Protocol

Protocol Title: A randomized placebo-controlled trial of methylphenidate in Veterans with a diagnosis of post-traumatic stress disorder and recent cerebral stroke
Protocol Version: 5
Protocol Date: 7/11/24
Principal Investigator: Chen Lin, MD

1. Purpose - in nontechnical, lay language

a. Summarize the purpose and objectives of this protocol in one short paragraph. **Veterans with post-traumatic stress disorder (PTSD) have an increased risk of developing ischemic stroke. Veterans enduring PTSD face difficulties in managing their PTSD severity after suffering from a stroke. Methylphenidate (MPH) is a central nervous system stimulant that blocks dopamine and norepinephrine transporters. MPH can improve PTSD symptoms: avoidance behaviors, social withdrawal, hyperarousal, and working memory. The high prevalence of PTSD in Veterans with stroke provides strong justification for development of interventions that effectively and simultaneously target both conditions. The overarching goal of our proposal is to understand how MPH improves PTSD severity in Veterans with comorbid stroke.**

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 for those without standard MRI contraindications, 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).

Veterans with post-traumatic stress disorder (PTSD) have an increased risk of developing ischemic stroke. Veterans enduring PTSD face difficulties in managing their PTSD severity after suffering from a stroke. Currently, clinical trials in PTSD exclude patients with stroke and patients with significant premorbid psychological conditions like PTSD are usually excluded from stroke clinical trials. Methylphenidate (MPH) is a central nervous system stimulant that blocks dopamine and norepinephrine transporters, selectively increasing prefrontal cortex (PFC) activity. MPH can improve PTSD symptoms: avoidance behaviors, social withdrawal, hyperarousal, and working memory. The suspected mechanism is MPH activates PFC, enhancing fear extinction and improving PTSD symptoms. MPH can also improve post-stroke outcomes: mood, activities of daily living, and motor functioning. In clinical trials for PTSD or stroke, MPH has been shown to be well-tolerated with minimal adverse events. The high prevalence of PTSD in Veterans with stroke provides strong justification for development of interventions that effectively and simultaneously target both conditions. The overarching goal of our proposal is to understand how MPH improves PTSD severity in Veterans with comorbid stroke.

This proposal is a single-site, phase 2, randomized double-blind placebo-controlled trial of MPH in the treatment of Veterans with a diagnosis of PTSD who are within 1-12 months of cerebral stroke. The purpose of the clinical trial is to evaluate the therapeutic effects on PTSD symptoms and post-stroke recovery of placebo-controlled MPH in Veterans diagnosed with PTSD and cerebral stroke. The outcome of the proposed work is expected to develop an intervention for patients with PTSD and stroke, thus improving their outcome by reducing symptom severity. Following successful screening and baseline randomization, eligible patients will be treated with a regimen of MPH vs placebo. 60 participants will

be randomized in a 1:1 ratio to placebo or MPH. We will perform a mechanistic study by examining changes in connectivity of the PFC pre- and post- MPH. Thus, we propose to conduct a randomized double- blind placebo-controlled trial of MPH to evaluate PTSD and stroke outcomes.

3. Participants (Screening and Selection)

a. How many participants are to be enrolled?

Up to 300 patients will undergo the screening process. Our goal is to enroll 60 patients. We anticipate having to randomize 60 patients to reach the anticipated 50 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: **40-75**
Health status: **stroke patients with PTSD**

c. From what population(s) will the participants be derived? **Patients with stroke and PTSD 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 (all must be met):
1. Male or female Veteran of US military [40 to 75] years of age; signed informed consent
2. Criterion A Index Trauma(s) resulting in PTSD occurred during adulthood prior to stroke
3. CAPS-5 score ≥23 at baseline visit
4. Willing to refrain from antipsychotics, mood stabilizers, stimulants, and any formulation of MPH
5. Most recent symptomatic ischemic stroke radiologically verified, occurring within past 1-12 months
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
Exclusion Criteria (one or more will exclude the Veteran):
1. Moderate to severe cognitive impairment (Montreal Cognitive Assessment score <16/30).
2. Poor pre-stroke baseline function of a modified Rankin score >2.
3. Current diagnosis of DSM-5-defined bipolar disorder I, schizophrenia, schizoaffective disorder, obsessive-compulsive disorder, or major depressive disorder with psychotic features in medical record review.
4. Diagnosis of moderate or severe substance use disorder (except for caffeine and nicotine) during the preceding 3 months. Patients who utilize alcohol or cannabis but do not meet criteria for moderate or severe disorder are permitted at the discretion of the investigator. Participants must agree to abstain from illicit drugs during the study.
5. 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).
6. Use of any investigational drug, MPH formulation, antipsychotics, mood stabilizers, monoamine oxidase inhibitors, stimulants or any medication known to be a potent (strong) cytochrome P450 subtype 3A4 inhibitor within 2 weeks of baseline.
7. Treatment with evidence-based trauma-focused therapy for PTSD within two weeks of baseline

(If participant is receiving therapy, he/she must complete treatment prior to entering study). Supportive psychotherapy in process at time of Screening may be continued during the study.
8. History of moderate or severe TBI as defined by the Ohio State University TBI Identification Method. Based on investigator's clinical judgment, history of mild TBI is not excluded.
9. Any clinically significant, uncontrolled, or medical/surgical condition or laboratory abnormality that would contraindicate use of MPH (see Human Subjects section)
10. Severe allergic reaction, bronchospasm, or hypersensitivity to any MPH formulation.
11. Litigating for compensation for a psychiatric disorder. Veterans who are in the process of applying for or receiving VA service-connected disability are eligible.
12. Current enrollment in another intervention trial for PTSD or stroke
13. Persons imprisoned, diagnosed with terminal illness, or require surrogate for consent.

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 300 patients will undergo the screening process. Our goal is to randomize 60 patients with 30 in the placebo and 30 in the active medication group. We anticipate having to randomize 60 patients to reach the anticipated 50 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 PTSD and Stroke will be recruited at the BVAMC through the inpatient neurology service, stroke clinic, mental health clinic, and self-referral from clinic. Flyers will be given by study team to providers to give to potential interested participants to contact study team. Letters will be sent to the patients (by the study team) from the clinics after they have been identified as potential candidates via mail or VA email. After 7 days from sending the study letter, the study team will call, text, and/or send a VA email to potential candidate(s) 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. We are requesting a waiver of documentation of the informed consent to perform a CAP-5 survey that will determine if a potential participant meets eligibility to participate in the research study. If the score reflects eligibility, the participant will be consented to participate in the study.**

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. Flyer/advertisement submitted for review**.** The following will be the texted from a VA phone sent to participant number:

"Dear Mr./Mrs./Ms. _____,

I am with the Birmingham VA Medical Center. I was reaching out to you to potentially discuss participating in a study evaluating how well an FDA-approved drug works to reduce symptoms of Post-Traumatic Stress Disorder (PTSD) in patients that have suffered recent stroke. Participation in this study is voluntary and a decision to join or not will have no impact on your VA healthcare or other benefits. Please let me know whether you are interested or not interested by texting or calling this number 205-240-6552. Thank You!"

The following will be the emailed from a VA email if a participant's email is provided:

"Dear Veteran:

The Birmingham VA Medical Center invites you to consider participating in a research study evaluating how well an approved study drug works to reduce symptoms of Post-Traumatic Stress (PTSD) in patients that have suffered stroke. The symptoms of PTSD commonly include distressing memories, nightmares, or flashbacks of a prior traumatic event, significant avoidance of people or situations that remind you of the traumatic event, difficulty sleeping through the night, negative thoughts or feelings, difficulty experiencing positive feelings, poor concentration, anger and increased worry about your safety.

If you are interested in participating, please contact a member of our team for a brief phone call that will help determine if you are potentially eligible. If you are still interested, we ask you to stop by our clinic for further evaluation located on the 2d floor of the Birmingham VAMC, in Clinic 2K, office 2819. All information is kept confidential. Participation in this study is completely voluntary and a decision to join or not will have no impact on your VA healthcare or other benefits. As an alternative to participating in the study, the VA Medical Center closest to you offers treatment for PTSD to eligible veterans.

If you consent to be in the study, you will be evaluated by the medical research team. You will be treated with either the study drug or placebo for 12 weeks, and we will follow-up with you over a 16-week period as explained below.

There are no costs for you to participate in this study. In return for your time, effort, and travel expenses, you will be paid for taking part in study assessments. If you stop participating for any reason, you will be paid for only the assessments that you complete. The total possible compensation for attending all visits is $300, as described below:

- Screening and Eligibility Assessments, including an MRI: $50
- Week 4 assessment: $50
- Week 8 assessment: $50
- Week 12 assessment: $50
- Completion of final 1-month follow-up: $100

For more information, to find out if you qualify, or if you wish to opt out from being contacted further, call 205-240-6552 or email megan.baker6@va.gov. If we have not heard from you within 7 days, a study

member may contact you to gauge your interest. You can also stop by the Birmingham VAMC Research Service offices, located on the 2d floor of the Birmingham VAMC, in Clinic 2K, office 2819. Thank you for considering this invitation to participate in this study."

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

Screening: **The screening procedure includes informed consent, vital signs, demographics, disability status, medication history, neurologic and psychiatric diagnostic evaluation, imaging studies including CT and MRI scans, review of medical conditions, physical exam, ECG, and laboratory tests (hematology, chemistry, liver and thyroid function tests, blood chemistry, urinalysis, urine screen for drugs of abuse, lipid profile, and serum pregnancy test for women of child-bearing potential). If laboratory test or ECG is not available to review in the Veteran's medical records, the study will obtain prior to randomization. Clinical characteristics including time since stroke and stroke location will be recorded. We will document recent PTSD therapies completed within last 6 months. A Veteran who is meeting eligibility criteria except for an excluded medication that is not tolerated or beneficial may undergo a tapered washout of the excluded medication if this plan is clinically indicated regardless of study participation.**

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 Methylphenidate or placebo. Schedule of events are shown in Table 1. Following successful screening and baseline randomization described above, eligible patients will be treated with a regimen of MPH vs placebo and treated for 12 weeks. They are assessed in-person every 4 weeks (4, 8, 12) and conclude with a final follow-up at 30 days. The participant is assessed by telephone every 2 weeks when not evaluated in-person (week 2, 6, and 10) for treatment-emergent side effects. 60 participants will be randomized in a 1:1 ratio to placebo or MPH. Specifically for the CAPS-5 measure, the measure will be recorded by a VA-approved audio recorder (Philips DPM-8000). Co-investigators will review the recording to ensure agreement in scoring.

Table 1: Schedule of Events

Assessments	Screen	Baseline	Wk 4	Wk 8	Wk 12	30 days after taper
Informed Consent and HIPAA	X					
Demographics, Medical History, Physical, Height, ECG, Labs.	X					
Verify Eligibility Criteria in CPRS	X					
Ohio State University TBI	X					
Emory Treatment Resistance Interview for PTSD	*X*					
Life Events Checklist	X					
Vital Signs and Weight	X	X	X	X	X	X
CAPS-5	X	X	X	X	X	X
PTSD Checklist for DSM-5		X	X	X	X	X
Columbia-Suicide Severity	X	X	X	X	X	X
Patient Health Questionnaire 9		X	X	X	X	X
Fatigue Severity Scale		x			x	x
modified Rankin Score		X	X		X	X
NIH Stroke Scale		X			X	X

Montreal Cognitive Assessment		X	X		X	X
Stroke Impact Scale-16		X	X		X	X
Study Drug Adherence			X	X	X	
Concomitant Medication			X	X	X	X
Adverse Events			X	X	X	X
Review PTSD therapies completed	X					X
Neuroimaging		X				X

Medication Protocol: The study drug is dispensed from the VA pharmacy according to the assignment after the medication order is entered by the investigator. In this double-blind design, both participants and research team will remain blinded to drug/placebo for the duration of the trial; however, pharmacy has procedures for breaking blind for emergency situations to non-research provider of care. At randomization, the study personnel will provide participants the instructions for taking the drug. The dose of MPH for this proposal will be similar to that used in prior PTSD trials. Study drug (MPH vs look-alike placebo) is initiated at 10 mg once daily for the first week, 10 mg twice daily for the second week. After the second week, participants will stay on the 20mg twice daily dosing until week 10. Participants start tapering at week 10 for a 2-week taper. The first week taper will be at 10 mg twice daily, followed by 10mg once daily for a week, and then stop the medication. If an adverse effect is believed to be associated with medication, participants' dose will be held or decreased to a prior dose instead of proceeding with the scheduled increases.

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, or at a private 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)? **5 years**

c. What is the total amount of time each participant will be involved? **4-5 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. **See Table 1: Schedule of events**

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 or direct deposit
ii. Amount or Value: $300 total
iii. Method (e.g., mail, at visit): at visit

iv. Timing of Payments: (e.g., every visit, each month): $50 each after completing the following: baseline visit, week 4, week 8, and week 12 visits. $100 for completing the final 1-month follow-up.
v. Maximum Amount of Compensation per Participant: $300

5. Benefits

Describe the potential benefits of the research. **There may or may not be direct benefit to participants no direct benefit to the subjects. However, the investigators hope that knowledge gained in this study will help with patient with PTSD and 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

Methylphenidate: Participants will be screened by the eligibility criteria and be excluded if participants have any contraindications to methylphenidate including hypersensitivity reactions such as angioedema and anaphylactic reactions to methylphenidate.

Nervousness and insomnia are the most common adverse reactions reported in clinical trials and post-marketing surveillance. In addition, patients have reported loss of appetite, abdominal pain, weight loss during prolonged therapy, and tachycardia. Other potential side effects include:

• Cardiac: angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia.
• Gastrointestinal: abdominal pain, nausea.
• Immune: hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme, and thrombocytopenic purpura.
• Metabolism/Nutrition: anorexia, weight loss during prolonged therapy.
• Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis
• Vascular: blood pressure increased or decreased; cerebrovascular vasculitis; cerebral occlusions; cerebral hemorrhages and cerebrovascular accidents.
• Blood/Lymphatic: leukopenia and/or anemia
• Hepatobiliary: abnormal liver function, ranging from transaminase elevation to hepatic coma
• Psychiatric: transient depressed mood, aggressive behavior
• Skin/Subcutaneous: scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

The investigators will closely monitor the veteran for all possible side effects and adverse events. This study uses a low dose and duration of methylphenidate, which reduces the chances of an adverse event.

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: MRI will be obtained in patients that pass routine MRI screening. 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 serious physical risks would be possible and not reversible but are highly unlikely and rare. The transient milder symptoms associated with methylphenidate (i.e., nervousness, insomnia) are more likely and frequent based on post-marketing surveillance data as noted above. These are reversible symptoms and should not be persistent. 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 Mental Health or Stroke clinic and be given pharmacologic options to treat their PTSD symptoms. No known a pharmacologic treatments exist to improve outcomes for the combination of patients with PTSD symptoms and stroke recovery.**

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 participant 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. _____

From the screening point forward, diphenhydramine or a nonbenzodiazepine hypnotic may be used sparingly (not to exceed three times per week) for severe insomnia or agitation.

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.

Overall Protection: The investigators are experienced neurologists and a psychiatrist who are operating in a supportive medical center environment where medical, mental health, and PTSD 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. While we do not anticipate any serious adverse events, participants will be given detailed information (verbal and written) regarding the steps to take in the event of a serious side effect or emergency. 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.
Adverse Event Monitoring: Common side effects are listed in the informed consent and are reviewed by the participant at screening visit. Adverse events, weight, and vital signs are evaluated at each assessment visit. All adverse events are recorded at each visit (description, severity, relationship to study medication, intervention, date onset, date resolution) regardless of relationship to study medication, and are MedDRA coded. Serious adverse events are reported to the data monitoring committee (DMC) and IRB.

Data and safety monitoring for this study will be provided by the Clinical Science Research & Development (CSR&D) centralized Data Monitoring Committee (DMC). The DMC is provided by CSR&D to ensure independent oversight of the safety and integrity of the project. The DMC is an independent multidisciplinary group, whose members have collectively – through research, education, training, experience, and expertise – the requisite knowledge pertinent to the subject areas to be reviewed. Membership details are available on the CSRD website. The DMC will provide an ongoing independent evaluation of this study focused on safety and feasibility, including participant accrual and retention, adverse events monitoring, and data analyses. Meetings will be held two times per year at which time recommendations will be made to the Director of CSR&D for endorsement. These recommendations will range from approval to continue (unconditionally or with conditions to be addressed) to probation or possibly termination, if there are problems with enrollment or safety concerns.

Concomitant Medication and Psychotherapy: Participants may remain on antidepressants, prazosin, or sleep medications if every effort is made for the doses to remain stable during the study. Opiates and other medications for pain conditions will be allowed and recorded in the concomitant medication inventory. All concomitant medication use will be carefully documented. While dose stability is the goal, any changes in dosages during participation that are medically warranted are recorded and
may be leveraged in outcomes data interpretation. The following psychotropic medications are not allowed during the study: mood stabilizers (lithium, carbamazepine, valproate, lamotrigine), benzodiazepines, and neuroleptics. Treatment with trauma-focused therapy (e.g., CPT, PE, or EMDR) for PTSD within two weeks of baseline (if participant is receiving therapy, he/she must complete treatment prior to entering study) is not allowed. Veterans who want this type of treatment may enroll in a course of treatment and complete it prior to study participation. Participants may attend supportive-educational appointments that were initiated prior to entry.

Allowed Rescue Medication: From the screening point forward, diphenhydramine or a nonbenzodiazepine hypnotic may be used sparingly (not to exceed three times per week) for severe insomnia or agitation. We considered the use of other low dose psychotropics, but for safety reasons it is important to avoid benzodiazepines in this population.

Protections Against Physical Risks of Methylphenidate or Placebo: The eligibility criteria will exclude patients who have contraindicated conditions. The investigators will closely monitor the veteran for all possible side effects and adverse events. This study uses a low dose and duration of methylphenidate, which reduces the chances of an adverse event. The Principal Investigator will evaluate adverse events at the study assessments and is available for consultation as needed by the participant or the family. Further, the Co-Investigator, Dr. Davis, is board certified in psychiatry with many years of experience developing

psychopharmacologic clinical trials for veterans with PTSD. Common side effects will be listed in the informed consent and will be reviewed by the participant at screening visit. Adverse events, weight, and vital signs are evaluated at each visit.

Contraindications and monitoring requirements for the study: hypersensitivity reactions such as angioedema and anaphylactic reactions to methylphenidate, marked anxiety, tension and agitation since drug may aggravate, glaucoma, motor tics, concomitant use of monoamine oxidase inhibitors or within 14 days after their discontinuation. Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder such as bipolar illness, emergence of new psychosis or manic symptoms. Patients that develop seizures, gastrointestinal obstruction, need for surgery that might interfere with participant's ability to participate, and/or oral/dental condition that interferes with oral administration, priapism, peripheral vasculopathy including Raynaud's Phenomenon will be monitored during the study. Clinically significant cardiac disease, (e.g., significant arrhythmia or heart block, heart failure, or myocardial infarction within the past 2 years) or QTc >450 msec (male) or >470 msec (female) on electrocardiogram (ECG) will be excluded. Stimulant medications cause a modest increase in average blood pressure (about 2 to 4 mm Hg) and average heart rate (about 3 to 6 bpm), and individuals may have larger increases. Blood pressure and heart rate will be monitored after initial methylphenidate dosing. Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment will be asked to undergo a prompt cardiac evaluation.

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 and psychiatrists who are operating in a supportive medical center environment where medical, neurologic, 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.

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 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 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 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, including any audio recordings, will only be accessible to study personnel. All private data will be stored behind a 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).**

11. Statistical Analysis

Based on feasibility of enrollment within the time period and budget allowed, 60 Veterans (30 in each group) will be randomized and included in the analysis. Since the effect sizes estimated from Lin's study will be used to help design future large-scale efficacy studies, we follow the recommendations derived via simulation by Whitehead et al. to justify our sample size. Our sample is sufficient to generate estimates to be used in designing a subsequent larger trial that will have approximately 85% power to detect even small effect sizes (d = 0.1 to 0.3). An effect size of Cohen's d = 0.43 which we shall approximate represents the minimum significant effect size reported in previous PTSD clinical trials (range = 0.43-1.3) and is greater than the minimum effect size needed to achieve clinically meaningful changes in symptoms on the CAPS-5

(d = 0.39). While these trials are PTSD-specific and do not account for PTSD comorbid with stroke, we expect the averages of outcome measures to be different but the variability and deviation of measures to be the same.

The investigators estimate that with equal numbers of subjects randomized to each of two treatments groups the samples size will have about an 80% power to detect a moderate effect size=0.41, two-sided alpha level of 0.05) at 12 weeks for CAPS-5. In the PTSD and TBI study by McAllister et al (2016), MPH (n=9) was shown to have significant differences in decreasing the PTSD symptoms compared to placebo (n=12) with an effect size of 0.88 at week 12 and with similar effects for PTSD symptom clusters. According to McAllister et al. (2016) the effect sizes for the improvement of MPH over Placebo for the PTSD are well above 0.41 which would increase the power to close to 0.80 with a moderate effect size for the change in endpoint results over the baseline to final assessment. In addition, we theoretically will see synergistic effects of the combination treatment that further amplifies the effect size.

Analytic Approach: The analyses will include all available observations (i.e. from the various assessment times) from each subject. Mixed-Effect Model of Repeated Measure (MMRM) provides valid inference under the assumption of ignorable missingness. No imputation processes will be used to replace missing data. However, every effort will be made to minimize missing data. Because missing observations have the potential to alter the results of analyses, the analysts will examine whether the pattern of missing data is different among the two groups. The analysts will also examine the distribution of baseline covariates between those with and without missing outcome data. If there are no systematic differences between those with and without missing data, the data will be considered to be missing at random. If there are significant differences in dropout or missing data patterns between treatment arms, the analysts will conduct sensitivity analyses to determine the impact of missing information on the treatment comparisons. Continuous data will be analyzed using MMRM with treatment group (adjusting if needed for age, gender, site, presence/absence of concomitant antidepressants, and other potential confounders) as between-subject factors and visit as a within-subject repeated measure. The model will also include the two-way interaction between treatment group and visit. When appropriate, significant differences between treatment groups will be further analyzed with post-hoc comparisons. Adjusted marginal means (also called LS means) will be used to report and test for differences in mean change at 12 weeks for the placebo and MPH groups providing 95% confidence intervals and a p-value for the difference between them. If our attrition rate is larger than proposed, a secondary analysis will be performed based on patients who completed at least 4 weeks of treatment to determine if it would be worthwhile to conduct a future study where attrition due to causes other than adverse effects of MPH were better controlled.