychological stress in a some individuals. All participants will be 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. The biomarker and genetic testing is strictly for research purposes only and results of the genetic testing will not be released to anyone outside of the research project including participants, family, physician, or any other third party.

viii. The risks of the Economic well-being.

No risks to economic well-being are anticipated.

ix. 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 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.

Screening, neuropsychological, psychiatric interviews and questionnaires: Participants will be informed that these procedures may be fatiguing and/or distressing for some individuals. Study participants will be

informed that they are free to decline to answer any questions or to stop the assessments at any time. Neurocognitive and psychiatric interview sessions will include breaks. In the event that a study participant appears to be under undue strain, the test or interview session will be discontinued. Participants will be reminded that they are free to withdraw from participation at any time.

iTBS-TMS administration: The iTBS-TMS operator will be the PI (Dr. Durazzo) or a RA specifically trained by Dr. Durazzo. The PI is fully trained and qualified to administer the procedure according to current safety practices and standards of care in research and clinical settings. Co-Is trained in rTMS (Drs. Yesavage, Ashford) will closely monitor the PIs and RAs adherence to safety protocols and administration for this proposal. This application employs all current established and standard iTBS-TMS treatment safety and monitoring for adverse events guidelines.

The iTBS-TMS operator will monitor all participants for ear protection, coil placement, and seizure activity during all sessions. All participants will be required to have abstained from alcohol or non-prescribed medication for 5 consecutive days prior to the first rTMS session. Prior to the first iTBS-TMS session, participants will be administered the Clinical Institute Withdrawal Assessment for Alcohol-Revised and must score < 8; scores > 8 are indicative of potential autonomic instability); participants with a score > 8 will immediately be escorted to their VAPAHCS Addiction Treatment Services clinic for further evaluation. Participants will be randomly screened x6 for alcohol (breath alcohol) and substance use (urine toxicology) prior to rTMS sessions during the 2 week treatment phase. If a participants test positive or report any alcohol or substance use during the 2 week rTMS treatment period, they will be immediately withdrawn from the study. Additionally, prior to each participants will complete a rTMS screen, including inquiring about any changes in medications or comorbid medical conditions, amount of sleep, and suicide screening questionnaire prior to each rTMS session to assess for current suicide risk. Although patients in the are regularly screened for alcohol and substance use and suicide risk while in treatment, we will conduct random alcohol/substance screening and pre-rTMS session suicide risk assessment to ensure participant welfare. Should a headache or site discomfort occur, these symptoms usually readily respond to acetaminophen or ibuprofen. Any reported painfulness typically improves over time or completely remits. To protect against possible hearing damage, participants will wear ear protection during rTMS sessions (foam ear plugs and noise attenuating headphones. This will greatly reduce the possibility of hearing loss. Hearing acuity testing pre-and-post rTMS is no longer a standard practice, given the remote likelihood of rTMS-related hearing loss.

Additional Procedures for the Monitoring of Seizures and Suicidal Ideation/Behavior:

Screening, Baseline and Treatment Phase: In the unlikely event that a seizure does occur, participants will be closely monitored and treated for any medical or psychological consequences. rTMS sessions will be conducted at the VAPAHCS MIRECC, which fully equipped to safely handle a seizure. If at any point during study participation, a participant has a seizure, the participant will be withdrawn from the study immediately although they will still be followed for protocol assessments. All seizures will be considered serious adverse events (SAE) and as such, will be reported to the study PI. We will immediately suspend enrollment if 10 participants experience a seizure during study participation, and request that the Data Monitoring Safety Board (DMSB)evaluate the SAE data, to determine if enrollment of new participants should be resumed without protocol changes, if protocol modifications should be made before resuming enrollment, or if the study should be terminated. We recognize that study termination or modification based on SAEs, such as seizures, ultimately rests with the DMSB and the study PI. If a participant expresses suicidal ideation/intent, and is determined to be a risk to self, a clinical evaluation will be immediately conducted by the PI (a licensed clinical psychologist), Co-Is ((board certified psychiatrists) or by the participant's individual mental health provider, and/or a mental health emergency clinician. The participant will remain with qualified study personnel or a MIRECC clinician until the evaluation has been completed and a decision made about disposition in conjunction with the Chief of Mental Health Outpatient Clinic or the emergency mental health clinician.

Follow-up Phase: If a participant discloses active suicidal or homicidal ideation or other clinically significant psychiatric symptomatology during the follow-up phase of the study, they will provided with the

number and encouraged to call Veterans Crisis Hotline or present to a local hospital emergency department. In the event of a seizure (or other medical issues possibly secondary to rTMS, the participant will be requested to immediate contact their primary health care provider. In the event of disclosure of the above psychiatric emergencies or a seizure, the PI or psychiatrist Co-Investigator will also be immediately notified and will contact the participant for further assessment and determine the appropriate intervention. If a participant discloses that they relapsed during the follow-up period, they will be encouraged to recontact VAPAHCS Addiction Treatment Services for re-evaluation and possible re-engagement in treatment.

Magnetic Resonance (MR)Studies: Participants will be informed of risks, using the text provided and required by Stanford University's Institutional Review Board the VA. Our Research Assistants (RA) have been trained by the PI, CO-Is carefully pre-screen each participant for MRI safety before the MRI appointment. RA also have been certified to independently operate the CNI magnetic resonance scanner by qualified CNI personnel. Minimal risks are associated with MR scanning and 3T MR scanners are now routinely used in clinical practice. Study participants who have metal implants, cardiac pacemakers, metal fragments or a known tendency for claustrophobia will not be admitted to the study. Study participants will be scanned with a metal detector before entering the 3T scanner room, and all metal objects will be removed. There is a remote possibility that the magnet will attract a metal object, producing physical injury. To make certain
such event do not occur, the door to the magnet room is closed and there is a metal detector outside the door to ensure no ferromagnetic metals are allowed into the scanner. One theoretical hazard of the experiments is heating of the body due to radio waves, but the machine has several safety devices to prevent such an occurrence. There is also a slight risk of nerve stimulation during a portion of the procedure. While there are safety devices that prevent such events, this can occur in rare cases. To reduce this risk, volunteers will be instructed to avoid skin-to-skin contact between their extremities, such as clasping their bare hands or crossing their bare feet. In any case, such sensation is temporary and harmless. Fatigue, boredom, feelings of claustrophobia, or discomfort due to loud banging sounds of gradient coils may accompany the MR procedures. Earplugs and supplied MR-safe headphones will be used during MR scanning. A communication system is set up inside each scanner so that study participants can contact the researchers at any time, and will be immediately removed from the scanner upon request. A communication system is set up inside each scanner so that study participants can contact the researchers at any time, and will be immediately removed from the scanner upon request. In case of adverse effects, medical intervention can be provided by Stanford Emergency Department staff. Study physicians will be available in the case of an adverse event to debrief with the participant.

Identification of clinically significant psychiatric symptomatology other than suicidal ideation or plan), or neurocognitive abnormalities: Although unlikely, it is possible that during the screening process, on the psychiatric interview and questionnaires or during other study procedures, participants may manifest or disclose clinically significant psychiatric symptoms (e.g., homicidal ideation, hallucinations) or disorders that were not previously identified/diagnosed by VAPAHCS Addiction Treatment Services staff. In this case, the participant will be immediately assessed by the PI a licensed clinical psychologist/neuropsychologist, the participant's individual mental health provider, or a mental health emergency clinician. The participant will not be left alone until the evaluation has been completed and a decision made about disposition in conjunction with the Chief of Mental Health Outpatient Clinic, or the emergency mental health clinician. If any participant manifests grossly clinically significant neurocognitive impairment > 2 standard deviations below mean performance of the normative reference group)on any domain of functioning, Dr. Durazzo will debrief the participant and inform his current mental health treatment providers, with the participant's explicit approval and written consent obtained in the informed consent) for further assessment. If a participant discloses that they relapsed during the follow-up period, they will be encouraged to recontact VAPAHCS Addiction Treatment Services for re-evaluation and possible re-engagement in treatment.

Loss of confidentiality: Every precaution will be taken to minimize loss of confidentiality. A triple lock system will be maintained: within a locked lab, locked office, and locked file cabinet. All electronic data will be secured on an encrypted, password-protected database behind a VA or Stanford RedCap firewall. The participant's name will not be used in any reports or publications resulting from this study. The

participant's name will not be recorded on test material or other research records. An identification code will be used instead. The participant's identification code will be kept in a secured database. The PI and trained and qualified research team members will have access to the participant's information. The coded, de-identified
data for each participant, which has been stripped of any information that could be used to identify the participant, may be shared with consultants. However, the participant's personal health information cannot be used for additional research without additional approval from either the participant or a review committee.

Adverse Events (AEs) and Adverse Device Effects (ADEs:)

1. Adverse Device Effect (ADE) and Adverse Event (AE)

Definitions:
An Adverse Device Effect (ADE)is defined by 21 CFR 812.3s as any adverse effect/event caused by orassociated with the use of a device.

An Adverse Event (AE) is defined by the ICH for Clinical Safety Data as any untoward physical or psychological occurrence in a human subject participating in research. The AE does not necessarily have to have a causal relationship with the pharmacological product, study intervention, or assessment. An AE can, therefore, be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medicinal investigational) product.

Reporting: In this study, all ADEs and AEs that occur during the acute treatment and follow-up phases will be collected and followed until resolution or the individual's participation in the study ends. All events will be recorded on the appropriate case report form. "Relatedness" involves an assessment of the degree of causality between the study intervention and the event. PIs will be asked to provide an assessment of relatedness. The assessment provided by the PI is part of the information used by the sponsor to determine if the adverse event or effect presents a participant safety concern. An ADE is deemed to be associated with the use of the study device if there is a reasonable possibility that the experience may have been caused by the device or by participation in the trial. Thus, all adverse events or effects with a reasonable causal relationship to the rTMS treatment should be considered related. A definite relationship does not need to be established. The following levels of relatedness will be used in this study:
• Not attributed to iTBS-TMS treatment
• Possibly attributed to the iTBS-TMS treatment
• Attributed to the iTBS-TMS treatment

Serious Adverse Events (SAEs)and Unanticipated Adverse Device Effects (UADEs)Definitions:
Serious Adverse Events (SAEs)are a subset of adverse events and are defined by the ICH for Clinical

Safety Data Management as any untoward medical occurrence that:
• Results in death
• Is life-threatening
• Requires inpatient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability or incapacity
• Is a congenital anomaly/birth defect or
• Any other condition that, based upon medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes.

An Unanticipated Adverse Device Effect UADE)is defined as: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect,problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants. For this study an UADE is considered a category of SAE, which will be reported on the same form.

Collection and Recording: For this study, all SAEs and UADEs will be recorded on the SAE form, regardless of cause. The PI will be
asked to determine whether the serious adverse event is related to:
• iTBS-TMS device
• iTBS-TMS treatment
• Medications used to treat AUD and/or co-occurring conditions

Collecting and recording SAEs/UADEs will begin at randomization and will continue throughout the follow-up phase. For a participant who ends study participation prior to the study's completion date, unresolved SAEs will be monitored and reported for 30 days after the End of Study date for that participant. In addition, the investigator must collect all SAEs reported to them for a period of 30 days after the study's completion.

Expedited Reporting of Serious Adverse Events SAEs)and Unanticipated Adverse Device Effects UADEs:)Study personnel will be responsible for initially evaluating all serious adverse events for participant safety concerns and will confer with the PI as required during this evaluation process. After being reviewed by the PI, any event deemed to be related, serious and unexpected will be reported to study investigators.
Expedited Reporting by the Sponsor to the FDA: PI will review the SAE report to assess completeness of documentation and to determine whether the SAE requires expedited reporting to the FDA. Specifically, if an event meets the criteria for unexpectedness (i.e., not previously reported) and seriousness it will be reported as required by regulation to the FDA within 10 working days for UADEs and within 7 calendar days for unexpected SAEs (Safety Reports) of the sponsor receiving the report as required by regulation.

Data Monitoring Safety Board (DMSB): Reporting of Adverse Events, Adverse Device Effects, Serious Adverse Events, and Unanticipated Adverse Device Effects. Study Personnel will generate tabulations of AEs and SAEs and present a summary of these to the DMSB on a schedule set by the DMSB. The DMSB will also determine when they should be unblinded to treatment assignment for the reviewing of adverse event data. The DMSB will advise the PI concerning whether the study should continue or be stopped for safety
reasons. Communication among the Investigative Team: The PI will have a weekly group lab meeting with all RAs, and there will be a monthly lab meeting with all Co-Is and consultants some via Skype. Additionally, the VAPAHCS MIRECC has weekly PI meetings to discuss issues relevant to ongoing MIRECC research projects. All key VA Co-Is associated with this project
attend these weekly meetings.

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. Participants will be asked to complete the brief monthly in person or telephone assessments as described in the follow-up phase. In the event that an interim analysis demonstrates futility, the PI, or Co-I determines unacceptable level of risk, regulatory agencies mandate discontinuation of the study, or a product recall occurs that necessitates stopping the study, any planned iTBS-TMS treatments will be immediately discontinued.

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.

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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:

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

Although this study protocol is low risk, and will enroll a modest number of participants, we will create a DSMB as we believe this is consistent with best clinical practices. Types of data and events that will be reviewed are: 1) Aggregate Data Analysis Reports; 2) Progress toward Study endpoints; 3))AEs, SAEs and unanticipated problems;)4) Protocol deviations.

2. 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). a style='font-style:italic;color:#0000CC' href=https://researchcompliance.stanford.edu/eprotocol/ephelp_dsmp#dsmp2 more...

The grant will utilize a DSMB that will review the progress of the study. The DSMB will monitor patient enrollment, aggregate outcomes, adverse events, and other issues related to patient safety. The safety monitoring plan reflects the low risk of the rTMS intervention, the 2-week duration of intervention, the extra precautions taken (e.g. MRI safety screening and exclusions of individuals with a risk of seizure, the modest number of subjects involved, and the single-site nature of the study.

3. 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.

The composition will include a Senior VA neuroscientist scientist and senior VA neurologist, who are have experience in the procedure used in this study and not affiliated with the study.

4. 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 SAEs will be reported within 24 hours of learning of the SAE. Unanticipated problems involving risks to participants or others will be reported within 5 days.

5. 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?

Given the modest number of participants studied per year (approximately 25, the DSMB will meet once per year to review data reports prepared by the PI's research team. Any member of the DSMB can ask for an emergency meeting of the group. The DSMB will issue written reports to the PI on the safety and progress of the trial. The report will include recommendations to the PI concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study. The PI will provide of the DSMB reports to the IRB.

6. 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

7. 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.

See 2g

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8. 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

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.

iTBS-TMS could potentially generate substantial health benefits for VHA patients. Repetitive iTBS-TMS may offer a viable and more efficacious treatment option for Veterans with AUD. Moreover, it could bedisseminated 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, iTBS-TMS has the potential to dramatically improve access to effective mental and cognitive health and rehabilitation for a large number of Veterans with AUD. For these reasons, the anticipated risks are reasonable in relation to the anticipated benefits to study participants. However, if shown safe and effective, the budgetary cost of rTMS will likely be an important consideration relating to its subsequent evaluation and implementation. If our hypotheses are confirmed, replicated in independent samples, and critically evaluated by peer review, the VAPAHCS Mental Illness Research and Education Clinical Center MIRECC is well-suited to lead a nationwide roll-out of an iTBS-TMS treatment protocol for AUD. The VAPAHCS MIRECC has developed treatment protocols and led highly successful nationwide roll-outs of evidence-based practices (EBP) of cognitive-behavioral therapy for depression and insomnia to well over 2000 VA clinicians. VISN-21 MIRECC Education Core currently is funded for core resources for such tasks. The VISN-21 MIRECC has been funded a roll-out for TMS for depression concurrent with the conclusion of CSP 556 "The Effectiveness of rTMS in Depressed VA Patients." Thus, the findings and protocol for our iTBS-TMS intervention for AUD can be readily disseminated to VA (and non-VA)researchers, clinicians, and leadership through the MIRECC EBP program. In clinical research studies at VAs and universities throughout the nation, multiple forms of rTMS are currently routinely and safely administered by trained non-medical personnel, under the supervision of qualified medical professionals. As described in this proposal, iTBS-TMS is a very safe treatment when standard safety protocols are followed. Therefore, it is highly feasible that rTMS can be safely and effectively implemented at both VA medical centers and CBOCsto treat AUD by trained non-medical technicians under the supervision of qualified medical personnel. This will significantly increase Veteran access to the rTMS intervention throughout the VA system and substantially reduce the costs of treatment delivery.

11. Privacy and Confidentiality

Privacy Protections

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a) Describe the setting and method (e.g. crowded waiting room, patient exam room, telephone or email communication) in which interactions will occur and how the privacy interests of participants will be maintained. Note, high risk data such as PHI must be sent via "Secure:" email per https://uit.stanford.edu/security/hipaa/email-policy Stanford policy.

During the consenting process, in-person screening, and the collection of other study data, participants will meet in a private interview room with a member of the study team at the study site Bldg 5 at VAPAHCS). Saliva samples will be obtained in a private setting at the study site Bldg. 5, VAPAHCS.

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 will collect the following HIPAA identifiers, as mentioned on the VA HIPAA form:
- Social security number for participation compensation i.e., participant payment, and entry of required research notes into VA medical records;
- Name, address and telephone number for follow-up assessments and to mail participation compensation; and to mail payment;
- Birth dates & visit dates.

We will collect the following PHI, as mentioned on the HIPAA:
- Demographic information including age and race/ethnicity;
- Results of past routine laboratory tests;
- Physical examinations and related past medical records;
- Magnetic resonance neuroimaging data, MRI digital images and clinical reads of MRIs;
- Research data, questionnaires, saliva specimens, and study progress notes, which may include: cognitive test scores; questionnaires about mood and everyday function; current and past medical history; current and past medications; adverse effects during the study; and height and weight.

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.

Stanford University IT approved platforms (https://uit.stanford.edu/guide/riskclassifications https://uit.stanford.edu/guide/riskclassifications) should be used for data management. Consult with your Department IT representative for more information.For data security policies and links to encrypt your devices see http://med.stanford.edu/irt/security and target=_blankhttp://www.stanford.edu/group/security/securecomputing/mobile_devices.html. Additionally, any PHI data on paper must be secured in a locked environment.

By checking this box, You affirm the aforementioned. Y

Paper data with PHI will be kept in locked file cabinets in locked offices. Data collected on paper forms and questionnaires will be entered into encrypted, password-protected databases. Electronic files and databases are maintained on a secure VA network, on a server that is backed up and located in a secure server room accessible only by authorized personnel. Only staff listed for a given protocol are granted access to appropriate server folders. Staff's computers are password protected, encrypted, and backed up. The VA prohibits removable drives. At the VA, REDCap data are transmitted from behind the VA

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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. VA
REDCap is only available to VA researchers through a web URL that requires a VA
generated login and email address.
Each subject will be assigned a participant ID number (PID). All
computer-entered data will be coded using PIDs only.
Biomarker/genetic information is stored in a separate password
protectefile, which can only be accessed by the PI, Co-PI ,the data
manager/analyst, and appropriately delegated staff. Only the data
manager/analyst can match genetic information with the participant
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 LAR consents to future use and sharing of genetic data
and samples as documented on the informed consent form.
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. Any data,
specimens,forms, reports, and other records that leave the site will be identified
only by a participant id number (PID) to maintain confidentiality. Information will
not be released without written permission of the participant, except as necessary
for monitoring by the IRB.

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, specimens and image files will be labeled by a participant ID
number (PID). Information linking the PID code and PHI will be kept
on a secure, password protected computer behind a firewall. The Data
Manager is responsible for de-identification of data. The PI 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).

Data, specimens and image files will be labeled by a participant ID
number (PID). Information linking the PID code and PHI will be kept on a secure,
password protected computer behind a firewall. The Data
Manager is responsible for de-identification of data. The PI is
ultimately responsible for de-identification of samples.

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.

Members of the research team will have access to all non-genetic data. The data
manager has access to both non-genetic and genetic
data; however, the data manager has no access to subject names, SSNs,
or contact information. If the participant requests explicitly in
writing, we will send information about neuropsychological assessments and
clinical results to his/her the medical or mental health care provider of their choice.
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 genetic data (other

than de-identified genotype or de-identified quantitated plasma/serum results) and physical biomarker specimens will be shared with anyone outside of this research study unless the subject or legally authorized representative consents future use and sharing of genetic data and samples as documented on the informed consent document.

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.

A participant ID number PID is assigned to a subject after they sign a consent form. This numeric code is independent of any identifying information.

h) If sharing data with others, describe how data will be transferred or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, confirm a Stanford University IT approved platform will be used (see https://uit.stanford.edu/guide/riskclassifications https://uit.stanford.edu/guide/riskclassifications) or that data will be encrypted while in transit. Additionally, confirm appropriate agreements are in place to allow for the sharing (see https://ico.stanford.edu/stanford-researchers/who-will-handle-my-agreement https://ico.stanford.edu/stanford-researchers/who-will-handle-my-agreement). If using or sharing PHI, refer to the following policies: https://uit.stanford.edu/security/hipaa https://uit.stanford.edu/security/hipaa.

No PHI will be transferred to any person/organization outside of the or VA 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 PI, along with VA Research Administration, also reinforce the importance of maintaining confidentiality.

12. Potential Conflict of Interest

Investigators are required to disclose any outside interests that reasonably appear to be related/li to this protocol.

Outside Interest Tasks

Investigators	Role	Potential COI?	Date Outside Interest Answered	Date OPACS Disclosure Submitted	COI Review Determination
Timothy Durazzo	PD	N	01/27/2025		N/A
Claudia Beatriz Padula	OC	N	01/27/2025		N/A

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Keith Humphreys	OP	N	01/27/2025		N/A
Laura Lazzeroni	OP	N	01/27/2025		N/A
Jerome A Yesavage	OP	N	01/27/2025		N/A

13. Consent Background

13. 1 Waiver of Documentation Screening Waiver of Documentation

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.

Qualified research personnel will conduct this screen to determine basic eligibility. We believe it is an excessive burden on the potential participant to require participants to complete the entire informed consent to conduct this brief screen for study eligibility. It will be administered prior to obtaining written informed consent, but after the potential participants have already expressed interest and willingness to provide study personnel to contact them.

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 purpose of the screening interview is given in the script preceding screening. Participant oral assent will be obtained for this screening interview. VA waiver of HIPAA authorization for recruitment has also been included in the protocol.

c) What steps are you taking to determine that potential participants have the capacity 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.

The clinical staff who refer patients to the study will be asked if the patient has capacity to consent for the study. In addition, if it appears that a patient does not understand the consent procedure or does not have the capacity to consent to screening, we will not screen them for participation in the study.

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 PI, VA Co-I or qualified VA research staff have responsibility of obtaining oral assent prior to conducting the screening interview individuals for the study.

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

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N/A

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?

Potential participants will be given information about the study and it will be made clear that participating in the screening interview is completely voluntary and choice of participation will not affect their current or future VA treatment in any manner.

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

Patients screened for participation will be explicitly informed that completing the screening interview is completely voluntary and there will be no compensation for the screen. The participants are told there is no compensation for the screening interview.

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

No.

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 ALL applicable regulatory criteria for a Waiver of Documentation and provide a protocol-specific justification:

1) **45 CFR 46.117(c)(1)(i)., that 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 (or legally authorized representative) will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.**

2) Y **45 CFR 46.117(c)(1)(ii)., that the research 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)(1)(iii)., if participants or legally authorized representatives (LAR) are members of a distinct cultural group in which signing forms is not the norm, the research presents no more than minimal risk and there is an appropriate alternative mechanism for documenting that informed consent was obtained.**

4) Y **21 CFR 56.109(c)(1)., 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:

We believe it is an excessive and unreasonable burden on the potential participant to require those with a potential history of bipolar/cyclothymia or schizophrenia-spectrum disorders to complete the entire lengthy informed consent process to conduct this brief screen for study eligibility. Such individuals would be immediately excluded after reading through the entire consent, which would likely be highly frustrating for many potential participants. We request the IRB consider the patient population of this study and our desire to minimize any unnecessary burden on potential participants.

13. 2 Consent — Informed 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.)

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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) Study personnel obtaining consent will be one of the investigators, or RA, who have been trained to give informed consents. (ii)The consenting is always done after the potential research subject 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 will typically takes place in one of the private interview rooms in the VAPAHCS MIRECC Bldg 5, 4th floor or at the participants VAPAHCS Addition Treatment Program. (iii)Sufficient time will be allowed for participants to read the consent and to ask any and all questions they may have and discuss the study with study personnel obtaining consent. We estimate this will take approximately 30 minutes. (iv) The potential participant may take the consent to review, and contact study personnel to ask further questions or sign it. (v)Participants will be told that involvement in the study is completely voluntary, and that they can withdraw at any time, for any reason. Research personnel will also emphasize that any treatment they receive at VAPAHCS will not be affected by their choice to participate in the study. (vi)n/a

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

Participants will be given an explanation of the consent form by trained research staff. In addition, they will be given ample time to read and review the consent forms and given the opportunity to ask questions or clarification. Given the nature of the study, individuals must be fluent in English and not have visual or auditory acuity impairment that would prevent them from completing the assessments, including the consent.

c) What steps are you taking to determine that potential participants have the capacity 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.

The study will not enroll individuals who are not able to give written, informed consent. If there is any question regarding the potential participant's capacity to give informed consent, they will be screened by the study PI/PD, who is a licensed clinical psychologist/neuropsychologist for the cognitive competency to provide written informed consent.

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.

Drs. Timothy Durazzo, Claudia Padula, Leanne Williams, Jerome Yesavage, J. Wes Ashford, Ansgar Furst and study RAs are all delegated responsible staff to obtain written informed consent. All have been trained in the study, and process for obtaining consent. To-be-hired research personnel will be trained in the consent processes and completed the required training in Human Subjects, Good Clinical Practice, and HIPAA prior to obtaining informed consent.

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

No. Individuals who are not able to competently provide independent written informed consent will not be included in the study.

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 will be given ample time to consider participation in the study and for signing the written consent form. Participants will also be told that their involvement in the study is completely voluntary, and that they can withdraw at any time, for any reason. Study personnel obtaining informed consent will also emphasize that the treatment they receive at the VAPAHCS will not be affected by whether they decline or participate in the study.

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

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Participants will be informed that participation in the study is completely voluntary, and that they can withdraw at any time, for any reason. Study personnel obtaining informed consent will also emphasize that the treatment they receive at VAPAHCS will not be affected by whether they decline or participate in the study minimizing risk of coercion. The level of participant compensation is appropriate for the population being studied and no cash or checks will be dispensed.

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

No. All information presented to the participant, including documents they must sign, will be 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.

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

15. HIPAA Background

15. 1 Authorization — **va hippa**

15. 2 Waiver of Authorization for Recruitment — **waiver of authorization for recruitment**

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

Name, last 4 of SSN, age, date of birth, sex, telephone number (for contact about eligibility), medical, specific psychiatric history regarding bipolar/manic and schizophrenia-spectrum symptoms. • We believe it is an excessive burden on the potential participant to require them to complete the entire lengthy informed consent to conduct this brief screen for study eligibility. the rTMS treatment parameters proposed in this study have been associated with increased risk for a manic symptoms in those with bipolar disorder and cyclothymia. Although the research on schizophrenia-spectrum disorders is equivocal, exacerbation of psychotic symptoms have been reported with the rTMS treatment parameters proposed in this study.Qualified research personnel will conduct this screen specifically to determine basic eligibility for the study. The screen is will be 15-20 minutes in duration. • The purpose of the screening interview is given in the script preceding screening. Participant oral assent will be confirmed prior to screening. VA waiver of HIPAA authorization for recruitment has also been included in the protocol. • Potential participants will be given information about the study and it will be made clear that participating in the screening interview is completely voluntary, they will not be compensated for the screening interview, and choice of participation will not affect their current or future VA treatment in any manner.

b) Please Answer:

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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 screening documents will be stored in a locked office in a locked file cabinet at the PAVAHCS, building 5 C-441.

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.

VA requires screening documents are retained for the 6 years after completion of the study.

16. Attachments

Attachment Name	Attached Date	Attached By	Submitted Date
VA RR&D grant application	08/03/2017	tdurazzo	
Seizure protocol	08/03/2017	tdurazzo	
TMS_SessionSafety_tcd	08/03/2017	tdurazzo	
Alcohol_Abstinence_Self_Efficacy_Scale_17 copy	08/03/2017	tdurazzo	
Alcohol_Craving_Questionnaire_Short_Form_Revised_20	08/03/2017	tdurazzo	
BAM_Scoring_Clinical_Guidelines_01-04-2011	08/03/2017	tdurazzo	
Barratt Impulsiveness Scale	08/03/2017	tdurazzo	
Brief COPE	08/03/2017	tdurazzo	
Cannabis Use Disorder ID Test	08/03/2017	tdurazzo	
DSM 5 Alcohol Use Disorder	08/03/2017	tdurazzo	
DSM 5 Substance Use Disorder	08/03/2017	tdurazzo	
Early Life Stress	08/03/2017	tdurazzo	
Emotion Regulation Questionnaire	08/03/2017	tdurazzo	
Epworth Sleepiness Scale	08/03/2017	tdurazzo	

Fagerstrom Test for Nicotine Dependence	08/03/2017	tdurazzo	
Insomnia Severity Index	08/03/2017	tdurazzo	
NM-ASSIST	08/03/2017	tdurazzo	
OCDS	08/03/2017	tdurazzo	
WebNeuro Manual	08/03/2017	tdurazzo	
WHO Quality of Life	08/03/2017	tdurazzo	
MarinaLOS_RRD	08/04/2017	tdurazzo	
VA required questions	09/11/2017	tdurazzo	
Durazzo_RRD_DMSB_report_FY1	07/25/2018	tdurazzo	
Durazzo_RRD_DMSB_report_FY2	06/27/2019	tdurazzo	
Durazzo_RRD_DMSB_report_FY3	07/08/2020	lcnguyen	
Durazzo_RRD_DMSB_report_FY4	06/23/2021	mmkaur	
CITI training Certificate_DURAZZO	08/03/2021	mmkaur	
Durazzo_RRD_DMSB_report_FY5	07/07/2022	tdurazzo	
DSMB FY6	05/02/2023	tdurazzo	
DSMB letter_FY7	04/09/2024	tdurazzo	

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

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- Apply relevant professional standards.

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

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

https://stanfordmedicine.box.com/shared/static/qbsi8u8h47qsotxhdpuzz50xlrqa0sgo.pdf Report promptly any new information, complaints, possibly serious and/or continuing noncompliance, or unanticipated problems involving risks to participants or others.

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)

APPROVAL LETTER/NOTICE NOTE: List all items (verbatim) that you want to be included in your approval letter (e.g., Amendment date, Investigator's Brochure version, consent form(s) version(s), advertisement name, etc.) in the box below.

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.

Data Analyses

Primary Hypothesis:

1a) Veterans who receive active rTMS treatment for AUD demonstrate a significantly lower frequency of relapse at 6 months following treatment than controls (i.e., Veterans with AUD who receive sham rTMS).

Statistical Approach: Primary Hypothesis 1a will be tested with binary logistic regression. The criterion/dependent measure is relapse status (abstained or relapsed during the 6 months after last rTMS session). Treatment group (active rTMS vs. control) is the target predictor, and covariates will include age and composite neurocognitive functioning (based on demographically adjusted RBANS total score) as these variables may account for both within and between subject group variance [89, 91]. PTSD severity (based on PCL-5 total score), substance use severity (based on NIDA Drug Survey composite score), depression severity (based on BDI total score), and/or smoking severity (based on pack-years) will be considered as covariates if, after random assignment, there are post-hoc differences between treatment groups on these variables following breaking of the blind.

1b) Veterans who receive active rTMS treatment for AUD will demonstrate a significantly greater duration of abstinence in the 6 months following treatment than controls.

Statistical Approach: Primary Hypothesis 1b will be tested with Cox regression. The criterion/dependent measure is duration of abstinence after final rTMS session, and covariates include those listed for Primary Hypothesis 1a.

Secondary Hypothesis:

In the active rTMS group, Veterans with: (a) lower Glx concentration, (b) lower perfusion (blood flow), and (c) smaller volume of the left DLPFC at baseline will demonstrate a longer duration of abstinence over 6 months post treatment. Confirmation of this hypothesis will indicate that participants who exhibit lower baseline Glx concentration, lower perfusion (blood flow), and/or smaller left DLPFC volume, and receive active rTMS, demonstrate the most robust rTMS treatment response because rTMS addresses these key neurobiological deficits that are associated with increased relapse risk. Confirmation of this hypothesis will advance our understanding of the neurobiological characteristics that predict the greatest benefit from rTMS at entry into treatment for AUD.

Statistical Approach: The Secondary Hypothesis will be tested with generalized linear mixed modeling or linear mixed modeling, depending on the distribution of the dependent measure. Duration of abstinence is the dependent measure. Neuroimaging measure (e.g., Glx level) and treatment group (active rTMS vs. control) are the target predictors, with age as a covariate because it will likely account for significant within and between subject variance [20]. Smoking, PTSD and/or substance use severities will be used as covariates if there are post-hoc differences between treatment groups on these variables after random assignment. We predict an interaction between the specific neuroimaging measure (e.g., Glx level) and treatment group; follow-up simple effect tests will indicate that participants in the active rTMS group with lower Glx concentration, lower perfusion (blood flow), and smaller volume of the left DLPFC at baseline will show the longest duration of abstinence. Separate models will be run for each neuroimaging predictor to minimize the risk of overfitting and corresponding inflated Type I error. To control significance levels of main effects and interactions for multiplicity of tests, we will employ a modified Bonferroni procedure described in our previous studies (see [71] for details).

Exploratory Hypothesis 1

1a) Veterans with co-occurring MDD, who receive active rTMS, demonstrate a significantly lower frequency of relapse over 6 months following treatment than controls (i.e. Veterans with co-occurring MDD who receive sham rTMS).

Statistical Approach: Exploratory Hypothesis 1a will be tested with binary logistic regression. The criterion/dependent measure is relapse status (abstained or relapsed during the 6 months after last rTMS session). Treatment group (active rTMS vs. control) is the target predictor, with antidepressant use (binary, yes/no) as a covariate. Education and severity of PTSD, substance use, and/or depressive symptomatology will be considered as covariates if, after random assignment, there are post-hoc differences between treatment groups on these variables following breaking of the blind.

1b) Veterans with co-occurring MDD, who receive active rTMS, demonstrate significantly greater duration of abstinence in the 6 months following treatment than controls.

Statistical Approach: Exploratory Hypothesis 1b will be tested with Cox regression. The criterion/dependent measure is duration of abstinence after the final rTMS session. The target predictor and covariates include those for Exploratory Hypothesis 1a.

Exploratory Hypothesis 2

2a) Cigarette smokers, who receive active rTMS, demonstrate a significantly lower frequency of relapse over 6 months following treatment than controls (i.e., Veterans with co-occurring smoking who receive sham rTMS).

Statistical Approach: Exploratory Hypothesis 2a will be tested with binary logistic regression. The criterion/dependent measure is relapse status (abstained or relapsed during the 6 months after last rTMS session). Treatment group (active rTMS vs. control) is the target predictor and with current pharmacotherapy for smoking cessation use (binary, yes/no) as a covariate. Education and severity of PTSD, substance use, and/or smoking severity (based on pack-years) will be considered as covariates if, after random assignment, there are post-hoc differences between treatment groups on these variables following breaking of the blind.

2b) Smokers, who receive active rTMS, demonstrate a significantly greater duration of abstinence over the 6 months following psychosocial treatment than controls.

Statistical Approach: Exploratory Hypothesis 2b will be tested with Cox regression. The criterion/dependent measure is duration of abstinence after final rTMS session. Treatment group is the target predictor and covariates include those for Exploratory Hypothesis 2a.

Tertiary Analyses

We will concurrently examine the associations between treatment group, multiple neurobiological, neurocognitive and clinical variables (and their potential interactions) and relapse status via an advanced multivariate dynamic longitudinal latent variable modeling framework [23]. However, we are mindful of the proposed sample size and will avoid building models that risk overparameterization and overfitting.