Research Protocol: Exercise as an Adjuvant Therapy for Veterans with PTSD
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Posttraumatic Stress Disorder (PTSD) is a common psychological condition in Veterans. The prevalence of PTSD is highest among Veterans age 65 and older, with an estimated 31% of older Veterans reporting PTSD symptoms. Many of these older Veterans have endured 35-50 years with chronic PTSD symptoms, and have a host of physical and psychological health problems.[1-3] Over time, these symptoms can contribute to increased health risk and greater disability. My own work from the CDA-1 (RR&D E7822M) period provides compelling evidence of accelerated functional decline in Veterans with PTSD characterized by impaired mobility, severe cardiovascular deconditioning, and muscle weakness.[4] This all translates into a significant economic and logistical burden on the VA health care system.

Exercise training is an established intervention that holds great promise as an adjunctive therapy for PTSD. Clinical practice guidelines mention exercise as a potential approach for managing PTSD symptoms, with the caveat that there is insufficient evidence regarding exercise therapy for PTSD.[5] Given the potential impact of exercise to improve both PTSD symptoms and physical comorbidities, there is compelling need for an evidence-based approach to prescribing exercise for patients with PTSD. To our knowledge, studies of exercise and PTSD have been limited to observational, or single-arm studies, and have not been directed at older Veterans. This study would be the first randomized clinical trial of exercise for PTSD.

Despite the strong evidence for exercise in promoting physical and psychological well-being, the majority of Veterans with PTSD are physically inactive. A recent study of over 500,000 older Veterans reported that compared to Veterans with other psychiatric diagnoses, rates of physical inactivity were highest among Veterans with PTSD, with 67.5% reporting no regular activity. [6]

The goal of the current study is to evaluate the efficacy and feasibility of a tailored supervised physical activity program for older Veterans with PTSD. Proposed is a feasibility trial with a two-group design in which older Veterans (60 years and older) with PTSD followed by the VA will be screened and 80 will be randomized to either:

> **PHYSICAL ACTIVITY TRAINING (PA),** a 12-week supervised physical activity program that combines guideline-based exercise prescription with individual progression/tailoring, and utilizes social cognitive tools (e.g., goal setting, troubleshooting barriers) to promote initiation and maintenance.
>
> **VA USUAL CARE-WAIT LIST CONTROL (UC),** which includes all elements of care associated with enrollment in the VA healthcare system. Upon completion of the initial 12 weeks, patients will be offered enrollment in the 12-week supervised activity training portion of the study or a home-based exercise prescription.

Veterans with PTSD face physical (particularly pain and disability) and psychological (depressed mood/lack of motivation, avoidance of social activities) barriers that are known to hinder physical activity. [7, 8, 9, 17, 18] Therefore Veterans with PTSD need specific guidance on appropriate, graded exercise that accounts for these limitations. These

barriers are all addressed by the proposed exercise intervention. If physical activity promotion programs are to have a significant impact on changing health behavior, we must identify new and innovative strategies to increase treatment access and participation among vulnerable populations, including those with psychological conditions such as PTSD. Specific aims are to:

AIM 1: Determine the feasibility, fidelity and acceptability of a pilot study that consists of random assignment to Physical Activity or Usual Care. This includes feasibility assessment of screening and recruitment; fidelity to the intervention assessed by adherence and retention; and acceptability assessed by attrition, patient satisfaction and provider acceptability questionnaires.

AIM 2: Determine the effect sizes for planned future studies of physical activity, with PTSD symptoms and
physical function as primary outcomes of interest. Of secondary interest are: pain, sleep, psychological well-being, and durability of effects.

The funding source for the study is a VA Rehabilitation Research and Development Career Development Award awarded to Dr. Katherine Hall. Portions of the salaries of Dr. Hall's study team will be funded by this grant.

METHODS

Participants

We anticipate consenting and screening 110 older Veterans with PTSD in order to reach our goal of randomizing 80 participants. Based on the following conservative assumptions, we expect to be able to recruit approximately 120 Veterans in the 36-month enrollment period; we anticipate more than 15 screen outs at the screening visit. There are currently over 3,500 Veterans receiving care for PTSD in the Durham VAMC PTSD clinic, and approximately 15% of these Veterans are over the age of 60. If we only enroll 10% of eligible Veterans, we expect to achieve our recruitment goal of 80 eligible Veterans within a 36 months recruitment window. Based on our previous studies of older Veterans, we expect that 10-15% of our participants will be female, and 40% will be minorities. See Table 1 for a summary of the study's inclusion and exclusion criteria.

Table 1. Inclusion/Exclusion Criteria	
Veterans must meet **all** inclusion criteria:	Veterans who meet **any** one of the exclusion criteria will be excluded:

• 60-89 years of age • Live within 50 miles of the Durham VAMC and have reliable transportation to exercise facility • Registered for care at the Durham VAMC • Independently mobile (assistive devices acceptable) • Meet DSM-5 criteria for current PTSD • Exercising less than 30 minutes/day on less than 5 days/week • Free of cognitive impairments as measured by the Short Portable Mental Status Questionnaire or a diagnosis of Alzheimer's Disease • Speak and write fluent conversational English	• Active substance abuse or dependence other than nicotine (they will need to be abstinent for six months, i.e., in early remission) • Cognitive impairment (inability to complete study measures) • Current diagnosis of psychotic or bipolar disorder • Clinical history of CVD occurring within the past 3 months (angina, ventricular tachycardia, COPD with 2 or more hospitalizations within the past year and/or on oxygen, and stroke with moderate to severe aphasia) • Uncontrolled hypertension (diastolic BP > 110 mmHg or systolic BP >200 mmHg on medications at rest) • Renal disease or currently receiving dialysis • Non-recommended for supervised exercise by HCP • Proliferative retinopathy • Currently receiving trauma-focused therapy • Psychotropic medication initiation within 6 weeks prior to phone screen (excluded participants may be reconsidered for eligibility once medication stability has been achieved) • Lack of interest in exercising or unwilling to be randomized

Recruitment

Study staff will identify potential eligible Veterans using several different means. First, potentially eligible Veterans will be identified from the Traumatic Stress and Health Laboratory's "Contact Database," IRB #1080, directed by Dr. Jean Beckham. This database contains information about previous study participants who have agreed to be contacted about other studies for which they may qualify. Second, a list of potential veteran participants with PTSD will be obtained using the VA's DART system. Third, flyers that have been approved by Durham VAMC's Institutional Review Board (IRB) will be posted on research bulletin boards, program offices, and clinic areas. Fourth, VA clinicians may refer potential participants by obtaining their permission to forward their contact information to study staff.

For those Veterans identified through the Contact Database or the DART system, a review of their medical history (via CPRS) will first be conducted for every potential participant to assess initial eligibility (see exclusion criteria above). Potential participants identified from this database or DART will then be sent an introductory letter signed by the Pl that describes the study and informs them that they will be called regarding participation .. In the letter, potential participants will be given an "opt-out" number to call in order to decline participation and/or further contact regarding participation. Seven business days after the mailing, Veterans who have not called the study number to decline participation will be called by a study staff member to request their participation in the research study (see telephone screen script). In the telephone contact, the study staff member will inform the Veteran that he/she was selected for recruitment because he/she is an older Veteran with PTSD who previously expressed interest in other research studies at the Durham VAMC and is registered for care at Durham VAMC (Contact database participants only).

Any Veteran who contacts or is contacted by study staff will be told that their participation is voluntary, and they may choose not to answer any questions that they find too sensitive. Also, Veterans will be told that their participation will not affect their care at the VA. The study staff member will explain the study in detail, including compensation. No study procedures will begin until formal, written informed consent has been obtained.

Study Procedures

Table 2 depicts a summary of study procedures for control group participants; Table 3 depicts a summary of study procedures for PA group participants.

Table 2. Usual Care Group Study Procedures

Session	Tasks	Time	Payment
Screening (Phone)	• Screening assessments	15 min	None
1 (lab)	• Consent and complete screening • Baseline questionnaires • Height, weight, blood pressure • Physical performance tests & activity monitor	30 min 2.5 to 3 hours	$50
Week 12 (lab; end of wait-list study	• Questionnaires • Height, weight, blood pressure	2.5 to 3 hours	$75

period)	• Physical performance tests & activity monitor • First day of supervised exercise or home-based exercise prescription		
		TOTAL	**Up to $125**

Table 3. PA Group Study Procedures

Session	Tasks	Time	Payment
Screening (Phone)	• Screening assessments	15 min	None
1 (lab)	• Consent and complete screening • Baseline questionnaires • Height, weight, blood pressure • Physical performance tests & activity monitor • Set start date for exercise	30 min 2.5 to 3 hours	$50
Week 12 (lab; end of study period)	• Questionnaires • Height, weight, blood pressure • Physical performance tests & activity monitor • Last day of study exercise • Home-based exercise prescription or Gerofit referral	2.5 to 3 hours	$75
1 year post exercise (mail)	• ACLS Questionnaire, Mobile use survey • Activity Monitor	45 minutes to 1 hour	$25
		TOTAL	**Up to $150**

Telephone Screening. All potential participants will complete an initial telephone screening to determine eligibility. A researcher will explain the study in detail and lead the eligible participant through answering the screening assessments (see Table 4). Since current PTSD is an inclusion criterion, the Primary Care PTSD Screen (PC-PTSD) will be administered as an initial screen for presence of PTSD symptoms. Because substance abuse or dependence, not any drug use, is an exclusion criterion for this study, exclusion will be based on interview results using the three-item AUDIT-C (≥4 for men; ≥3 for women)[10] and ten-item DAST-10 (≥3).[11]

Baseline and Follow-Up. During the first lab appointment, informed consent with HIPAA authorization will be obtained, a final screening measure will be administered (CAPS -5),and a questionnaire battery and physical performance assessments will be completed (see Table 4).

At this first session, eligible participants will be randomized to one of the two treatment groups. Any Veteran who is randomized to the UC wait-list control condition will be told that he/she will be scheduled for a 12-week follow-up session, and that they may be contacted prior to this follow-up session for a brief check-in by study staff to inquire

about any adverse events that may have occurred, as well as changes they may have made in medications or mental health therapy. At the end of this initial 12 weeks, patients in the UC wait-list control condition will be enrolled in the supervised exercise program for an additional 12 weeks. All Veterans will be given the results of their physical performance tests and activity monitor (average daily steps) along with a home-based exercise prescription once the study is completed. For those Veterans aged ≥65 years, they will be offered a referral to the Durham VAMC Gerofit program.

As a sub-study of this larger protocol, we are also interested in learning more about technology access and use of VA apps in this population. This information will be particularly useful to inform future exercise interventions for older veterans that utilize technology to extend reach. All participants who completed the study protocol (UC + PA) will be eligible for this sub-study and will be contacted. Study participants will be sent a letter in the mail signed by the PI describing what this inquiry entails (see letter). In the letter, potential participants will be given an "opt-out" number to call in order to decline participation and/or further contact. Seven business days after the mailing, Veterans who have not called the study number to decline participation will be called to request their participation in the mobile device questionnaire (see telephone script). Phone contact will cease after 3 attempted (and unanswered) phone calls. The CRC will not contact anyone who withdrew their consent. Only Veterans who have completed the exercise program will be queried about if/how they use technology to track their health via 8 questions (see attached telephone script). Once contact is made, participants will be asked if they have a mobile device—and if so what type and if they have access to the internet on their devices. In addition, they will be asked how often they use the internet and their mobile apps per week and day. Specifically, the questions will ask about the VA PTSD coach app, fitness trackers and monitors, and if Veterans connect these devices to their computer. Responses to the telephone survey will be recorded on a paper copy by the CRC and entered in a VA REDCap database.

Table 4. Timeline of Study Assessments

Session: **Assessment:**	**Pre-screening**	**Week 1 (Telephone)Screening**	**Baseline Week 1**	**Week 12**	**1 year**
Medical History (CPRS review)	X				
Primary Care PTSD Screen		X			

(PC-PTSD)					
Alcohol consumption: AUDIT-C[10]		X			
Drug use: DAST-10[11]		X			
Demographics			X		
Short Portable Mental Status Questionnaire (SPMSQ)[19]			X		
Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[12]			X		
PTSD Checklist for DSM-5 (PCL-5)[13]			X	X-Pt. 3 only	
State Trait Anxiety Inventory –TRAIT[34]			X	X	
Mental Health Service Utilization			X	X	
Physical activity: ACLS[29]			X	X	X
Comorbidity			X	X	
Medical Outcomes Study (SF-36)[15]			X	X	
Depression Severity (PHQ-9)[35]			X	X	
Memory (FOF)[33]			X	X	
Sleep: PSQI + PSQIA PTSD Addendum[16]			X	X	
Nutrition			X	X	
Biometric data			X	X	
Physical performance tests: ...Single-Leg Stance 10-Meter Walk 30-Sec Chair Stand 8 Foot Up-and-Go Test[20] 6MWT[21]			X	X	
ActiGraph activity monitor			X	X	X
Program Evaluation				X	
Mobile device use telephone survey					X

Any Veteran who is randomized to the PA group will be offered a 12-week supervised exercise program. PA group participants will receive a personalized exercise prescription based on their exercise history and current health status as well as training in the proper use of exercise equipment. The exercise protocol consists of a 5-10 minute warm-up, followed by a series of progressive strengthening and aerobic exercises, and ending with a 5-10 minute cool-down. Walking will be the primary mode of aerobic exercise, the duration and intensity of which will be gradually increased over the course of the trial (see Table 5).

As this is expected to be a largely sedentary population, exercises will be introduced in a staged manner in order to maximize adherence and technique acquisition. Personalized

programs may include a selection of 8 to 12 of the muscle-strengthening exercises identified, will target major muscle groups as well as primary joints, and will include 1-3 sets of 8-12 repetitions for each exercise (see Table 5). The major muscle groups include chest (pectoral), shoulders (deltoids, rotator cuff, scapular stabilizers, trapezius), arms (biceps, triceps, forearm group), back (latissimus dorsi, erector spinae), abdomen (rectus abdominus, obliques, transverse abdominus, intercostals), and legs (gluteals, quadriceps, hamstrings, gastrocnemius). The primary joints include the knees, hips, and shoulders. A rest period of 2-3 min between sets of the same exercise will be programmed. Modalities may include body weight, free weights, cables and exercise bands. The amount of resistance will be determined by choosing a weight that can be moved the desired number of repetitions before it becomes too heavy. Participants will be encouraged to progress the resistance on at least a monthly basis, as tolerated. Once exercise technique is considered competent by our staff, participants will be advised to perform the exercises in a circuit-like manner. Participants will be encouraged to complete these strengthening exercises on 3 days/week. The duration of each exercise session is expected to last 45-60 minutes.

Table 5. Example Exercises and Progression of Intensity

Resistance Exercises	**Level 1**	**Level 2**	**Level 3**
Leg press/Squats	Seated leg press (single leg)	Sit-to-stand	Squats
Bent over row or seated row	1-2 sets, 8-12 reps*	2 sets	Increase reps/wt as tolerated
Leg extensions	1-2 sets, 8-12 reps, BW	2 sets	Increase reps/wt as tolerated
Chest press	1-2 sets, 8-12 reps	2 sets	Increase reps/wt as tolerated
Triceps kickback	1-2 sets, 8-12 reps	2 sets	Increase reps/wt as tolerated
Lat Pull down	1-2 sets, 8-12 reps	2 sets	Increase reps/wt as tolerated
Oblique side bend	1-2 sets, 8-12 reps, BW	Light DB	Increase reps/wt as tolerated
Lateral raise	1-2 sets, 8-12 reps	Increase reps as tolerated	Increase reps/wt as tolerated
Hip abduction	1-2 sets, 8-12 reps BW	Increase reps as tolerated	Increase reps/wt as tolerated
Internal/External shoulder rotation	1-2 sets, 8-12 reps with EB	Cable or light DB	Increase reps/wt as tolerated
Bird-dog (core)	1-2 sets, 8-12 reps	3 sets	Increase reps
Rear delt raise	1-2 sets, 8-12 reps	Increase weight as tolerated	Increase reps/wt as tolerated

Aerobic Exercise	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6+**
Walking duration (min)	5-10 min	15	20-25	25-30	30	30

Walking intensity (RPE)	3	3	3	3	3	4-7

EB = Exercise Band DB = Dumbbell BW = Body Weight

The American College of Sports Medicine recommends that activity intensity for older adults should be defined relative to an individual's fitness within the context of perceived physical exertion. As such, initial program intensity will be set using a 10-point scale, on which 0 ="no exertion at all/sitting" and 10 ="maximal effort." Participants will be instructed to exercise between 3 (light to moderate) and 7 (moderate to hard); these levels will be reinforced by advising participants to exercise at a level that is close to their "conversational limit" (i.e., "talk test"), which is associated with more labored breathing. This method of specifying intensity is easily understood, can be readily applied to individual activities, and will increase as an individual's fitness level improves. Individual limitations such as musculoskeletal conditions and balance will also be considered when prescribing the exercises.

Individuals who report pre-exercise resting systolic blood pressure> 200 mmHg or diastolic blood pressure> 110 mmHg will be asked to refrain from exercise for the day. Individuals who develop the following signs or symptoms during the exercise session will be asked to terminate their exercise session for that day and will be referred to their health care provider: moderate to severe angina, ataxia, dizziness or near syncope, or signs of poor perfusion such as cyanosis or pallor. As this supervised exercise program is held in a private fitness facility off-site from the Durham VAMC, in the event of emergency, emergency services (9-1-1) will be called.

Objective assessment of physical activity and sleep will be assessed at baseline and 12 weeks with the ActiGraph GT3X activity monitor (accelerometer). This monitor has been extensively validated in clinical populations to collect physical activity behavior and sleep quality and quantity. Accelerometers, small devices which measure intensity of acceleration, have the ability to quantify the intensity, duration, and frequency of activity. The accelerometer is a lightweight device (45 g) that is equivalent in size to a pedometer. Accelerometers such as the ActiGraph are programmed to detect body movement and reject other forms of movement (such as vibration). The acceleration signal is digitally converted, resulting in a numerical value of "activity counts" per time interval. On their own, raw activity counts are uninterpretable, and can only be accessed using Actilife software. Upon download with the Actilife software, these activity counts can then be translated into estimates of energy expenditure using activity-count cut points which have been developed to characterize activity intensity levels. In addition to quantifying time spent in various intensity levels the ActiGraph also assesses sleep activity, which can be scored according to sleep onset, sleep latency, amount of sleep, and sleep efficiency.

Participant Reimbursement. As described in Tables 2 and 3 above, study participants in the PA Arm may receive up to $150 for full participation in the study, while participants in the UC wait-list control arm may receive up to $125 for full participation in the study. In our previous studies, the follow-up rates for assessments have been

approximately 85%. We have added an incremental incentive structure ($50 for baseline and $75 for 12-week assessments) for each subsequent time point to encourage follow-up assessment completion. Payment for participation will be by direct deposit issued by VA Financial Services.

Consumer and Expert Advisory Board. We will convene a Consumer and Expert Advisory Board comprised of Veteran consumers and expert clinician provider(s). The Advisory Board will meet annually with the research team to review the research project. In addition, the Advisory Board will provide guidance and technical assistance to the project. In year 1, the board will review the proposed study measures and the study procedures and provide an external perspective; advising the research team about issues of importance to Veterans with PTSD. In years 2 and 3, the implementation progress of the study will be reviewed by the board, and the board members will be specifically queried for input regarding any obstacles in regard to recruitment and retention. In year 4 the board will advise the research team regarding dissemination issues including suggestions for specific venues, and translating scientific langue to consumer language.

Participant photographs/videos. Study participants may occasionally be asked to let us photograph/video record them doing their exercises, for use in potential future professional presentations and/or promotional materials. This is certainly voluntary on the part of the participant, and written authorization (VA Form 10-3203 CONSENT FOR USE OF PICTURE AND/OR VOICE) from the participants will be obtained prior to any photography/video. These forms will be stored in the secured study cabinet located in the research coordinator's office. All recordings will be done using Samsung HMX-W300 or Toshiba Camileo x200 Full HD Camcorder. Verbal consent will be obtained from the participant at the start of the recording by saying "the video tape is running, can you please affirm that you are ok with being recorded." The digital photo and video files will be transferred to the VA computer via a VA-issued encrypted thumb drive (issued to Dr. Hall). All media files will be encrypted and stored on the secure directory (S:\Research\Hall_Physical Activity Research\Participant Records).

RISK/BENEFIT ASSESSMENT

The clinical interview to establish diagnosis can cause some psychological distress in the form of a temporary increase in anxiety, but any ensuing distress is usually well tolerated. There are no known psychological hazards or risks associated with completing questionnaires. If during the study any information reveals suicidal intent, depression, or other major clinical findings, the participant's primary physician will be notified. In addition, if an individual reveals current intent to harm him/herself or someone else, we will escort (or have escorted) the patient to the hospital's emergency room to be seen by staff in the Psychiatric Emergency Clinic (PEC). In the event this information is revealed over the phone, we will transfer this person directly to the Veterans Crisis Line.

The physical performance tests include activities such as walking, standing, stepping, and stretching. These activities reflect common activities of daily living and as such, are associated with minimal risk for injury. However, there is a small risk of falls or muscle soreness with physical testing. To minimize risk, trained study personnel will oversee

physical performance testing at all times. The risk of doing moderate exercise is low, and may be associated with risk of injury, falls, fainting, dizziness, or muscle soreness. There is even the risk of sudden death or stroke. To minimize these risks during exercise, participants will be instructed to exercise at a comfortable level and to never push themselves to a point beyond where they feel safe. Participants will also be monitored and instructed to report symptoms such as unusual shortness of breath, dizziness, tightness or pain in the chest or arms, skipping heart beats, numbness, loss of balance, nausea, or blurred vision. In both conditions, there is a potential risk associated with the loss of confidentiality of study data.

PA participants have a greater risk of violation of confidentiality and/or privacy in the study, as they will be participating in a facility-based group exercise program. Study participants will be encouraged to socialize with one another to promote group cohesion, and complete confidentiality cannot be guaranteed as this space will be utilized by other Durham VAMC patients. Additionally, exercise logs with participant names and exercise prescriptions will be available to patients during their exercise time. Access to these cards will be limited to study participants; however, it is possible that these may be visible to others using the exercise space as participants move from station to station. Importantly, no PHI or other PII, other than participant name, will be included on these documents.

Regular moderate-intensity exercise should enhance rather than jeopardize health status, and potential serious adverse events (SAE) for participants in this project are not expected. Regardless, we will minimize potential risk by careful screening of potential participants. Serious adverse events will be promptly reported to the VA IRB as required. All project staff will complete educational units required by the Durham VAMC Human Subjects Committee.

Participants may benefit from this study by improving their health through increased physical activity participation.

DATA SAFETY AND MONITORING

The individuals responsible for data safety and monitoring will be the PI, the Research Coordinator, and the study Co-Investigators (Drs. Morey, Beckham, and Bosworth). Further data safety and monitoring will be provided by the PI. There will be several ongoing mechanisms for monitoring and reporting of adverse events:

1) ongoing participant contact via study personnel; 2) study telephone number provided to participants to report concerns related to study participation; and 3) weekly meetings between the PI and study personnel.

The PI will meet at least weekly with study personnel to discuss participants' reactions to the intervention, proper delivery of the intervention, and any adverse events or unanticipated problems. Monthly meetings between the investigators and the Research Coordinator will allow for ongoing progress reports, including the number of participants currently involved in the study groups, attrition rates, and scheduled data collection from participants, as well as notification and review of any adverse events (AE). Safety

monitoring for AEs will be conducted in real time by the PI and/or Research Coordinator. The following information about adverse events will be collected: 1) the onset and resolution of the AE, 2) an assessment of the severity or intensity (use existing grading scales whenever possible), 3) an assessment of the relationship of the event to the study (definitely, probably, possibly or not related), 4) organ system involved, and 5) action taken (e.g., none, referral to physician, start or increase concomitant medication). The PI will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution. Any adverse events will be reported to the IRB in accordance with the local Human Research Protection Program's Standards of Practice.

DATA MANAGEMENT AND SECURITY

Several types of data will be collected over the course of the study. As described under the Request for Waiver or Alteration of Informed Consent and HIPAA Authorization for Research, PHI to be collected during recruitment activities includes name, age, medical history, address, telephone number, and social security number. Other data to be collected over the course of the study (as described in the HIPAA authorization) include name; address; phone number; social security number; dates of study visits; and account numbers (for Veterans who have bank accounts, payment will be issued via direct deposit, which requires a Vendorizing Coversheet that asks for account information and VA Form 10-7078 to be obtained). Additionally, a unique study ID will be assigned to each participant. Sources of health information include medical history and physical exam information, progress notes in CPRS, laboratory test results, survey responses, alcohol and/or drug use information, and mental health notes. This information will be used for research purposes only.

DATA ANALYSES

AIM 1-Feasibility: This AIM revolves around testing the feasibility, fidelity and acceptability of the proposed exercise intervention. We will track number of patients contacted, screened, eligible, and enrolled to determine acceptability rates. Reasons for refusal will be tracked. Once enrolled, we will monitor the fidelity of the intervention by measuring adherence to the intervention arm.

Feasibility proportions for screening and recruitment will be calculated at the end of the intervention using the following:

1. Source of patients screened for potential enrollment will be determined by calculating the number of patients enrolled from the Contact Database and Durham VAMC clinics.
2. Proportion of patients recruited will be calculated as the number of patients deemed potentially eligible and contacted for enrollment divided by the total number of patients enrolled.

Fidelity proportions will be calculated for adherence and retention at the end of the intervention using the following:

1. Proportion adherent to in-class attendance will be computed as the number of sessions attended divided by the number of possible sessions among all randomized subjects.
2. Proportion retention will be computed by dividing the number of retained subjects at the end of the intervention by the total number randomized into the study.

We will calculate these rates of retention and adherence and their respective confidence intervals overall and by group. While non-powerful, we will assess if these rates differ by chi-square test of proportion and Poisson regression respectively. In a series of sensitivity tests, we will assess if adherence overall was impacted by demographic or symptomatic variables (such as obesity, severity of pain or PTSD symptoms).

AIM 2-Efficacy: This study is a randomized two-arm pilot study with replicate measures at two time points: baseline and 12 weeks. Analysis will be based on intention to treat principles; the overall intervention effect will be measured for the entire sample assuming participants have followed their randomized assignment. The main conclusions drawn from this trial will be based on the pre-specified hypotheses outlined below and will be tested with two-sided p-values at the standard 0.05 level. Statistical analyses will be performed using SAS (Version 9: SAS Institute Cary NC) and SPSS.

Following the Good Clinical Practice Guidelines[22] for the analysis of a clinical trial, we will employ mixed models,[23] analyze under an Intent to Treat (ITI) criteria, and control for baseline (leaving 2 post-randomization measures per outcome) and assess the impact of Time, Treatment Group and the interaction of these variables on the outcomes. Relative to the usual repeated measures designs, mixed models have several advantages: (1) missing values present no particular difficulties in estimation and the estimates are unbiased as long as the set of variables leading to MAR are estimated, (2) the usual assumption of conditional independence (compound symmetry) used in standard repeated measures need not be made, and (3) the actual times of measurement need not be equivalent across subjects. Controlling for the individual baseline values for the particular outcomes, the trajectories over time and differences in those trajectories will be assessed. Following the statistical principles section from the International Conference on Harmonization,[24] we will select covariates (e.g., age, race, number of comorbidities) for the primary models a priori, but we also will conduct auxiliary sensitivity analyses that evaluate whether potential group imbalances bias the treatment effect estimate. These analyses will be performed using conventional testing for confounding.[25]

As defined, the overall test of the intervention effect will be the joint effect of group and group*time on 2 df ((3_1 and (3_2) assessing an overall effect of group, and if this group effect is constant over time. If significant, follow-up tests will assess where group differences lie. In particular, we note that if the time by group interaction is rejected, we will test if the groups differ at the end of 12 weeks (a test of effect at the completion of the intervention). Lf time and funds permit, we may also test if the groups differ several weeks post-intervention (a test of the durability of the effect).

We note that we have listed numerous measures to be analyzed as outcomes but have listed only 3 outcomes as primary (physical activity, aerobic endurance, PTSD symptoms). We will not adjust for Type-I error rate for these primary outcomes. Rather, in any resulting publications, readers will be informed of the multiple testing issues and the exploratory nature of the investigations.

Compliance. It will be of particular interest to assess the mediation impact of level of compliance during the intervention (days of exercise) on the estimated effects, to derive a 'perprotocol' effect estimate.[22, 24] Compliance and level of exercise will be included in the models to assess the sustainability of the intervention and to develop a measure of dose-response for the intervention. However, these analyses will need to be carefully controlled, since 'compliance' is not randomized and may be confounded by other factors such as PTSD symptom severity and functional status. If fully controlled models demonstrate a compliance effect, such evidence will provide support to the notion that the intervention is the agent affecting physical activity behavior and cardiovascular improvements.

Mobile Device Use Telephone Survey. Univariate statistics and frequencies (% of respondents) will be used to assess and summarize responses to the 8-item telephone survey about mobile device use.

Post-Program Evaluation Interviews. We plan to use directed content analysis/applied thematic analysis, organizing the data in response to the questions contained in the interviews. Transcripts will be examined for common and emergent themes as well as a priori themes. Open coding will be used to identify manifest and latent content, followed by axial coding to identify patterns between code categories. Dr. Hall and the Qualitative Research Analyst will develop a codebook of definitions and exemplars, which will be presented to the team for feedback. We will also employ theme matrix techniques to facilitate data analysis and presentation. Initial matrices will be developed and further refined. Quotes will be separately aggregated and displayed in matrices with columns identifying critical dimensions of the quotes. NVivo 11 qualitative software will be used to assist with qualitative data analysis. At least a subset of interviews will be coded by both Dr. Hall and the QRA to determine and facilitate inter-coder agreement. First cycle coding approaches to be utilized include elemental (i.e., descriptive, in vivo, and process coding) and affective (i.e., emotion, values, evaluation coding) methods. Both inductive and deductive codes will be created. Second cycle coding processes will involve analytic memos about the data and reconfiguration of the first cycle codes. Pattern coding will allow us to group the summaries into a smaller number of themes, categories, and/or constructs.

Missing Data and Attrition Rates. Because the main predictors of interest, treatment group and demographics, are collected at baseline, we do not anticipate much missing data. We do, however, anticipate missing values in the longitudinal outcomes owing to dropout or an inability to reach the patient by phone. Missing data problems are ubiquitous in aging research. Participants are, in general, compliant to protocols, but drop out due to a variety of reasons, primarily due to health events, which render them unable to complete protocols.

Based on our previous studies of physical activity and older adults, we project an attrition rate of 20%. We will use several strategies proven to enhance retention in our past projects. First, the intervention strategy itself is designed to improve compliance and retention. The primary theoretical basis of this intervention relies heavily on Social Cognitive Theory (SCT}, [26] in which behavior influences, and is influenced by, within person factors and factors in the social and physical environments. The primary intervention strategy is designed to enhance self-efficacy, an important predictor of physical activity in older adults.[27•28] Elements of SCT integrated into this intervention include modeling, self-monitoring, goal setting, reinforcement, and cognitive reframing. Second, our study staff will strive to establish positive relationships with participants (e.g., in scheduling, testing, telephone reinforcement, and exercise instruction interactions}. Third, we will provide incentives for all study assessments. Participants will receive $50 for baseline, $75 for Week 12 assessments, $50 for Week 24 assessments (Usual Care wait-list control only}, and $25 for 1 Year assessments (completely mail-based}. Total participant payment is thus $150/$200 if all visits and follow-ups are completed. Finally, our weekly contact provides a means for quickly identifying non-adherent participants and "recovering" lost participants early.

REFERENCES

1. Boscarino JA. A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: implications for surveillance and prevention. *Psychosomatic Medicine.* 2008;70(6):668-676.

2. Buckley TC, Mozley SL, Bedard MA, Dewulf AC, Greif J. Preventive health behaviors, health-risk behaviors, physical morbidity, and health-related role functioning impairment in veterans with post-traumatic stress disorder. *Military Medicine.* 2004;169(7):536-540.

3. Dedert EA, Calhoun PS, Watkins LL, Sherwood A, Beckham JC. Posttraumatic stress disorder, cardiovascular, and metabolic disease: a review of the evidence. *Annals of Behavioral Medicine.* 2010;39(1):61-78.

4. Hall KS, Beckham JC, Bosworth HB, Sloane R, Pieper CF, Morey MC. PTSD is negatively associated with physical performance and physical function in older overweight military veterans. *Journal of Rehabilitation Research and Development.*2014; 51(2):285-96..

5. The Management of Post-Traumatic Stress Working Group. VA/DoD Clinical Practice Guideline for Management of Post-traumatic Stress. In: Department of Veterans Affairs DoD, ed. Vol 2.0: Washington, D.C.; 2010.

6. Chwastiak LA, Rosenheck RA, Kazis LE. Association of psychiatric illness and obesity, physical inactivity, and smoking among a national sample of veterans. *Psychosomatics.* May-Jun 2011;52(3):230-236.

7. Manger TA, Motta RW. The impact of an exercise program on posttraumatic stress disorder, anxiety, and depression. *International journal of emergency mental health.* Winter 2005;7(1):49-57.

8. McAuley E, Jerome GJ, Marquez DX, Elavsky S, Blissmer B. Exercise self-efficacy in older adults: social, affective, and behavioral influences. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine.* Winter 2003;25(1):1-7.

9. Mori DL, Sogg S, Guarino P, et al. Predictors of exercise compliance in individuals with Gulf War veterans illnesses: Department of Veterans Affairs Cooperative Study 470. *Mil Med.* Sep 2006;171(9):917-923.
10. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction.* Jun 1993;88(6):791-804.
11. Bohn MJ, Babor TF, Kranzler HR. Validity of the druge abuse screening test (DAST-10) in inpatient susbtance abusers: Problems of drug dependence. *Addiction.* 1991;88(6):791-804.
12. Weathers FW, Blake DD, Schnurr, PP, Kaloupek, DG, et al. The Clinician-Administered PTSD Scale for DSM-V. *www.ptsd.va.gov*.
13. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD Checklist for DSM-5 (PCL-5). 2013:Scale available from the National Center for PTSD at www.ptsd.va.gov.
14. Sundman MH, Hall EE, Chen N. Examining the relationship between head trauma and neurodegenerative disease: a review of epidemiology, pathology and neuroimaging techniques. *Journal of Alzheimers Disease and Parkinsonism* 4: 137.
15. Ware JE, Jr. SF-36 health survey update. *Spine.* Dec 15 2000;25(24):3130-3139.
16. Germain A, Hall M, Krakow B, Katherine Shear M, Buysse DJ. A brief sleep scale for Posttraumatic Stress Disorder: Pittsburgh Sleep Quality Index Addendum for PTSD. *Journal of anxiety disorders.* 2005;19(2):233-244.
17. Kohl HW, Blair SN, Paffenbarger RS, Jr., Macera CA, Kronenfeld JJ. A mail survey of physical activity habits as related to measured physical fitness. *Am J Epidemiol.* Jun 1988;127(6):1228-1239.
18. Cutrona CE, Russell DW. The provisions of social relationships and adaptation to stress. In: W.H. Jones & D. Perlman, eds. *Advances in personal relationships.* Greewich, CT: JAI Press; 1987:37-67.
19. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc.* 1975;23(10):433-441.
20. Podsiadlo D, Richardson S. The timed up & go: a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society.* 1991;39:142-148.
21. Balke B. A simple field test for the assessment of physical fitness. *CARI Report.* 1963;63:18.
22. Committee for Proprietary Medicinal Products (CPMP): points to consider on adjustment for baseline covariates. *Statistics in Medicine.* 2004;23(5):701-709.
23. Laird N, Ware, JH,. Random-effects models for longitudinal data. *Biometrics.* 1982; 38:963-974.
24. International Conference on Harmonisation: Statistical Principles in Clinical Trials (E9)1997.
25. Berger V. *Selection bias and covariate imbalances in randomized clinical trials.* Hoboken, NJ: Wiley; 2005.
26. Bandura A. *Self-Efficacy: The Exercise of Control*. New York: W.H. Freeman; 1997.
27. McAuley E, Blissmer B. Self-efficacy determinants and consequences of physical activity. *Exercise and sport sciences reviews.* Apr 2000;28(2):85-88.
28. McAuley E, Jerome GJ, Elavsky S, Marquez DX, Ramsey SN. Predicting long-term maintenance of physical activity in older adults. *Preventive medicine.* Aug 2003;37(2):110-118.

29. Kohl HW, Blair SN, Paffenbarger RS, Jr., Macera CA, Kronenfeld JJ. A mail survey of physical activity habits as related to measured physical fitness. *Am J Epi.* 1988;127(6):1228-1239.
30. McAuley, E. (1992). The role of efficacy cognitions in the prediction of exercise behavior in middle-aged adults. *Journal of Behavioral Medicine*, 15(1), 65-88.
31. Kozma, A., & Stones, M. J. (1980). The measurement of happiness: Development of the Memorial University of Newfoundland Scale of Happiness (MUNSH). Journal of Gerontology, 35, 906-912
32. Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24,* 386-396.
33. Zelinski M, Gilewski MJ. A 10-item rasch model memory self-efficacy scale. *Aging Ment Health*. 2004;8(4):293–306.
34. Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.
35. Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press