Protocol Title: Feasibility of combination exercise and neuromodulation rehabilitation to improve post-stroke chronic pain
Protocol Version: 2
Protocol Date: 4/22/24
Principal Investigator: Chen Lin

1. Purpose - in nontechnical, lay language

a. Summarize the purpose and objectives of this protocol in one short paragraph. **There are over 7 million people living with stroke in the United States. Per year, approximately 17,000 veterans are admitted to the VA for acute stroke. Chronic pain after stroke can occur between 10-50% of stroke survivors. Post-stroke pain (PSP) can lead to further complications in a stroke survivor's recovery. Exercise has improved PSP and associated symptoms such as mobility, fatigue, and quality of life. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique using electromagnetic induction for cortical neurostimulation. The use of rTMS has been explored shown to be effective in treating chronic PSP but is limited in effect duration. Our proposal will test the hypothesis that rTMS is feasible and safe to be paired with exercise. Additionally, we believe a complementary effect can develop to enhance the neurostimulation duration of rTMS.**

b. Describe how outcomes will be measured for this protocol. **We will collect outcome measures as listed in Table 1: Schedule of Events below. Additionally, we will collect feasibility metrics (recruitment, refusal, attrition and retention rates) and safety outcomes. Finally, neuroimaging will be obtained and we will perform structural and functional connectivity analysis of the pre- and post-intervention imaging.**

2. Background - in nontechnical, lay language

Summarize in 2-3 paragraphs past experimental and/or clinical findings leading to the design of this protocol. Include any relevant past or current research by the PI. For drug and device studies, summarize the previous results (i.e., Phase I/II or III studies).

Chronic pain after stroke can occur between 10-50% of stroke survivors. Post-stroke pain (PSP) can lead to further complications in a stroke survivor's recovery including worsening depression, causing cognitive dysfunction, and even increasing suicidality rates. PSP is caused by the stroke itself and produces moderate or severe pain. It can manifest as new onset or worsening of prior headaches and/or somatic pain in the topographic region of the brain affected by the stroke. In 2018, persistent post-stroke headache, the pain syndrome focused in this proposal, was defined in the International Classification of Headache Disorders, 3rd ed. While acute headaches after stroke resolve within 3 months, persistent post-stroke headache have been defined to last >3 months and no other pain diagnosis better explains the symptoms. While the mechanisms are poorly understood, persistent post-stroke headaches are more frequent and more severe than acute stroke-related headaches.

In stroke survivors, exercise has improved symptoms such as mobility, fatigue, and quality of life. Exercise has the added benefit of promoting social interactions that can be associated with improved self-management. A recent clinical trial of stroke patients during inpatient rehabilitation who received aerobic exercise in combination with traditional physiotherapy had significantly less pain scores than those receiving traditional physiotherapy alone. A statement by the American Heart/Stroke Association recommended that exercise should be incorporated into the management of stroke survivors, noting the evidence strongly support the benefits early after stroke. In stroke patients, optimal exercise programs have begun at least a month after stroke and durations have ranged anywhere from frequency of 3-5x a week that last 1-3 months. With exercise protocols, the goal is target-based dosing using target heart rate

reserve and target heart rate dosing. Thus, repetition and time spent exercising matters less but reaching a certain physiologic state demonstrates reaching a sustainable target benefit from exercise. In stroke studies involving exercise, intervention begins ≥1 month after stroke. Our target population of persistent post-stroke headaches are required to have had symptoms >3 months after their stroke. Exercise can be performed in patients with walking difficulty because of the stationary cycle, to reach target dosing.

Repetitive transcranial magnetic stimulation (rTMS) uses noninvasive electromagnetic induction for cortical neurostimulation. The use of rTMS has been explored in several trials for patients with neuropathic pain including those with chronic PSP. The primary motor cortex has been used as the primary site for stimulation in several studies, including multicenter double-blind sham-controlled randomized clinical trials, examining the efficacy of rTMS for chronic PSP. Studies suggest that neurostimulation of the motor cortex modulates interconnected neural structures modulate pain pathways. rTMS allows for mapping of the brain, specifically locating the motor cortex and stroke lesion, to deliver more targeted stimulation compared with transcranial direct current stimulation. One-month post-intervention follow-up evaluation has precedent in prior studies using rTMS to treat headaches to estimate treatment effect. The clinical trials that showed improvement in pain scores received high frequency rTMS at the motor cortex.

rTMS was shown to be beneficial in multiple type of pain syndromes including musculoskeletal [30] and myofascial pain. A commissioned panel of European experts to establish rTMS guidelines on therapeutic use gave high frequency rTMS of the contralateral primary motor cortex a Level A recommendation for the evidence as a definite analgesic effect with few safety issues. However, the effects of the treatment are transient, usually lasting only a few hours to days. For rTMS to be a practical therapy for chronic PSP, more sustained efficacy would need to be demonstrated. In rTMS studies for stroke rehabilitation, neurostimulation was delivered prior to the physical activity. This additional neurostimulation was thought to help sustain motor recovery from the physical activity. We hypothesize that pairing rTMS prior to exercise develops a paired effect to enhance the duration of symptomatic relief in veterans suffering from chronic PSP.

3. Participants (Screening and Selection)

a. How many participants are to be enrolled?

Up to 100 patients will undergo the screening process. Our goal is to enroll 32 patients. We anticipate having to randomize 36 patients to reach the anticipated 32 patients that complete the study in entirety.

b. Describe the characteristics of anticipated or planned participants (if multiple groups, repeat list for each group).

Sex: **both**
Race/Ethnicity: **all**
Age: **19-89**
Health status: **stroke patients with headaches**

c. From what population(s) will the participants be derived? **Patients with stroke and headaches presenting to the Birmingham VA hospital will be recruited.**

Describe your ability to obtain access to the proposed population that will allow recruitment of the necessary number of participants: **Dr. Lin is a stroke neurologist at the BVAMC and has access to all stroke patients admitted to the BVAMC.**

d. Describe the inclusion/exclusion criteria:

Inclusion Criteria: 1) Male or female Veteran of US military ≥19 years of age; signed informed consent; 2) Minimum of 3-months since time of stroke and medically stable; 3) Headache has persisted for >3 months after stabilization of the stroke; 4) Ability to walk or tolerate recumbent cycle ergometry for 10 mins

without assistance; 5) Stable pain medication regimen for ≥1 month prior to study; 6) Females of child-bearing potential (i.e. not postmenopausal or surgically sterile) must be using a medically acceptable method of birth control and should not be pregnant nor have plans for pregnancy or breastfeeding during the study; 7) Completed diagnostic, maximal graded exercise test including 12-lead ECG and indirect calorimetry (i.e. oxygen uptake, minute ventilation, respiratory exchange ratio, etc.), and cleared for participation by an nurse research coordinator; 8) Minimum pain intensity of 30 on the Mechanical Visual Analogue Scale on average with pain symptoms.
Exclusion Criteria: 1) Moderate to severe cognitive impairment (Montreal Cognitive Assessment score <16/30); 2) Pre-stroke modified Rankin >2; 3) History of seizures; 4) Presence of any standard TMS or MRI contraindications (see human subjects); 5) Current diagnosis of DSM-5-defined bipolar disorder I, schizophrenia, schizoaffective disorder, or obsessive-compulsive disorder; 6) Diagnosis of moderate or severe substance use disorder (except for caffeine and nicotine) during the preceding 3 months (Participants must agree to abstain from illicit drugs during the study); 7) Increased risk of suicide that necessitates inpatient treatment or warrants additional therapy excluded by the protocol; and/or intensity of suicidal ideation (Type 4 or Type 5) or any suicidal behavior in the past 3 months on Columbia Suicide Severity Rating Scale (C-SSRS); 8) Litigating for compensation for a psychiatric disorder. Veterans who are in the process of applying for or receiving VA service-connected disability are eligible; 9) Current enrollment in another intervention trial for pain or stroke; 10) Persons imprisoned, of minor age, diagnosed with terminal illness, or require surrogate for consent; 11) Fails baseline exercise screening activities; 12) Persistent post-stroke headaches not better accounted for by another diagnosis; 13) Is unable to reliably attend intervention sessions i.e. planning to move, transportation issues; 14) Neurological disorder pre- or post-stroke affecting subject's ability to follow study directions.

e. If participants will comprise more than one group or stratification, describe each group (e.g., treatment/intervention, placebo, controls, sham treatment) **and** provide the number of participants anticipated in each group. **Up to 100 patients will undergo the screening process. Our goal is to randomize 32 patients with 16 in the sham and 16 in the active rTMS group. We anticipate having to randomize 36 patients to reach the anticipated 32 patients.**

f. Indicate which, if any, of the special populations listed below will be involved in the protocol. Include the Special Populations Review Form (SPRF) if indicated.
☐ Pregnant Women: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Fetuses: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Neonates/Nonviable Neonates: SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Prisoners: Attach SPRF—Prisoners
☐ Minors (<18 years old): Attach SPRF—Minors
☒ Employees or students at institution where research conducted
☐ Persons who are temporarily decisionally impaired
☐ Persons who are permanently decisionally impaired
☐ Non-English Speakers
For each box checked, describe why the group is included **and** the additional protections provided to protect the rights and welfare of these participants who are vulnerable to coercion: **NA**

g. List any persons other than those directly involved in the protocol who will be at risk. If none, enter "None": **none**

h. Describe the recruitment process (e.g., medical record review, referrals, letter of invitation, existing patients) that will be used to seek potential participants (e.g., individuals, records, specimens). Research recruitment by non-treating physicians/staff may require completion of Partial Waiver of Authorization for Recruitment/Screening. **Recruitment: Veterans with chronic PSP will be recruited at the BVAMC through the inpatient neurology service, stroke clinic, pain clinic, and self-referral from clinic. The patients that are deemed eligible will have a recruitment letter mailed to them for further discussion of the study by the**

study team. After 7 days from mailing the study letter, the study team will call and/or email potential candidate from the contact information listed on their health records to confirm if they received the study letter. Recruitment prospects are high, as the Birmingham region encompasses one of the largest catchment areas for stroke in Veterans in the United States. Dr. Lin is a neurologist at the BVAMC and has direct access to the study population through the inpatient neurology service and outpatient neurology clinic.

i. If you will use recruitment materials (e.g., advertisements, flyers, letters) to reach potential participants, attach a copy of each item. If not, identify the source (e.g., IRB Protocol Number for approved databases) from which you will recruit participants. **None at this time.**

j. Describe the screening process/procedures for potential participants.

Screening: The screening procedure includes informed consent, vital signs, demographics, medication history, neurologic and psychiatric diagnostic evaluation, imaging studies, and medical history. Participants return for the baseline visit (within 2 to 30 days of screening). All potential participants will need to pass an Exercise Tolerance Test before randomization at the baseline visit. The test includes maximal graded exercise test including 12-lead ECG and indirect calorimetry (i.e. oxygen uptake, minute ventilation, respiratory exchange ratio, etc.), and clearance for participation by an Certified Registered Nurse Research Coordinator using established Exercise Clearance criteria followed the UAB Exercise Center.

4. Protocol Procedures, Methods, and Duration - in nontechnical, lay language

a. Describe the procedures for all aspects of your protocol. Tell us what you are doing.

Participants who continue to meet eligibility criteria are randomized into sham rTMS or active rTMS. Both groups receive exercise sessions. Schedule of events are shown in Table 1.

Table 1: Schedule of Events

Assessments	Screen	Baseline	Weekly from 0-8			Post 1-month
Informed Consent and HIPAA	X					
Demographics, Medical History, Physical, Height, ECG, Exercise Tolerance Test	X					
Vital Signs and Weight	X	X	X	X	X	X
Visual Analogue Scale (VAS) for Pain		X	X	X	X	X
Multiple Intelligences Development Assessment Scales (MIDAS), Pain Journal, and Brief Pain Inventory (BPI)		X	X	X	X	X
PTSD Checklist for DSM-5		X				X
Columbia-Suicide Severity/PHQ-9	X	X	X	X	X	X
modified Rankin Score and Stroke Scale		X			x	X
Montreal Cognitive Assessment		X			x	X
Stroke Impact Scale		X			x	X
Adverse Events and medications			X	X	X	X
Neuroimaging		X			x	

rTMS protocol: Both rTMS groups, active and sham, will be conducted identically. During the 8-weeks exercise protocol, patients will receive assigned rTMS treatment (rTMS vs sham rTMS) on the same day prior to each session of exercise 3x/wk. The PI will directly supervise/perform all rTMS procedures performed at the BVAMC Neuromodulation Center and will consult with Dr. McGregor from the Atlanta VA at study inception and as necessary during the project. Dr. Lin is certified in the application of TMS by Maastricht University. Dr.

McGregor has TMS certification from Harvard University's Berenson-Allen Center. First, resting motor threshold (RMT) is measured by the motor evoked potentials in the hand's first dorsal interosseous muscle on the same side as pain, to standardize procedure. RMT is defined as the minimal intensity of stimulation while muscle is relaxed to elicit motor evoked potential of more than 50 mV in amplitude. Stimulation will be delivered using the Magstim magnetic stimulator. Each rTMS session consists of a series of 30 trains of 10 seconds in duration (30-second intertrain interval) at a stimulation rate of 10 Hz (3,000 pulses) and an intensity set at 90% of RMT. The frequency and duration were chosen because significant pain relief were obtained in prior studies in chronic neuropathic pain. Pain intensity will be examined in each patient before and after rTMS using the Visual Analogue Scale for pain and in the pain journal.

Exercise sessions: All participants will begin the exercise protocol for weeks 0-8. The 8-week standardized aerobic exercise training prescription progress from 20-minute to 40-minutes in-person sessions occurring 3 times per week on non-consecutive days (10 total sessions). Each session includes a combination of treadmill (TM) walking and stationary cycle ergometry (CE), and a combination of high-intensity interval training (HIIT) and moderate intensity steady- state exercise training (SST). Each session will be conducted under full supervision by a certified nurse at the BVAMC VA Therapy Gym. The exercise protocol has been successfully completed in multiple patient populations. Each exercise session begins with seated resting assessments for blood pressure (BP), heart rate reserve (HRR) and heart rate (HR), followed by 3-4 min warm-up at low intensity. Stopping rules: Exercise will be stopped due to inappropriate HR or BP responses, or at the participant's discretion. In cases where the participant reports intolerance or undue fatigue, workload adjustments (e.g., 10% reduction) may be made (and recorded) to encourage completion of the exercise session. Participant monitoring: Each individual session during supervised exercise training is monitored closely by a research nurse.

Outcome measures for subjects are collected per Table 1 schedule of Measures will be collected either while patients are in clinic during a standard of care visit at the VA Clinic, at a private preparation area either before or after their imaging at Highlands, at a private rTMS clinic room in the 7th Floor VA Neurology Clinic.

Data to be collected on subjects from the electronic medical record for this study includes demographics (sex, age, race, symptoms, medical history, smoking history, anatomical level/grade of intracranial stenosis); lab results, medications, inpatient records related to stroke, imaging results, and standard clinical assessment from rehabilitation stay and clinical visits.

b. What is the probable length of time required for the entire protocol (i.e., recruitment through data analysis to study closure)? 2 **years**

c. What is the total amount of time each participant will be involved? **3 months**

d. If different phases are involved, what is the duration of each phase in which the participants will be involved? If no phases are involved, enter "None." **none**

e. List the procedures, the length of time the procedure takes, the total # of times the procedure is performed

Table 1: Schedule of Events

Assessments	Screen	Baseline	Weekly from 0-8			Post 1-month
Informed Consent and HIPAA (20 mins)	X					
Demographics, Medical History, Physical, Height, ECG, Exercise Tolerance Test (1 hour)	X					
Vital Signs and Weight (5 mins)	X	X	X	X	X	X
Visual Analogue Scale (VAS) for Pain (2 mins)		X	X	X	X	X

Multiple Intelligences Development Assessment Scales (MIDAS), Pain Journal, and Brief Pain Inventory (BPI) (15 mins)		X	X	X	X	X
PTSD Checklist for DSM-5 (10 mins)		X				X
Columbia-Suicide Severity/PHQ-9 (10 mins)	X	X	X	X	X	X
modified Rankin Score and Stroke Scale (10 mins)		X			x	X
Montreal Cognitive Assessment (10 mins)		X			x	X
Stroke Impact Scale (10 mins)		X			x	X
Adverse Events and medications (10 mins)			X	X	X	X
Neuroimaging (60 mins)		X			x	

f. Will an interview script or questionnaire be used? ☒Yes ☐No

If Yes, attach a copy.

g. Will participants incur any costs as a result of their participation? ☐Yes ☒No

If Yes, describe the reason for and amount of each foreseeable cost. _____

h. Will participants be compensated? ☒Yes ☐No

If Yes, complete i-v.

i. Type: (e.g., cash, check, gift card, merchandise): Check

ii. Amount or Value: 250

iii. Method (e.g., mail, at visit): $50 after screen and baseline visit, $50. After visits 5 and visit 10. With a $100. Payment after their 30-day follow-up visit.

iv. Timing of Payments: (e.g., every visit, each month: See above

. Maximum Amount of Compensation per Participant: $250

5. Benefits

Describe the potential benefits of the research. **There is no direct benefit to the subjects. However, the investigators hope that knowledge gained in this study will help with patient stroke recovery outcomes.**

6. Risks - in nontechnical, lay language

a. List the known risks for participants as a result of participation in the research. This should not include the minimal risk of loss of confidentiality. However, it should include any physical, psychological, social, economic, and/or legal risks. If there is a greater than minimal risk of loss of confidentiality describe why this is so. Do not list risks associated with the standard-of-care procedures.

NOTE: Risks included here should be included in the consent form or information sheet, as applicable.

Physical Risks

rTMS: Although extremely rare, seizures have been described with rTMS, mainly in subjects who have a history of seizure. In some case reports, it was difficult to differentiate seizures from fainting or a convulsive syncope. The TMS coil makes noise, much like a loud pop when it produces its magnetic energy. Subject may or may not feel thumb twitch depending on the strength of the TMS pulse, but subject might also feel your facial muscles twitch slightly just around the eye. It is not painful. TMS can cause heating or movement of metallic objects in or near the head. In addition, the inactivation of pacemakers, medication pumps, cochlear prostheses and other implantable hardware may occur but subject with these metal implants are excluded from the study.

Exercise: Exercise Tolerance Testing: The risks of the exercise tolerance tests are minimal but could include fainting, falling, irregular heartbeat, and very rarely heart attack, stroke, or death (less than 1 in 2500 cases). Professional staff (clinically trained nurse practitioner and/or exercise physiologist) will be present and available throughout and emergency treatment will be available if it becomes necessary. Testing clearance will be required before enrollment into trial. Exercise Training (ET): There are no significant risks to the subjects in the proposed ET methods. The risks to individuals participating in this portion of the study are no greater than the risks when providing conventional physical therapy services to an individual after stroke. The same precautions and safety guidelines

will be taken that are used in Exercise Centers such as the UAB Center for Exercise Medicine to patient care.
Clinical Testing: The functional assessments used in the proposed study are routine, clinical assessments of gait and stroke impairments used in stroke outpatient and therapy clinics. The experimental protocol to be used in this portion of the proposal involves minimal risk and is considered standard clinical practice.
MRI Neuroimaging: The MRI scanner contains a very strong magnet. Therefore, participants may not be able to have the MRI if they have certain types of metal implanted in their body, for example, any pacing device (such as a heart pacer), any metal in their eyes, or certain types of heart valves or brain aneurysm clips. Although there is no indication that MRI is unsafe during pregnancy, if the participant is female, she will be asked to take a urine pregnancy test to verify that she is not pregnant. There is not much room inside the MRI scanner. The participant may be uncomfortable if they do not like to be in close spaces ("claustrophobia"). If the participant becomes uncomfortable at any time, they can request that the scan be stopped. All participants will pass an MRI screen to decrease risk of adverse events.

b. Estimate the frequency, severity, and reversibility of each risk listed. **Possible physical risks would be serious and possibly not reversible, but are highly unlikely and rare. There is also a possibility of experiencing a localized twitching sensation due to magnetic field changes during rTMS and imaging; this is expected, should not be painful, and is reversible after exiting the magnetic environment. The ET program and the clinical testing should not present a risk for the patient but could result in muscle soreness and/or joint stiffness, but these symptoms should not persist more than a few days. There is a minimal risk for muscle strains during the testing and training.**

Assessments/Questionnaires: Risk is minor and readily reversible.

c. Is this a therapeutic study or intervention? ☒Yes ☐No
If Yes, complete i.-iii.
i. Describe the standard of care in the setting where the research will be conducted: **these patients would typically be followed in the Headache or Stroke clinic and be given pharmacologic options to treat their headaches/post-stroke pain.**
ii. Describe any other alternative treatments or interventions: **continued standard of care treatments with pharmacologic approaches.**
iii. Describe any withholding of, delay in, or washout period for standard of care or alternative treatment that participants may be currently using: **N/A**

d. Do you foresee that participants might need additional medical or psychological resources as a result of the research procedures/interventions? ☐Yes ☒No
If Yes, describe the provisions that have been made to make these resources available. _____

e. Do the benefits or knowledge to be gained outweigh the risks to participants? ☒Yes ☐No
If No, provide justification for performing the research: _____

7. Precautions/Minimization of Risks

a. Describe precautions that will be taken to avoid risks and the means for monitoring to detect risks. **The UAB Highlands facility screens for any MRI safety concerns to reduce imaging risks. Subjects that are fatigued during assessment will be offered breaks.**

If the protocol involves drugs or devices skip Items 20.b. and 20.c. and go to Item 21. Instead include this information in the Drug Review Sheet or Device Review Sheet, as applicable.

b. If hazards occur to an individual participant, describe (i) the criteria that will be used to decide whether that participant should be removed from the protocol; (ii) the procedure for removing such participants when necessary to protect their rights and welfare; and (iii) any special procedures, precautions, or follow-up that will be used to ensure the safety of other currently enrolled participants. **A participant will be able to withdraw from the study at any time, at their request. If for any reason an unforeseen hazard arises with an individual participant, the session will be terminated, and the protocol will be modified to prevent the hazard with other participants. The investigators are experienced neurologists who are operating in a supportive medical center environment where medical, pain, exercise, and mental health specialists are conveniently located for immediate consultation if needed. Before any tests are conducted, the protocol and tests to be used in this study and the potential risks and benefits of participation will be explained to each potential subject. All participants will review and sign an informed consent form approved by the local Institutional Review Board prior to initiating any portion of the study. A physician will be available 24 hours and 7 days per week for the participant to contact or be evaluated by in the event of a serious adverse event or emergency. Inpatient medical or psychiatric care is available at our study site.**

Protections Against Physical Risks of rTMS: In order to protect research subjects, study staff have to strictly follow inclusion and exclusion criteria of this study (see exclusion criteria). In addition, our site will follow general TMS procedures to ensure the safety of subjects. TMS is applied by only trained staff. There will be a training workshop at the beginning of the study. The risk of seizures with rTMS is extremely rare and occurs only in patients with a history of seizure. Subjects with a history of seizures will be excluded from this study.

Protections Against Physical Risks of Exercise: A licensed exercise physiologist, licensed physician, or trained clinical coordinator will be present during all exercise treatment sessions. The research staff will closely monitor subjects to ensure their comfort. Any adverse events will be recorded and monitored as required by the local Institutional Review Board. In the event of an adverse medical event, standard facility at the Center for Exercise Medicine emergency procedures will be followed and proper personnel notified. The PI on this proposal is a Board-Certified Vascular Neurologist with years of experience in managing patients with stroke. Further, our exercise advisor, Dr. Bamman, was the former Director for the Center of Exercise Medicine and the GRECC with decades of experience in the development and implementation of exercise interventions for individuals following stroke. Subjects will be able to terminate sessions at their request at any time without prejudice. Minimization of risk will be accomplished by monitoring vital signs within prescribed criteria for termination of the exercise sessions. We will follow the American College of Sports Medicine criteria for terminating an exercise session which includes subject complaints of light-headedness, confusion, or dyspnea; onset of angina; excessive blood pressure changes (systolic BP greater than 220 mmHg, diastolic BP greater than 110 mmHg); and inappropriate bradycardia (drop in heart rate >10 beats per minute).

If medical assistance is required during the MRI, researchers will follow the CINL protocol for emergencies: 1) Remove participant from the magnet, 2) Call UAB Police and Security (205-934-3535) who will page Health and Safety, 3) Once the immediate safety of the participant has been assured, researchers will contact CINL staff (MRI technologist and director). As the scanner is housed in the UAB Highlands Hospital, medical staff will also be accessible.

c. If hazards occur that might make the risks of participation outweigh the benefits for all participants, describe (i) the criteria that will be used to stop or end the entire protocol and (ii) any special procedures, precautions, or follow-up that will be used to ensure the safety of currently enrolled

participants. **If such adverse events occur the PIs will discuss the issues with IRB staff and consider terminating the entire study.**

In the event of incidental findings on imaging, researchers will follow CINL policy.

8. Informed Consent

a. Do you plan to obtain informed consent for this protocol? ☒Yes ☐No
If Yes, complete the items below.
If No, complete and include the Waiver of Informed Consent or Waiver of Authorization and Informed Consent, as applicable.

b. Do you plan to document informed consent (obtain signatures) for this protocol? ☒Yes ☐No
If Yes, complete the items below.
If No, complete the items below **and** include the Waiver of Informed Consent Documentation.

c. How will consent be obtained? **Consent will occur in person in a private setting. The consent discussion will occur for as long as necessary for the participant to understand the study. The participant will be able to ask questions and take as much time as needed to consider whether or not to participate. Participants will be able to review the consent form at their leisure and not be pressured by the research team to participate.**

d. Who will conduct the consent interview? **Only members of the research team.**

e. Who are the persons who will provide consent, permission, and/or assent? **Participants**

f. What steps will be taken to minimize the possibility of coercion or undue influence? **Participants will be able to review the consent form and be given adequate time to consider whether or not they want to participate.**

g. What language will the prospective participant and the legally authorized representative understand? **English**

h. What language will be used to obtain consent? **English**

i. If any potential participants will be, or will have been, in a stressful, painful, or drugged condition before or during the consent process, describe the precautions proposed to overcome the effect of the condition on the consent process. If not, enter "None." **none**

j. If any protocol-specific instruments will be used in the consenting process, such as supplemental handouts, videos, or websites, describe these here and provide a copy of each. If not, enter "None." **none**

k. How long will participants have between the time they are told about the protocol and the time they must decide whether to enroll? If not 24 hours or more, describe the proposed time interval and why the 24-hour minimum is neither feasible nor practical. **24 hours unless the subject would like to enroll sooner at the time they are approached for their own convenience.**

9. Procedures to Protect Privacy

Describe how you will protect the privacy interest of the participants. Include how you will make sure others cannot overhear your conversation with potential participants and that individuals will not be

publicly identified or embarrassed. **Other will not be able to overhear conversations about or with potential participations. No participants will be publicly identified or embarrassed. Study discussions will occur in private.**

10. Procedures to Maintain Confidentiality

a. Describe how you will store research data to maintain confidentiality (both paper records and electronic data), including how access is limited. If data will be stored electronically anywhere other than a server maintained centrally by UAB, identify the department and all computer systems used to store protocol-related data. **Names, contact information, and eligibility for rTMS, exercise, and MRI will be necessary to ensure safety and to allow follow-up. No PHI will be disclosed outside our research group. Research paperwork data will be kept in Dr. Lin's locked office in BVAMC Room 8305. All electronic data will be identified by a study code number. The coded data will be stored on a password- and firewall-protected VA server on a VA computer. The research data will only be accessible to study personnel. All data analysis will occur behind VA firewall- and password-protected on VA computers in a research folder. The document linking the subject id to subject PHI will be kept in a separate secure location from the study database with access to study personnel only.**

Since the MRI images are created at UAB for research purposes, UAB agrees to provide a copy of the imagery, via a CD, to the VA PI for record retention. At the completion of imaging for each patient, a report will be documented in their medical record stating: "A MRI Brain was performed at UAB Highland for research purposes only." Along with the study team information.

b. Will any data from this protocol be given to any person, including the subject, or any group, including coordinating centers and sponsors? ☒Yes ☐No

If Yes, complete i-iii.

i. Who will receive the data? **publications**

ii. What data will be shared? **Aggregate data**

iii. How will the data be identified, coded, etc.? **de-identified**

c. Records Management: **Research records maintained by the investigator that span the entire lifecycle of the project and the records required by regulations such as the investigator's regulatory file will be maintained and destroyed per the VHA Records Control Schedule (RCS 10-1).**