TOBI-SET IRB PROTOCOL

1.0 General Information

Please enter the full title of your study: Treatment Optimization of Brain-injured Warfighters: A Prescribed Sub-symptomatic Exercise Treatment (TOBI-SET)

Please enter the Protocol Number you would like to use to reference the protocol: NHCP.2022.0031

Is this a multi-site study (i.e. Each site has their own Principal Investigator)? – NO

Does this protocol involve the use of animals? – NO

2.0 Add Sites

List sites associated with this study: Intrepid Spirit Center, Naval Hospital Camp Pendleton

3.0 Assign Project Personnel access to the project

4.0 Project Information

Is this a research study? YES

What type of research is this? Behavioral Research

Are you conducting this project in pursuit of a personal degree? NO

Is this human subjects research? YES

Do you believe this human subjects research is exempt from IRB review? NO

5.0 Personnel Details

List any Research Team members without EIRB access that are not previously entered in the protocol:

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Will you have a Research Monitor for this study? NO

6.0 Data/Specimens

Does the study involve the use of existing data or specimens only (no interaction with human subjects)? NO

7.0 Funding and Disclosures

Source of Funding: _CDMRP Grant W81XWH-22-2-0069

Total amount of funding: $2,991,582.00

Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study? NO

8.0 Study Locations

Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?) NO

Study Facilities and Locations:

Institution – Navy
Site Name – NHCP – Intrepid Spirit Center
Site Role – Performance Site
FWA or DoD – FWA00002342

Assurance Expiration Date – 08/21/2024
Is there an agreement - MOU
IRB Reviewing for Site – NMCSD IRB

Are there any international sites? NO

Is this an OCONUS (Outside Continental United States) study? NO

9.0 Study Details

9.1 Key Words *(Up to Five):* Post-concussion Syndrome, Exercise Intolerance, Warfighter Readiness, Exercise Treatment

9.2 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

This study will translate and validate an intervention that promotes sustained functional recovery of warfighters after traumatic brain injury (TBI) in terms of locomotor and cognitive functioning using a personalized prescribed sub-symptomatic exercise treatment program that can be delivered in a variety of settings including large military brain injury specialty clinics as well as rural areas with limited resources. The treatment will focus on improving long-term outcomes by maximizing service member (SM) health/performance as well as return to duty (RTD).

TBI remains a major health concern for the United States Military Health System and a threat to warfighter preparedness and readiness (Lee, Khatri, & Fudge, 2020). In the last two decades almost 450,000 SMs have experienced a TBI, primarily mild TBI (mTBI) (Excellence, 2021) and many others have experienced functional impairments from other types of head injury (i.e., repetitive low level blast exposure) (Belanger, Bowling, & Yao, 2020).

Inadequate treatment for SMs with a history of TBI remain a detriment to their mental and physical readiness (Lee et al., 2020). Interventions are needed that treat warfighters holistically and address all aspects of warfighter readiness including cognitive, psychological, and physical well-being. Treatments are needed that can be applied to more diverse clinical and operational environments and that prioritize functional improvement in warfighter health and performance. For active duty SMs, in addition to promoting mTBI recovery, treatment plans must also prevent physical deconditioning and address locomotor dysfunction to optimize warfighter readiness. Prescribed sub-symptomatic adaptable exercise treatment (SAET) is a potential solution that meets these needs.

Sub-symptomatic Adaptable Exercise Treatment (SAET): Efficacy

The important interconnectedness between physical activity and recovery from mTBI has emerged through both scientific efforts and direct clinical care. It is recognized that

progressive increases in physical activity after a mTBI improves recovery in both athletes (Leddy, Haider, Ellis, & Willer, 2018) and SMs (Bailie et al., 2019; Remigio-Baker et al., 2019a; Remigio-Baker et al., 2019b). Our group completed an earlier line of inquiry into the management of physical activity in acute recovery in SMs with a mTBI. With funding from DHP 6.7 (D6.7_14_C2_I_14_J9_1077) we provided better guidance on prescriptions for physical activity of injured warfighters following a mTBI. We observed that there was a notable improvement in recovery rates where 82% of patients with prescribed activity had recovered at 1 month from injury which was drastically higher than the control condition which had only a 36% recovery rate (Bailie et al., 2019). Our work on this award, among other key publications, also observed that increasing rates of activity was important in facilitating recovery in later months of injury (Remigio-Baker et al., 2019b).

The work from our group focused on the military is very consistent with civilian studies. It is well recognized and widely accepted that complete rest following a concussion diagnosis may ultimately worsen symptoms and prolong recovery (Schneider et al., 2013). An accumulating body of work continues to support the abandonment of the “rest is best” treatment philosophy with evidence showing that early intervention of sub-threshold aerobic exercise speeds recovery (Leddy et al., 2019) and reduces the risk of developing persisting post-concussive symptoms (Grool et al., 2016). Both the athletic (McCrory et al., 2009) and military (McCulloch et al., 2015) communities have updated clinical guidelines to recommend that individuals undergo a stepwise, progressive return to activity following a mTBI as this has been shown to improve recovery in both athletes (Leddy et al., 2019) and active duty service members (Bailie et al., 2019). However, these updated clinical recommendations have focused exclusively on the recovery of acutely concussed individuals. It remains to be elucidated whether exercise has the same effect in the estimated 16% to 60% of the population that have prolonged symptoms into the chronic phase of recovery following a mTBI (Ettenhofer, Remigio-Baker, Bailie, Cole, & Gregory, 2020; Schneiderman, Braver, & Kang, 2008; Terrio et al., 2009).

The possible mechanisms that may be underlying exercise’s effectiveness as a recovery tool from a mTBI are varied, robust, and span multiple body systems. Based on this, SAET is a very strong treatment candidate to rehabilitate SMs with persistent symptoms following a mTBI. Studies have shown some preliminary evidence that SAET is effective in remediating individuals with persistent post-concussive symptoms. In a recent meta-analysis, studies showed prescribed exercise had a large effect size (g= 0.92) in reducing persistent post concussive symptoms, however, these studies are extremely limited particularly to athletes who are more than two weeks from injury but less than six months from injury (Carter, Pauhl, & Christie, 2021).

SAET: Mechanisms of Action

Though not entirely understood, exercise is believed to rely on multiple mechanisms of action on the mind and body which results in decreasing the severity and frequency of lingering symptoms following a mTBI. Primarily, exercise may help rehabilitate the autonomic nervous system (ANS) which is disrupted following a concussion (Leddy, Kozlowski, Fung, Pendergast, & Willer, 2007; Pertab et al., 2018). The ANS regulates

cerebral blood flow (CBF) through three mechanisms. First, cerebral autoregulation occurs in which the brain maintains relative constant blood flow despite changes in perfusion pressure. The second way the ANS regulates CBF is through cerebral vasoreactivity which is how the body adapts to change due to increase in vasoactive compounds such as increased carbon dioxide. The third way ANS regulates CBF is through neurovascular coupling which corresponds to the body's need for oxygen. It has been shown in concussed athletes that the ANS has difficulty controlling the blood flow due to disruption in these systems. Specifically, following a concussion the body has a disproportionate rise in CBF that is inconsistent with intensity of the exercise and the body's need for oxygen (Clausen, Pendergast, Willer, & Leddy, 2016). This atypical ANS response was associated with symptoms of headache and dizziness.

Concussion undoubtedly negatively affects the ANS response which corresponds to disproportionate responses to external demands (e.g., exposure to vasoreactive agents) as well as internal demands (e.g., increased need for oxygen). In a normal recovery this resolves. Interestingly though SAET has been shown to promote ANS regulation. This has been shown in vasoreactive paradigms, where a SAET program was able to restore normal cerebral blood flow regulation in response to carbon dioxide (Clausen et al., 2016). This normalization of the ANS was also associated with resolving clinical symptoms in patients who had persistent post-concussive symptoms. This lends credence to the theory that SAET can "re calibrate" the ANS.

SAET may also promote recovery at a molecular level. Exercise has been shown to increase brain derived neurotrophic factor (BDNF) (Sleiman et al., 2016), an important biomarker of neuroplasticity and neurogenesis. BDNF is involved in modulating the neuroinflammatory process and promoting neuronal plasticity. The role of BDNF and concussion is also well established. BDNF is known to be diminished following a concussion and has been explored as a diagnostic agent (Korley et al., 2016). Further, given its neuroprotective properties BDNF has also been explored as a treatment option for TBI (Kaplan, Vasterling, & Vedak, 2010). Perhaps given these benefits it is not surprising that SAET has been shown to attenuate the negative impacts of cognitive dysfunction following MTBI by improving processing speed and executive function (Chin, Keyser, Dsurney, & Chan, 2015). A recent meta-analysis offered evidence of the positive effects of resistance training (in isolation of aerobic exercise) on composite cognitive scores, screening measures of cognitive impairment, and executive functioning (Landrigan, Bell, Crowe, Clay, & Mirman, 2020). These findings provide important evidence for the potential compound effect of subthreshold aerobic exercise in conjunction with resistance training in mTBI recovery.

Exercise's effect on mood may offer an alternative supportive mechanism by which exercise can improve mTBI recovery. It is an unfortunate reality that depression, post-traumatic stress disorder, and other mood-related disorders frequently impact SMs and veterans who have had a mTBI (Cole & Bailie, 2016; Stein et al., 2019). In SMs and veterans, the presence of a mood disorder was the strongest predictor of poor long-term outcome as many as 10 years from injury (Lange, French, Lippa, Bailie, & Brickell, 2020). In non-concussed individuals, it has been well documented that regular physical activity benefits individuals with depressive and anxiety symptoms (Pascoe et al., 2020;

Peluso & Guerra de Andrade, 2005). Possible mechanisms for the psychological advantages of exercise include distraction, improved self-efficacy, and increased social interaction. Exercise is also associated with increased endorphins which may explain enhanced mood associated with exercise. Also of importance is the negative impact of reduced physical activity when injured. Both SMs and athletes are accustomed to high levels of exercise. While they rehabilitate from an injury, they may be removed or eliminated from participating in exercise. It has been shown that adults who exercise regularly, then abruptly cease exercising for a few days, report a more negative mood and more symptoms of depression (Berlin, Kop, & Deuster, 2006; Glass et al., 2004). Thus, for military SMs accustomed to regular physical activity, there may be additional mental health considerations if they are to discontinue exercise during TBI recovery.

A final consideration when evaluating the importance of continued physical activity for active duty service members is the importance of mission readiness. The ability to maintain a complete yet tailored cardiovascular and strength training exercise program during recovery from a mTBI helps maintain the physical readiness of the force while also reducing or eliminating long-term effects of TBI, both of which are priorities outlined in the DoD's recent publication on Warfighter Brain Health (Lee, 2020).

9.3 Objectives/Specific Aims/Research Questions

Describe the purpose and objective(s) of the study, specific aims, and/or research question/hypotheses

1. Objective

Past research demonstrates that SAET is a safe and effective treatment to improve neurobehavioral symptoms and return patients to pre-injury activities following concussion. However, this work has almost exclusively involved civilian populations with sport-related concussion. Its translation to military mTBI has yet to been examined. Mechanism of injury (e.g., blast vs blunt), time since injury, and co-morbid psychological trauma differs notably in the military-related brain injuries compared with sport-related brain injury.

Incorporating personalized exercise into the management of mTBI in a military population is advantageous on multiple levels. It is believed to improve treatment efficacy on physiological, cognitive, and psychological parameters and may also facilitate the integration of injured warfighters back to their units at full readiness (a primary objective of military medicine) by improving locomotion and mitigating deconditioning during convalescence.

The objective of this study is to develop a prescribed exercise treatment program for warfighters with mTBI that can be personalized for SM needs (i.e., medical and occupational) and is adaptable to variable clinical resources (e.g., forward operating bases, rural clinics, and mTBI specialty programs). This clinical trial is proposed to evaluate the efficacy of an exercise treatment for MTBI as determined primarily by symptom resolution, improved mental health, enhanced physiological functioning/locomotion, as well as RTD.

2. Specific Aims/Hypotheses:

The study will be a randomized clinical trial among active duty service members (SMs) with persistent cognitive complaints following mTBI, comparing a prescribed sub-symptomatic adaptable exercise treatment (SAET) to an active stretching control group (SCG). SAET's overall effectiveness will be assessed by neurobehavioral symptom resolution. Additional exploratory aims will include cognitive performance, physiological adaptation and locomotion as well as functional changes in military performance. These items will be addressed in the following aims:

Primary Aim:
To determine whether SAET is more effective than the control condition in reducing neurobehavioral symptoms among SMs with persistent complaints following mTBI.
Hypothesis 1: There will be a greater reduction in the Neurobehavioral Symptoms Inventory (NSI) from pre- to post-SAET compared to the control condition. A similar finding will continue from immediate to 3 month post-SAET.

Secondary Aims:
Sub-aim 1 Cognitive Status: To determine if SAET is effective at improving cognitive impairment among SMs with persistent complaints from mTBI.
Sub-hypothesis 1: There will be a greater decrease in the Global Deficit Scores (GDS; an overall measure of cognitive impairment) post SAET in comparison to the control condition.

Sub-aim 2 Physiological Adaptation: To measure physiological adaptation associated with SAET compared to the control condition.
Sub-hypothesis 2: SAET will be associated with improved cerebrovascular blood flow regulation, as measured by Transcranial Doppler and improved cardiovascular function, as measured by changes in heart rate variability (HRV) and estimated maximal oxygen consumption (est. VO_2 max) compared to the control condition.

Sub-aim 3 Warfighter Performance: To determine if SAET participants will have improved locomotion and a higher level of occupational performance compared to the control condition.
Sub-hypothesis 3: SAET participants will have improved locomotion and physical performance (based on the Marine Corps Combat Fitness Test(CFT)) and higher ratings of occupational performance (based on supervisor ratings on the Checklist of Military Activities of Daily Living [M-ADL]) after completion of treatment and 3 months post-treatment compared to the control condition.

9.4 Study Design

Describe study design in one to two sentences (e.g., prospective, use of existing record/data/specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, IV – for FDA-regulated investigational drug research.

This study will be a prospective, randomized study, with two arms, among an active duty military population with persistent cognitive complaints following a mTBI, comparing two types of physical rehabilitation-- SAET and SCG.

9.5 Target Population

Describe the population to whom the study findings will be generalized

140 participants will be recruited for the study. Participants will be active duty service members with a history of mTBI based on the DoD diagnostic criteria (Management of Concussion/m, 2009) who have persistent elevated neurobehavioral symptoms more than 1 month from injury compared to published normative data (Soble et al., 2014). mTBI diagnosis will be confirmed through a structured clinical interview, using the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) (Corrigan & Bogner, 2007), as well as through a review of participant electronic medical records (e.g., MHS GENESIS).

Participants will include male and female active duty service members who are between the ages of 18 and 55 years.

Potential service members will be recruited from the Intrepid Spirit Center at the Naval Hospital Camp Pendleton, as well as other branch clinics on Marine Corps Base Camp Pendleton. A recent report by the TBICoE Office of Surveillance identified Camp Pendleton as having the sixth most TBI encounters for active duty service members across the entire DoD, with over 400 SMs seeking treatment for a brain injury in the second quarter of 2021 alone.

Participants interested in the study will be screened for study eligibility based on inclusion/exclusion criteria dictated for this study (see details below). Individuals will be included if they report a history of at least one previous TBI, as well as elevated neurobehavioral symptoms compared to healthy SMs (Soble et al., 2014).

After screening and consent, a pre-treatment evaluation will be completed to determine baseline functioning. For each treatment, evaluations will be completed immediately post-treatment (approximately 8 weeks from baseline) and at 3 months post-treatment.

9.6 Benefit to the DoD

State how this study will impact or be of benefit to the Department of Defense

More effective interventions and treatments for mTBI are needed that promote warfighter preparedness and readiness. This study will directly inform best practices for the rehabilitation of warfighters with specific focus on maintaining military readiness. It will also inform current clinical recommendations for Progressive Return to Activity in military personnel as it utilizes military-relevant outcome measures to ensure maximal translation of study findings into clinical care. Utilization of SAET in rehabilitation following a mTBI will likely expedite recovery, improve warfighter mental health, and increase physical fitness which, in combination, will return warfighters to duty at higher capacity post-injury.

10.0 Study Procedures, Data Management, and Privacy

10.1 Study Procedures

Describe step-by-step how the study will be conducted from beginning to end

Individuals who report interest in the study and report a history of at least one previous TBI, as well as persistent symptoms they believe to be related to that injury, will be enrolled in the study

(see **Figure 1)**. Participants will complete a short screen for inclusion and exclusion criteria as dictated for this study. After screening and consenting, participants will be randomly assigned to one of two study arms, the sub-symptomatic adaptable exercise treatment (SAET) treatment group or the stretching control group (SCG) control group, and given a pre-study evaluation to capture baseline functioning. Participants will then be scheduled to begin the study intervention and will receive appointment reminders via phone, text, and/or email. For each participant, randomized to SAET or SCG, additional evaluations will be completed following their last treatment session and at 3 months post-treatment. **Figure. 2** details the study procedure timeline.

Participants will be randomized into either the exercise or the stretching condition group in a 1:1 fashion within a block size of 6, which will be utilized until all potential participants are assigned to a group (70 in exercise group and 70 in stretching condition group). Halfway during recruitment, the sample size will be reassessed for balance between the two groups. If needed, adjustment of randomization, for example, to a 2:1 ratio, will be conducted but maintaining the block size of 6. Periodic adjustment may be necessary to obtain the minimum sample size for this project. The study biostatistician will conduct randomization and an assignment schedule will be provided to the project coordinator who will keep such schedule under a password-protected encryption.

Study Evaluations

Participants will undergo the following assessments and evaluations at three study time points: pre-, post-, and 3 months post-treatment.

Cognitive Assessments

Participants will undergo various neuropsychological assessments and complete self-report measures administered via paper and pencil or electronically using an approved data collection platform. Cognitive assessments will take approximately 1 hour to administer at each time point, pre-, post-, and 3 months post-treatment. Specific assessments are described below in Section 10.2.

Data will be collected through an online survey platform both on study site computers and through links sent via email to participants and supervisors. Identifying information, including PII, IP address and geo-location, will not be obtained or stored through these online surveys to maintain confidentiality. At the completion of study data collection, all data collected will be removed from the survey platform data server. The study will own and control all data collected through these means. Only approved study team members will have access to it. In lieu on the online survey platform the measures can also be administered via paper and pencil. Specific survey links are provided below:

T1 Survey Link - **https://nhcpr.gov1.qualtrics.com/jfe/form/SV_eznqUyZolnpsETQ**

T2 Survey Link - **https://nhcpr.gov1.qualtrics.com/jfe/form/SV_cHg3c0sRtFzJZIO**

T3 Survey Link - **https://nhcpr.gov1.qualtrics.com/jfe/form/SV_dgSqFmzW2eURG86**

M-ADL Survey Link - https://nhcpr.gov1.qualtrics.com/jfe/form/SV_71npwM0iv2K9XOm

ECQ Survey Link - https://nhcpr.gov1.qualtrics.com/jfe/form/SV_bIQyl8V76eOLTv0

EHQ Survey Link - https://nhcpr.gov1.qualtrics.com/jfe/form/SV_elj5UyjpKDS24rY

Physical Assessments

Participants will have cerebral blood flow measurements taken using the NovaGuide 2 Intelligent Ultrasound system as part of their study evaluations. This FDA-cleared system uses robotics and artificial intelligence to capture accurate transcranial blood-flow information without the need for a trained sonographer prior to receiving the scan Participants will have fiducial stickers placed near one eye and near one ear, and ultrasound gel applied at pre-determined locations on the scalp. According to manufacturer's instructions for use. While in a supine position, the participant will then place their head in the NovaGuide head cradle and automated transponders will move about the head to capture blood flow data. This non-invasive procedure should take approximately 15 minutes to perform.

Participants will have their oxygen consumption (VO2) estimated while performing a graded exercise stress test (GXT). Estimated VO_2 is a good indicator of cardiovascular fitness as it measures the heart's ability to supply blood during the demands of aerobic activity. During the GXT, study participants will wear an exercise wearable and/or heart rate monitor to monitor heart activity, as well as a special mask that collects oxygen consumption. The participant will then perform cardio exercise on a machine such as a treadmill or stationary bike for approximately 8 to 12 minutes. During this procedure, trained study staff will closely monitor participants to minimize any risks associated with this exercise. Alternatively, an estimated VO2 measure may be collected during a graded exercise stress test.

Participants will have their heart rate variability (HRV) measured. HRV is a non-invasive electrocardiographic measurement of the interaction of the sympathetic and vagal tone that is modulated by the ANS (Shaffer & Ginsberg, 2017; Smith, Thayer, Khalsa, & Lane, 2017). HRV describes the amount of variation in instantaneous heart beats as well as the difference between R-R intervals (intervals between QRS complexes that represent ventricular depolarization during normal sinus rhythm). HRV analyzes the tonic sinus rhythm and therefore has been used as an indicator of ANS dysfunction in MTBI (Tan et al., 2009).

Participants will complete a Buffalo Concussion Treadmill Test (BCTT) to determine tolerance to graded exercise. The BCTT protocol involves a modified Balke graded exercise test where participants walk at a steady pace and incline is increased 1% every minute. Symptoms, HR, and RPE are evaluated after each minute stage. The test concludes if participants experience significant symptom exacerbation, defined as an increase of three or more points (based on a 1-10 visual analog scale) above their baseline or reach volitional fatigue, defined as reaching an REP of 19 or 20. Maximum heart rate achieved when test termination criteria have been met will inform whether the participant is requires a subthreshold exercise prescription. Participants unable to complete the BCTT due to injury may have the option to complete a stationary bike equivalent, the Buffalo Concussion Bike Test.

Participants will be assessed for balance dysfunctions using the Bertec Balance master. This vestibular balance mechanism is designed to measure and treat balance impairments following an mTBI. During this assessment, participants will be secured to the balance platforms via straps with carabineers, which attach to a vest worn by the participant. Once the patient is properly secured, the balance test can begin by selecting the appropriate assessment such as motor control, mobility, and weight shifting. This assessment takes approximately 20 minutes to complete.

Participants will perform isometric strength test to assess the ability to produce force generated through the legs, hips, hands, and arms. The Isometric Midthigh Pull protocol will measure the force being exerted against an immobile object using a dynamometer instead of lifting heavy amounts of weight to determine strength. Participants will be asked to walk up to the racked barbell and resemble a deadlift position that's held at the midthigh. The barbell will be attached to an immobile object via straps and a dynamometer to measure the force being exerted when pulled. The Grip Strength protocol will measure maximal force generated through each hand using a handheld dynamometer. Participants will be asked to remain seated while holding the handheld dynamometer in a 90-degree position and squeeze as hard as possible when given the signal.

Participants will perform a mock Marine Corps Combat Fitness Test (CFT) as administered by study personnel. The CFT is composed of three specific tasks the SM must complete and will take approximately 20 minutes. Each test is scored independently and corrected for gender and age:

1) Run: SM completes an 880 yard run. Primary dependent measure is seconds to complete.

2) Lift: SM lifts a 30-pound ammunitions can (or equivalent) overhead from shoulder height. Dependent measure is max reps for two minutes.

3) Maneuverability: SM completes a simulated maneuver-under-fire event. This is a timed 300-yard shuttle run in which the SM completes a series of tasks: sprints, agility course, high crawl, low crawl, body drag, fireman carry, ammo can carry, push-ups and grenade throw. Dependent measure is seconds to complete.

Command Evaluation

Work-place evaluation is an important aspect of the study. Each participant will be asked to provide contact information for a direct supervisor who is familiar with on-site work performance. Questions focus on reliability, efficiency of task completion, quality of work performance, independence on the job, as well as military readiness. SMs functioning at their duty station will be assessed by the Checklist of Military Activities of Daily Living (M-ADL). The M-ADL includes 15 items that are detailed in Table 4. In addition to the standard items, 3 items assessing cognitive performance at the workplace will be included. Each item is rated on a Likert scale from "0: Unable to Participate (medical/administrative waiver)" to "7: Complete Independence (timely, safely)". Total score will be used as the primary variable of interest.

If participants are okay with supervisors being contacted the supervisors will fill out a blank survey and return it to the researchers. Participants will not see their supervisor's responses, and supervisors will not see any of the participant's study data. Surveys will be administered online via a secure email link:
https://nhcpr.gov1.qualtrics.com/jfe/form/SV_71npwM0iv2K9XOm

Because work performance evaluation may be a sensitive topic for this population, participants will be asked during the consent process if they give permission for the study team to contact their direct supervisor. If participants do not want their supervisor contacted, then the M-ADL will not be administered. We do not anticipate that the use of the M-ADL will have a direct negative impact on the subject; however, by participating in the M-ADL portion of the study, participants risk that their supervisors will know about the study, and therefore, their participation is no longer anonymous. If participants do not want to accept this risk, they can opt out of this portion of the study.

Study Intervention

Participants will attend two in-clinic sessions per week with a licensed Physical Therapist or Exercise Physiologist and complete three sessions per week independently outside of the clinic. Each session will be 1 hour in duration, 5 days a week for 8 weeks, for a total of 40 hours. Both SAET and SCG interventions will be completed by a trained licensed Physical Therapist or Exercise Physiologist.

During the initial therapy session, participants will perform the Buffalo Concussion Treadmill Test (BCTT) to see if they are exercise intolerant or not based on symptom exacerbation (Chizuk, Willer, Horn, Haider, & Leddy, 2021; Haider, Johnson, et al., 2019; Haider, Leddy, et al., 2019). Participants randomized to the SAET intervention will complete a combination of aerobic and resistance training exercises for a total of 40 hours. A sample of the sessions, concepts, activities, and time-per phase are detailed in **Figure 2**. SAET will be prescribed and adapted to the participant's personal needs (e.g., adjustments for orthopedic injury) based on evaluations by an Exercise Physiologist and Physical Therapist. Exercise will be adjusted to maintain sub-symptomatic levels, meaning that if a patient's neurobehavioral symptoms increase with activity, the intensity and/or exercise will be modified. Furthermore, participants will be asked to fill out an Exercise Habits Questionnaire (EHQ) in order to capture the exercises they are currently doing and the exercise equipment available to them in order to best prescribe a personalized treatment. Participants will be monitored for safety and receive feedback from the trainer on the execution of the activity regimen during in-clinic sessions.

Each workout will be structured in a similar format. The first 5 minutes will be devoted to stretching and warm up exercises. Then the next 20 minute segment will be devoted to light to moderate aerobic exercise in order for participants to meet their predetermined heart rate threshold (HRt), or 90% of their max HR, from the BCTT. The aerobic exercise can be completed in any format preferred by the participant with recommendations for treadmill, row machine or stationary bicycle. HR will be measured by an exercise wearable device which gives in the moment feedback. In exercises completed at home, the first 20 minutes will also be aerobic exercise with HR goals as the target variable with open format in terms of the type of aerobic exercise (walk, jog, bicycle, or equipment). When exercising at home, the participant will be asked to wear the exercise

wearable device and complete an Exercise Compliance Questionnaire (ECQ) logging the time of exercise and type of exercise via Qualtrics survey tool.

The second 20 minutes of each exercise session will be composed of a series of 5 predetermined exercises that rotate every day. Each workout will have one or two alternatives that the patient can complete either for modification to accommodate a physical limitation or to optimize preference. Resistance training each day will include multi-joint functional movements along with stability work. Exercise programs completed in the clinical space will be supervised by a Physical Therapist or Exercise Physiologist and HR will be recorded. For independent (home-based) exercise days, the patient will be prompted to use the wearable device and to complete the ECQ. The exercises will include the use of standard fitness equipment. All participants will have access to the clinic fitness center as well as military fitness centers for independent work out sessions. If needed, participants will also be given resistance exercises that can be completed at home without equipment. The last five minutes of the session will include more mobility work, and/or cooling down.

Participants randomized to the SCG control group will complete a total of 40 hours of stretching exercises. SCG will be led by an Exercise Physiologist or Physical Therapist and stretching exercises will be completed in the clinic two days per week and independently outside of the clinic 3 days per week for 8 weeks. Total duration will be for 8 weeks. Stretching exercises are designed not to increase heart rate or have excessive head motion. (**Figure 3).**

All participants will have their physical activity measures recorded using a wearable sensor, ECQ and EHQ:

Wearable sensor: Participants will use a consumer based wearable sensor that is designed to track health information during daily activities. Measurements may include heart rate, heart rate variability (HRV), respiration, body temperature, sleep data and movement. This device will be paired with app that will allow users to view their data in real time. Such devices have been used in DoD sponsored research (Altini & Kinnunen, 2021; Asgari Mehrabadi et al., 2020; Kinnunen, Rantanen, Kentta, & Koskimaki, 2020; Stone et al., 2020).

Exercise Compliance Questionnaire: To supplement wearable sensor information, participants will be instructed to record the type of exercise, date, time of exercise, duration of exercise, perceived exertion rating, self-reported symptoms and/or other data points that will gauge compliance and engagement.

Exercise Habits Questionnaire: To best prescribe a personalized exercise treatment, participants will be asked to complete an exercise habits questionnaire to capture their current exercise routine and available exercise equipment to them.

Figure 1. Study Procedure Overview

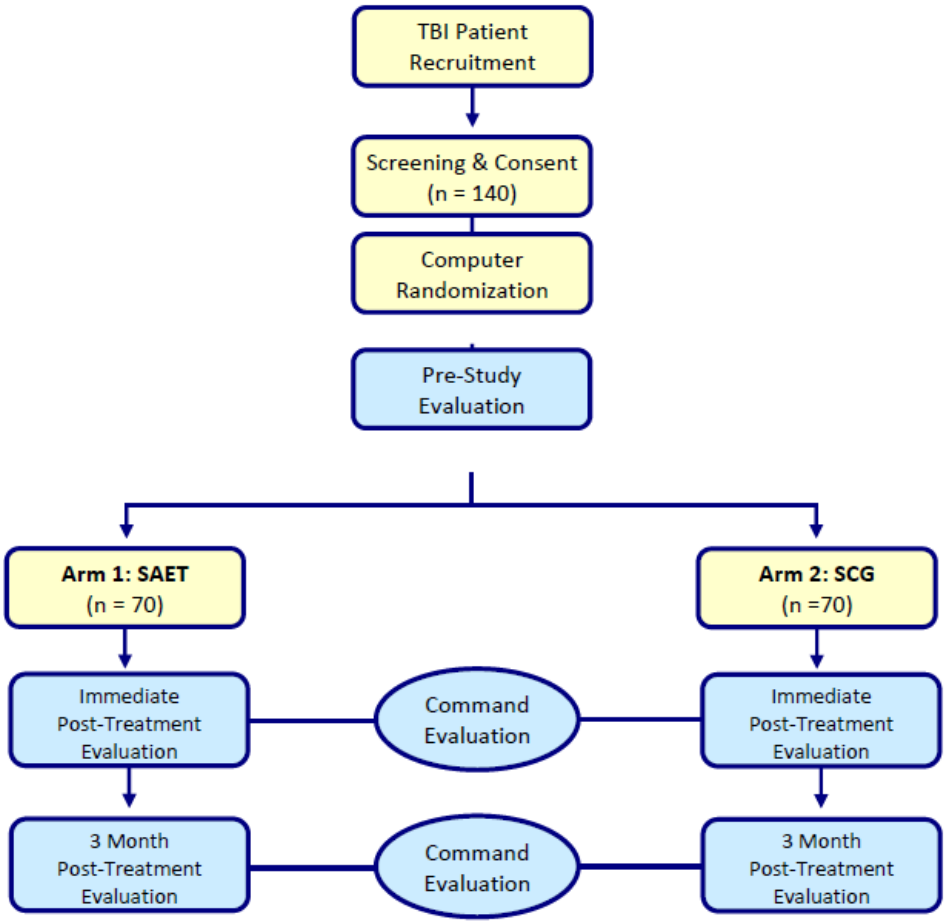


Figure 2. Example of SAET Program

Your clinician has given you a prescription for light to moderate aerobic and resistance training exercise. Each week, you will be given a specific workout to complete for 5 days. Two of these days will be completed with a trainer in the clinic and three other days will be completed on your own time.

This means you will exercise each day, but you will keep your heart rate at a specific level that is lower than it would get to during regular exercise. Your doctor has decided on a heart rate that is safe for you based on the results of your exercise test.

You can perform aerobic exercise how you want (i.e. walking, jogging, stationary cycling), but it is important to avoid a lot of neck motion during exercise. Exercise should include: A short warm-up such as stretching or walking (5 minutes), a minimum of 20 minutes at the prescribed heart rate, a minimum of 20 minutes on resistance exercises provided by your trainer, and a cool-down such as stretching or walking (5 minutes).

It is very important that you only exercise according to your prescription, and that you follow the instructions given by your doctor very carefully. Even if you start to feel better while you are at home, you should not change the heart rate at which you are exercising until you have seen your doctor again. Each clinical visit, your doctor will see how you are doing and provide a new exercise prescription if you have not recovered.

For this exercise prescription, you should use the wearable device provided to you at study enrollment. **Whenever you are exercising, you will wear the monitor to help you track your heart rate.**

Here is your exercise prescription that you should follow until your next follow-up visit:

Your treadmill test was performed on

We would like you to exercise at a heart rate of ± 5 bpm

When to stop?

If you experience an increase in your current symptoms (by 2 points on a 0-10 scale) or onset of two new symptoms of concussion while exercising at home and cannot continue, please stop for that day and try again the following day. If you experience a prolonged or severe increase of your concussion-related symptoms during exercise, then do not perform the prescribed exercises and contact your doctor.

Example Day 1 Prescribed Exercise Program

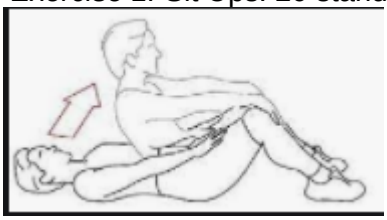
REMINDER: Note your target heart rate (page 1), wear your heart rate monitoring device, and stop exercising if your symptoms worsen.

Day 1: With Trainer

1: 5 Minutes Warm Up
2: Minimum 20 minutes at target heart rate
3: Minimum 20 minutes resistance training (see below)
4. 5 Minute Cool Down

Resistance Work-Out and Medications Day 1

Exercise 1: Sit Ups: 20 standard sit-ups, 3-5 sets



Modifications: 30 second plank or 20 crunches

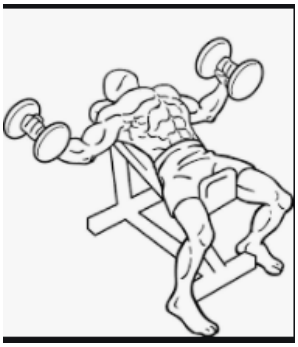
Exercise 2: Standard Bench Press, 3-5 sets with 10 repetitions

Modifications: dumbbell chest press or push ups

Exercise 3: Dumbbell Shoulder Press, *3-5 sets with 10-12 repetitions*

Modifications: Banded shoulder press or machine should press

Exercise 4: Incline Dumbbell Fly, *3-5 sets with 10-12 repetitions*



Modifications: incline chest press or decline push up

Exercise 5: Triceps Pushdown, 3-5 sets with 10-12 repetitions

Modifications: Triceps Dip, Bent Over Triceps Extension

Figure 3. Example SCG Program

YOUR PERSONAL STRETCHING PRESCRIPTION
Your doctor has given you a prescription for light stretching. For this research study, it is important that you follow the instructions given by your doctor below very carefully! You will do stretching exercises each day, without doing any other type of exercise that gets your heart rate up. Your doctor has decided on a stretching routine that is safe for you, and that should not cause you to

have any concussion symptoms. If your doctor appointment is during Days 1-6 of a stretching cycle, do not do the stretches for that day. The day after your appointment, resume doing stretches.

You will be asked to tell us how you are feeling and your activity level.

Please wear your heart rate monitoring device during the exercise.

HERE IS THE PRESCRIPTION THAT YOU MUST FOLLOW

Please see the attached sheet for instructions/demonstrations of stretches that you should do each day/week. They change each day, so be sure to follow the booklet as written.

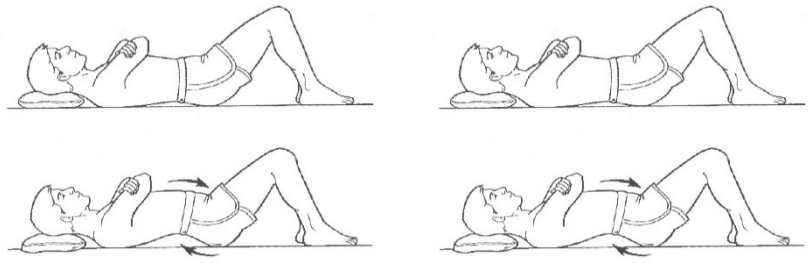
Example Day 1 Prescribed Stretching Program

Diaphragmatic breathing – Savasana

- Lie down on your back on the floor with your arms by your side, palms facing up
- Relax your legs, lay totally flat
- Breathe in deeply and slowly while counting 10
- Then breathe out deeply and slowly, counting 10, focus on pulling your stomach in
- Rest for 10 seconds

Pelvic Tilts

- Lie on floor with knees bent up
- Flatten your back to floor and hold 10 seconds (top photo below)
- Roll your pelvis the other direction and make an arch in the back hold for 10 seconds (bottom photo below)
- Rest 10 seconds and repeat 10 times



Repeat both stretches above 3 times.

10.2 Data Collection

Describe all the data variables, information to be collected, the source of the data, and how the data will be operationally measured.

All surveys, questionnaires, and other instruments will be aligned with Federal Interagency Traumatic Brain Injury Research Informatics System (FITBIR) when possible. FITBIR is a central repository for data from TBI studies built by the National Institutes of Health and the Department of Defense. Key FITBIR common data elements (CDE) include: age, gender,

education, marital status, military branch, rank, military occupational specialty (MOS), Combat Exposure Scale (CES), Neurobehavioral Symptom Inventory (NSI), injury date and time based on administration of the OSU-TBI ID. The legal name at birth, and city and country of birth are being collected to create the Global Unique Identifier (GUID) as required for submission of CDE to FITBIR.

The GUID Tool is a customized software application created by FITBIR that generates a Global Unique Identifier for each study participant. The GUID is a subject ID that allows researchers to share data specific to a study participant without exposing personally identifiable information (PII). The GUID is created locally and made up of random alpha-numeric characters and is NOT generated from PII/PHI. As such, it has been approved by the NIH Office of General Counsel. GUID Generation complies with HIPAA regulations for the protection of PII/PHI.

The following PII is required to generate a GUID: complete legal given (first) name, complete legal additional name, complete legal family (last) name, day of birth, month of birth, year of birth, name of city/municipality in which subject was born, and country of birth. Identifiers collected will be kept separate from study data. Identifiers will be kept in a secure password protected spreadsheet on the hospital server and will serve only for study staff to correctly identify research participants and create study IDs. Study data will be coded with a study IDs.

The study is a randomized clinical trial among active duty service members with persistent cognitive complaints following mTBI, comparing a prescribed sub-symptomatic adaptable exercise treatment (SAET) to an active stretching control group (SCG). SAET overall effectiveness will be assessed by symptom resolution. Additional exploratory aims will include cognitive performance, physiological adaptation and locomotion as well as functional changes in military performance. These items will be addressed in the following aims:

Neurobehavioral Symptoms (Primary Aim) will be assessed using the Neurobehavioral Symptom Inventory (NSI) which captures multiple neurobehavioral symptoms including cognitive, somatosensory, vestibular and affective.

Sub-aim 1 Cognitive Status: To determine if SAET is effective at improving cognitive impairment among SMs with persistent complaints from MTBI.

> *Sub-Hypothesis 1: There will be a greater decrease in the Global Deficit Scores (GDS; an overall measure of cognitive impairment) post-SAET in comparison to the control condition.*

Sub-aim 2 Physiological Adaptation: To measure physiological adaptation associated with SAET compared to the control condition.

> *Sub-Hypothesis 2: SAET will be associated with improved cerebrovascular blood flow regulation as measured by Transcranial Doppler and improved cardiovascular function as measured by changes in heart rate variability and maximal oxygen consumption (VO2 max) compared to the control condition.*

Sub-aim 3 Warfighter Performance: To determine if SAET participants will have improved locomotion and a higher level of occupational performance compared to the control condition.

> *Sub-Hypothesis 3: SAET participants will have improved locomotion and physical performance (based on the Marine Corps Combat Fitness Test (CFT)) and higher ratings of occupational performance (based on supervisor ratings on the Checklist of Military Activities of Daily Living (M-ADL)) after completion of treatment and 3 months post-treatment compared to the control condition.*

Surveys, Questionnaires, and Other Data Collection Instruments

Test	Purpose	Description
Neurobehavioral Symptom Inventory (NSI)	**Primary Aim**	The NSI is a 22 item self-report questionnaire that assesses PCS (Cicerone & Kalmar, 1995). The questionnaire is a preferred measure by the DoD and Veteran Affairs. It is well-validated in research studies on TBI and PTSD in military populations, it has known reliability and validity, as well as guidelines for assessment of change (Belanger et al., 2016; Soble et al., 2014). Test-retest reliability values ranged from .78 to .94 for the total score and from .52 to .91 for subscales (Silva, 2021).
Symbol Digit Modalities Test (SDMT)	**Secondary Aim 1**	Utilized to measure divided attention, visual searching and tracing, and motor speed (Smith, 2007). The test is comprised of a coding key made up of nine abstract symbols. Each symbol has a corresponding number. The test-taker is asked to visually search the key and record the number that matches each symbol as quickly as they can. The test-retest reliability is 0.80. The SDMT has good validity with other tests of attention (r = .62-.78). The test will be purchased from a commercial vendor, which will allow authorized use of this measure.
Paced Auditory Serial Addition Test (PASAT)	**Secondary Aim 1**	A serial addition task used to assess attentional processing by examining the role of immediate memory and attention (Gronwall, 1977). During administration, a series of single digit numbers are presented where the two most recent digits must be summed. The PASAT has well-studied psychometric properties with good test-test reliability and validity (Strauss et al., 2006).
Hopkins Verbal Learning Test- Revised (HVLT-R)	**Secondary Aim 1**	Used to assess verbal learning and memory (Brandt et al., 1998). It is a brief test with six alternate forms that can be easily administered in patients with varying cognitive disorders. The test consists of three learning trials with 12 nouns (targets) and includes a 25-minute delayed free recall trial. This measure will be purchased from a commercial vendor which will provide permission for use in the study.
Delis-Kaplan Executive Function System Trail Making (DKEFS TM)	**Secondary Aim 1**	The DKEFS TM is a paper-and-pencil test consisting of five trials assessing mental flexibility and processing speed (Delis et al, 2001). It is a measure of psychomotor speed, visual search abilities, working memory, and cognitive flexibility. The score on each part of the TMT is determined by the time required to complete each trial. The test has been shown to have good reliability and

		validity when assessing acquired brain injury (Delis et al., 2001).
Delis-Kaplan Executive Function System Color Word (DKEFS CW)	**Secondary Aim 1**	The DKEFS CW is a measure of inhibition and top-down brain control (Delis et al., 2001). The test has several conditions which require the participant to read words quickly fluidly, name colors, inhibit over-learned responses, and switch between competing tasks. This study will focus on four (i.e., color naming, word reading, inhibition, inhibition/switching). The DKEFS CW task is widely utilized with good psychometric properties and validity for the assessment of individuals with TBI (Delis et al., 2001).
Combat Exposure Scale (CES)	**Secondary Aim 1**	The Combat Exposure Scale is a 7-item measure used to assess the participants' exposure to combat stress such as enemy fire and in-theater life and death situations (Keane et al., 1989). The 5-point scale for each item is weighted according to severity of exposure. The CES has a coefficient alpha of .85 and a 1-week test re-test of $r = .97$, $p < .0001$.
Post-Traumatic Stress Disorder Checklist (PCL-M)	**Secondary Aim 1**	The PCL-M is a self-report questionnaire which includes 17 Items that are designed to assess symptoms of PTSD (Weathers et al., 1991). The PCL-M is extensively used both in clinical practice and is frequently used in research investigating PTSD and MTBI in military populations (Gerwitz et al., 2010; Belanger et al., 2010). This questionnaire is in the public domain and can be used without copyright restriction. The PCL-M has excellent diagnostic specificity. A conservative cut-off of 45 will be used which is consistent with recommendations from the National Center for PTSD. Empirical evidence suggests that this cut-off is associated with 97% specificity in active duty military (Bliese et al., 2008). Guidelines for assessment of changes for service members with MTBI have been published as well (Belanger et al., 2016).
Patient Health Questionnaire (PHQ-8)	**Secondary Aim 1**	The PHQ-8 is a version of the PHQ-9 that omits the question about suicidality. The PHQ-9 is the depression module of the self-administered version of the PRIME-MD diagnostic instrument (PHQ; Kroenke, 2001). The PHQ-9 is an instrument whose items are based on the SDM-IV diagnostic criteria for depression. Each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day). Its validity and reliability as a diagnostic measure as well as its utility in assessing depression severity and monitoring treatment response are well-established (Lowe et al., 2004). It also has demonstrated reliability and validity for diagnosing depression in patients with MTBI (Fann et al., 2005). This questionnaire is in the public domain and can be used without copyright restriction.
Patients' Global Impression of Change (PGIC) Scale	**Secondary Aim 1**	The self-report measure Patient Global Impression of Change (PGIC) reflects a patient's belief about the efficacy of treatment. Although widely used in chronic pain clinical

		trials, PGIC's validity has not been formally assessed. PGIC is a **7 point scale depicting a patient's rating of overall improvement.**
Pittsburgh Sleep Quality Inventory (PSQI)	**Secondary Aim 1**	A self-rated questionnaire which assesses sleep quality and disturbances over a 1- month time interval. It measures subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The PSQI takes approximately 3 minutes to administer.
Key Behaviors Change Inventory (KBCI)	**Secondary Aim 1**	The KBCI is a 64-item questionnaire that assesses behavioral areas such as lack of motivation, difficulties communicating, lack of insight into difficulties, and relationship problems (Kolitz et al., 2003). The instrument has good content and construct validity and an internal consistency reliability of 0.82-0.91.
Blast Exposure Threshold Study (BETS)	**Secondary Aim 1**	The BETS is a self-report survey that was designed to assess occupational blast exposure from military personnel. The standardized measurement tool efficiently records and calculates cumulative, life-long exposure to potential sources of blast overpressure. The BETS development was supported by the JPC-5 Exposure Standards Working Group and will be included in our study in order to better understand blast exposure history relative to outcome from CR in mTBI.
Rey-15	**Secondary Aim 1**	Rey-15 Item Test and Recognition The Rey-15 Item Test measures exaggeration or pretending to have memory problems. The test-taker is given a sheet of paper that has no markings. A card with 15 items is presented to the examinee. The test-taker is allowed to look at the card for a total of 10 seconds. Following this time period, the examinee is asked to record as many items from the card onto the paper as he or she can. Test-retest reliability is not available for the Rey-15. Inter-rater reliability has found 95% agreement for items correct, and 97% agreement for rows correct. Validity with other effort measures (e.g. Test of Memory Malingering (TOMM), Dot Counting Test (DCT)) ranges from r = .19-.78.
Test of Premorbid Functioning (TOPF)	**Secondary Aim 1**	The TOPF is used to determine premorbid intellectual functioning in adults (NCS Pearson Corporation, 2009). When administering the TOPF, the participant is given a list of 50 words and asked to pronounce the words as best they can in consecutive order even if they think the pronunciation is incorrect. Only when the participant has incorrectly pronounced 12 words in a row is the test stopped. The TOPF allows for a direct comparison to the WMS and the WAIS due to its development and standardization occurring at the same time. The internal consistency for the TOPF is excellent, ranging from .90-.97, and high test-retest reliability, .90-.94 is displayed. The TOPF also positively correlates with the Full Scale IQ (FSIQ), .63-.80, and the

		VCI, .61-.80 [NCS Pearson Corporation, 2009]. The TOPF takes approximately 5 minutes to administer.
Transcranial Doppler	**Secondary Aim 2**	Transcranial Doppler ultrasound is a non-invasive, painless procedure which is utilized to detect medical issues affecting blood flow/circulation in and around the brain using sound waves (Purkayastha & Sorond, 2012). Specifically, they are used to evaluate whether the small vessels regulating brain blood flow are working properly. This procedure is rapid and safe. It has been shown to be sensitive to changes in cerebral blood flow related to ANS dysfunction following TBI (Clausen et al., 2016)
Maximal Aerobic Capacity (VO_2max)	**Secondary Aim 2**	VO_2max is a numeric representation of the maximum amount of oxygen that is usable by the body during intense exercise, reflecting the aerobic or cardiovascular fitness level of an individual. The Korr Cardio Coach Plus will be used to capture VO_2. The Korr Cardio Coach Plus has been shown to accurately measure submaximal and maximal VO_2 (Dieli-Conwright, Jensky, Battaglia, McCauley, & Schroeder, 2009).
Balance	**Secondary Aim 2**	The Bertec Balance Master Smart Balance Manager will be used to asses balance dysfunction pre and post intervention. Patients are secured to the balance platforms via straps with carabineers which attach to a vest being worn by the patient. Once the patient is properly secured, the balance test can begin by selecting the appropriate assessment such as motor control, mobility, weight shifting, etc. The Bertec uses an encircled dome surrounding the balance platform, which projects a moving background giving patients the sensation that they are moving using virtual reality technology (Quintana et al., 2021).
Marine Corps Combat Fitness Test (CFT)	**Secondary Aim 3**	The CFT is composed of an 880 yard run, max repetitions of an overhead lift of a 30-pound ammunition can, and performance during an under-fire simulated event and completed by all Marines regardless of gender or age. A mock CFT will be proctored by study personnel at baseline, post-treatment, and three months post-treatment.
Military Activities of Daily Living (M-ADL)	**Secondary Aim 3**	The M-ADL is an evaluation survey which includes 18 items designed to assess performance of SMs by their direct supervisors
Ohio State University Traumatic Brain Injury Identification Method (OSU-TBI ID)		The OSU-TBI ID is a standardized procedure for eliciting a person's lifetime history of TBI via a 3-5 minute structured interview. The validity of the OSU TBI-ID is not based on a perfect accounting of a person's lifetime history of TBI, it is a means to estimate the likelihood that consequences have resulted from one's lifetime exposure

At any point in the study, will you request, use, or access health information in any form, including verbal, hard copy and electronic?

The Military Health System (MHS) is defined as all DoD health plans and DoD health care providers that are organized under the management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force

MHS workforce members are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS.

MHS business associates are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.

Are you an MHS workforce member? Yes

Are you an MHS business associate? No

Have you consulted with an MHS data expert to determine the data elements required for your study?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (DHA.PrivacyBoard@mail.mil)

Yes, then complete the questions below according to the data consult

No, then complete the questions below according to the best of your knowledge

Indicate how you will request data from the MHS. Select all that apply.

Talking with MHS health care providers or MHS health plans about specific research participants

Obtaining MHS hard copy records specific to research participants

Obtaining data from an MHS information system(s) YES

If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study.

Data Extract

Access YES

Do you intend to request de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:

1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information

2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

Yes

No

Indicate the MHS information system(s) from which you will seek to obtain data

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: DHA.PrivacyBoard@mail.mil.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the “Other MHS Systems” category below:

PHI Systems:

PII-only Systems

De-identified Data & Other Systems – MHS Genesis

Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

Yes, will merge data

No, will not merge data

Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS information systems.

List of requested variables from medical records

Category	Variables
Demographics	Age Sex Race/Ethnicity Highest level of schooling completed Marital status
Military information	MOS Rank Deployment number Unit Branch of service
Medical encounters	Encounters specific to concussion Encounters non-specific to concussion Specialties of providers seen

	Follow-up information
Mental health diagnosis	Depression Anxiety PTSD Current substance abuse disorder Current, active suicidal or homicidal ideation Other mental health conditions
Medications	List of any medications
Comorbidities	History of neurological disease other than concussion (e.g., multiple sclerosis, cerebral vascular accident, brain tumor, neurodegenerative disease, or neuro-motor disorder)
Cognitive assessments prior to study initiation	Determination of impaired decision-making capacity
Concussion diagnosis/history	History of TBI of any severity History of moderate, severe, or penetrating TBI as defined by DoD/VA guidelines during lifetime History of at least one MTBI sustained at least 1 month previously based on criteria of the DoD diagnostic criteria (VA/DoD) Any loss of consciousness (not to exceed 30 minutes) Any loss of memory for events immediately before or after the injury (not to exceed 1 day) Any alteration of consciousness or change in mental state (not to exceed 24 hours) Persistent post-concussive symptoms
Neuroendocrine test	Test results
Imaging records	MRI CT

If you will merge data, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.

Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the rank of general or admiral, or a race or gender, but within the context of other information could be identifiable.

Yes, I believe there is a reasonable possibility the MHS data will become identifiable

No, I believe there is no reasonable possibility the MHS data will become identifiable

Have you completed and uploaded an appropriate HIPAA document (i.e. HIPAA Authorization will be obtained or Waiver/alteration of HIPAA Authorization is being requested)?

Yes

No

N/A

10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

This study will follow best-practice standards regarding management of sensitive participant data, including personally identifiable information (PII) and protected health information (PHI). Each participant will be assigned a unique Subject ID upon consenting to the study. Each Subject ID will be a unique alphanumeric code and will not contain any personal identifiers of the participant assigned to it. Personal identifiers collected in this study include name, date of birth, address, phone number, email address, and DoD ID number. All personal identifiers will be stored separately in a secure password-protected database, and will not be linked to any clinical and/or research data collected in this study.

Electronic copies will be password protected and stored on the NHCP network, the specific server folder can be found at \\CPENFS01\Dept$\Director Of Branch Clinics\DVBIC\ADMIN\TOBI-SET\Data Management. Hard copies will be stored in a locking filing cabinet inside research office #324 located at the Intrepid Spirit Center Camp Pendleton.

A "master-list" roster of consented participants will be maintained electronically in a separate password-protected database in a secured (restricted-access) shared directory, as well as physically in a locked file cabinet inside a secured (locked) research office. This master list will include the personal identifiers described above, as well as the FITBIR GUID. This master list is the only location where personal identifiers of participants will be stored. Other records related to this study will be kept electronically in a password-protected database completely separate from the master list, and in hard copy form in a locked file cabinet separate from the master. All study records and data will be identified only by the Subject ID. The only individuals with access to the master list and to study records/data will be the PI and key research personnel. Lastly, DoD representatives will be granted access to review study records, accompanied by the PI, if requested in writing with a specific reason(s) for access.

Data will be obtained for this study at multiple time points in the following ways:

1) Self-report questionnaires which include standardized psychological tests, sleep measures, demographics, military information and combat exposure measures

2) a work performance questionnaire which will be completed, by direct supervisors regarding performance of consented participants.

3) Neuropsychological Assessments, which include measures of divided attention, visual searching, motor and processing speed, mental flexibility, inhibition, and verbal learning and memory.

4) Exercise Measures (HR, exercise log, etc.), which include wearables that measure HR, sleep data and an exercise compliance questionnaire to record exercise duration and types of exercises performed.

5) Physiological Assessments (Doppler, VO_2, BCTT, etc), which include measuring cerebrovascular blood flow (CBF), heart rate variability, oxygen consumption (VO_2), and isometric strength.

Data will also be verified in electronic medical records (e.g. health care utilization). Collection of this data will be handled by qualified research personnel using standardized protocols. Study records and data will be stored in hard copy form (if applicable) as well as electronically.

Data will be collected through Qualtrics, an online survey platform both on study site computers and through links sent via email to participants and supervisors. Identifying information, including PII, IP address and geo-location, will not be obtained or stored through these online surveys to maintain confidentiality. Qualtrics is FedRamp compliant and IT approved. At the completion of study data collection, all data collected will be removed from the survey platform data server. The study will own and control all data collected through these means. Only approved study team members will have access to it. In lieu on the online survey platform the measures can also be administered via paper and pencil.

A database will be developed for the purposes of storing and analyzing the study data. This database will be password-protected and housed in a limited-access shared directory on a DoD server only accessible to research personnel. Specifically, the database will be located in the following directory: \\CPENFS01\Dept$\Director Of Branch Clinics\DVBIC\ADMIN\TOBI-SET\DataManagement. As described above, this database will be entirely separate from the database containing the master list, and all research data will only be identified by the GUID.

This database will have robust functionality with regards to inputting study data and analyzing/exporting relevant data points. All data collected from questionnaires will be inputted into the database by research personnel. The database will allow researchers to organize and easily analyze relevant data through the use of custom queries. More complex research questions and data analysis will be done with additional software that has advanced statistical analysis functionality (e.g. Stata, SPSS). The study database will be designed to facilitate transfer of raw data in a compatible format for such purposes. De-identified data will be transferred from the database to the study personnel for analysis. Analysis will not occur within the database structure. The data will be analyzed by the study's statistician, PI and AIs.

Hard copies of study records, including raw measurement data, participant-completed forms, and database generated datasheets, will be kept in a locked file cabinet inside a secured (locked) office. In accordance with federal policy, data hard copies will be properly destroyed six years following study closure. Data elements will be reported using the National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements. If needed, new and unique data elements will be submitted to FITBIR only after grant office and IRB approval.

Data elements will be reported using the National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements. If needed, new and unique data elements will be submitted to FITBIR only after IRB and grant office approval.

We will safeguard the data from becoming identifiable through the following means:

- Using strong passwords to safeguard our data
- Allowing only research personnel with access to the NHCP server to access these password protected databases.
- Storing identifiers in a separate password protected file separate from the coded data
- Transmitting data without identifiers and only through approved platforms such as DoD safe and/or via an encrypted email.
- Storing physical identifiers in a locking office with limited access in separate filing cabinets from the coded data (e.g., test packets). Keys to the filing cabinets in which data is stored will be kept in a separate locking filing cabinet.

The study researchers acknowledge that there may be information gathered through the study that may be of interest or benefit to the patient. Therefore, at the conclusion of the participant's involvement in the study, the patient will be offered a feedback session with a study investigator to go over clinical data pertaining to neuropsychological testing results and/or improvement from study treatment. Additionally, should the participant choose to share these results with their primary care manager (PCM), a study investigator will forward the relevant data to the participant's PCM with the provision of a signed release form.

10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens/data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be re-contacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

De-identified data collected during the study will be deposited into the FITBIR Informatics System, which makes the data available to the TBI research community for future analysis and research. Study participants will be informed of such information sharing at the time of consent. Subjects will have the option to remove their data from the FITBIR system. In addition to data, research resources used in the study, which are funded will be made available to the research community using the FITBIR Informatics System. Further, our staff will ensure proper and timely documentation of the methodology and procedures for data collection, useful details about

codes, definitions of variables, variable field locations, frequencies, and any other unique background information. This document will also be deposited into the FITBIR Informatics System to be shared with the TBI research community who access our study data.

To upload data to FITBIR, study staff will download a CSV file for the form structure from the FITBIR Data Dictionary. The subject GUID is entered on the CSV along with the corresponding information that aligns with the data elements in CSV and form structure. Data is then uploaded through the FITBIR web portal. A Data Validation Tool is used on the CSV to ensure data quality, and a data submission tool writes the data to the study in the Repository. Our staff will contact the FITBIR Operations Center to arrange data entry support and to gather information regarding data formatting needs to ensure compatibility with the FITBIR system for uploading. Additionally, we will reach out to the FITBIR Operations Center for assistance in mapping study variables specific to Common Data Elements.

Study participants will be asked if they would like to be re-contacted for future research. During the consenting process, participants will initial the page to indicate that they would like to be contacted in the future; if they choose to decline they will leave that portion of the consent form blank. Participants who meet the eligibility criteria for future studies conducted by the study team may be contacted by phone or email.

Is this a data repository?

Yes No

If Yes, provide the name of the Repository

Federal Interagency Traumatic Brain Injury Research Informatics System

Who will have access to the Repository?

The general research community upon request and registration with the system administrators.

What data type will be stored in the Repository?

PHI

LDS

De-identified Data

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

1. ***Data Analyses***

The difference between treatment groups sample characteristics including demography, military information and co-variates will be evaluated using Student's 't' and chi-square tests for continuous and categorical variables, respectively. Wilcoxon Rank-Sum test will be used for two-group comparisons where continuous variables are non-normally distributed. We will leverage the statistical power of multilevel modeling to handle missing follow-up data. Please see section 11.6 for the data analysis plan.

11.2 Sample Size – 140 Participants

11.3 Total number of subjects requested (including records and specimens) – 140

11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm –

This research project will involve two study arms. Arm 1 participants will receive the SAET intervention. Arm 2 participants will receive the SCG intervention. There will be 70 subjects enrolled in each of the two arms.

11.5 Please provide a justification for your sample size

With 140 participants, 70 in each intervention arm, we will be able to potentially detect a significant difference in change in neurobehavioral symptoms between the two physical activity interventions (i.e., SAET and SCG) with an 85% power using a two-tailed test and an alpha of 0.05. This estimate is based on similar research on a civilian population (Kaplan, Vasterling, & Vedak, 2010), and takes into consideration a 20% attrition. The 140 participants recruited will suffice to address the research question for secondary aims given the same parameters.

11.6 Data Analysis Plan Complete description: Background, Objectives, Design, Step by Step how the project is going to be done

Primary Aim: *Neurobehavioral symptoms*: Primary analyses will evaluate whether change in neurobehavioral symptoms from pre- to immediate post-treatment, as well as from immediate post-treatment to 3 months post-treatment, differ between the physical activity interventions. In addition to assessing change in symptoms continuously, we will also evaluate reaching a clinically-relevant change in neurobehavioral symptoms (defined as a change in NSI score of 8 points) (Belanger et al., 2016). Secondary analyses will investigate differences in overall change in neurobehavioral symptoms from pre-treatment to 3 months post-treatment between the interventions using multilevel mixed-effect modeling. This approach will take into consideration between-subject variance based on randomized group, as well as within-subject variance for repeated measures. Analyses will be based on intention to treat (ITT).

Sub-Aim 1: *Cognitive Performance*: Similar statistical approach as Aim 1 will be conducted for Sub-Aim 1. Exposure will remain as the type of intervention (i.e. SAET vs. SCG); however, outcome will be on global deficit score based on the cognitive test scores.
Sub-Aim 2: *Physiological Adaptation*: Analysis of Variance (ANOVA) will be utilized to determine differences in continuous variables of physiological adaptation (i.e., cerebrovascular flow, improved cardiovascular health) between interventions.

Sub-Aim 3: *Warfighter Performance*: ANOVA will be utilized to determine differences in M-ADL scores between interventions. As described in Table 3, participants will be categorized as passing or not passing their CFTs. As such, given >10% with passing CFTs, we will utilize Poisson regression with robust error variable to determine the prevalence ratio of passing CFTs between the physical activity interventions.

A significant p-value of 0.05 will be used to assess main effects.

12.0 Participant Information

12.1 Subject Population

140 participants will be recruited for the study. Participants will be active duty service members with a history of mTBI based on the DoD diagnostic criteria (Management of Concussion, 2009) who have persistent elevated neurobehavioral symptoms more than 1 month from injury compared to published normative data (Soble et al., 2014). mTBI diagnosis will be confirmed through a structured clinical interview using the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) (Corrigan & Bogner, 2007) as well as through a review of participant electronic medical records (e.g., MHS GENESIS).

Participants will include male and female active duty service members who are between the ages of 18 and 55. Specific efforts will be made to recruit female participants given our site is an active duty military base predominantly of males.

12.2 Age Range – **18-55**

12.3 Gender – **Male, Female, Other**

12.4 Special categories, check all that apply – **Active Duty Military Personnel, Wounded Warriors, Pregnant Women, Fetuses, and Neonates**

12.5 Inclusion Criteria

Male or female ages 18 to 55 years.

History of mTBI: Participants will have a history of at least one mTBI sustained >1 month previously based on criteria of the DoD diagnostic criteria. This specifies an external force to the head which resulted in physiological dysfunction of the brain as manifested by one or more of the following acute symptoms:

o Any loss of consciousness (not to exceed 30 minutes)

o Any loss of memory for the events immediately before or after the injury (not to exceed 1 day)

o Any alteration of consciousness or change in mental state (not to exceed 24 hours)

Persistent Post-Concussive Symptoms: Participants will endorse atypical neurobehavioral symptomatology compared to published normative data (Soble et al., 2014). Atypical symptoms will be defined as less than the 25th percentile

12.6 Exclusion Criteria

- History of TBI (any severity) within 1 month of enrollment.
- History of a moderate, severe, or penetrating TBI as defined by DoD/VA guidelines.
- Current substance use disorder.
- History of a neurological disease other than mTBI such as multiple sclerosis, cerebral vascular accident, brain tumor, neurodegenerative disease, or neuro-motor disorder.
- Current, active suicidal or homicidal ideation.
- Impaired decision-making capacity.
- An acute orthopedic injury that limits your capacity to complete study procedures as determined by the study Physical Therapist, PI, and/or medical record review.

- EAS date within 6 months of study enrollment.

13.0 Recruitment and Consent

13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study

Potential participants will be identified through clinician referrals, responding to IRB-approved study advertisement flyers, through in-person recruitment, and/or word of mouth.

In-person recruitment to occur primarily at:
1. Marine Corps Base Camp Pendleton facilities
2. NHCP and MTF site clinics where SMs, with and without TBI, may receive care (e.g. post-deployment clinics, mental health clinics, pain clinics, PM&R clinics, primary care clinics, neurology clinics)

Additional methods of recruitment include:
1. Posting of recruitment flyers across Camp Pendleton facilities
2. Websites where SMs may find information about research studies will advertise the study with a posted study description, contact information, and a link to the study flyer.

ISC clinicians will be educated about the study by one of the study team members during regularly scheduled clinic meetings, through one-on-one conversations, and through email communications. They will be asked to refer patients who meet basic criteria and express an interest. The clinicians will provide eligible patients with a brief description of the study and ask if they would like to be contacted by a researcher for more information. If the patient is interested, the clinician will inform the appropriate researcher. The researcher will then contact the patient by phone to provide an overview of the study, answer questions, and schedule a screening and consent session.

If a participant self-refers, by contacting the research team in response to a study advertisement or from hearing about the study from someone (e.g., previous participant, friend, coworker, etc.), the research coordinator will take extra care to screen the candidate by verifying information in his/her medical record.

Clinicians and researchers will be responsible for providing potential subjects with an accurate depiction of the study's potential benefits. Subjects will be given an unbiased description of the treatment plan offered by the study. They will be informed that they may or may not benefit directly from the study, and they will not be receiving direct compensation.

Flyers will be disseminated at the ISC, NHCP, and/or Marine Corps Base Camp Pendleton facilities to extend the reach of recruitment efforts. The flyers will provide a brief description of the study, the study population, and provide direct contact information for the researchers. The material will not be coercive, and the participants will be informed that the study is not command-directed.

13.2 Compensation for Participation

Participants will be informed that they will not receive compensation for participation. A certificate of appreciation will be given at study completion to thank participants for their time.

13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor

Clinicians will have instructions to refer patients who have had a mTBI defined by DoD criteria (Department of Veterans Affairs and Department of Defense, 2016), are 1 or more months post-injury, and have been experiencing persistent symptoms dating from the event. Participants will confirm these facts with a researcher during the informed consent process. This screening conversation will also check for exclusionary conditions (see Section B). Researchers involved in the screening/consent process will have access to the patient's medical history through the electronic medical records system, MHS GENESIS. If any aspect of eligibility is in question or in the case of self-referral, researchers will have NHCP IRB approval to search the patient's record and ascertain eligibility.

13.4 Consent Process: Revised Common Rule, Section 219.116: General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens.
- No
Please explain the consent process:

After a potential participant expresses interest in the study, a researcher from the study with relevant credentials and human subjects training will provide a thorough description of the study and screen the candidate for inclusion and exclusion criteria. If the participant is a suitable fit for the study, the researcher will then go over each page of the Informed Consent form with him/her and answer any questions that arise during their discussion. The participant will be informed that at any time during the consent process and throughout the study they are free to ask questions of any of the researchers or contact a PI directly.

Participants will be given time to review the consent form and consider whether they would like to participate. They will be permitted to take the consent form home and/or consult others (friends, doctors, co-workers, etc.) prior to making their decision to participate or not. If the researcher conducting consent is unsure about a question s/he receives from a participant, the researcher will contact the PI for clarification. Consents will be conducted in person between 0800 and 1600 Monday through Friday, excluding holidays, in a private room at the Intrepid Spirit Center at NHCP. In order to monitor continuing consent, at the immediate and 3-month follow-up sessions, participants will be asked whether they wish to continue with their participation in the study.

13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman – **N/A**

13.6 Withdrawal from Study Participation
Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Participants may withdraw consent at any time and stop participating in this research study without affecting their eligibility for care or any other benefits to which they are entitled. In order to withdraw, participants must notify the point of contact for this study, Dr. Jason Bailie, PhD at (760) 719-4202. If participants are receiving treatment as part of this research study, they will no longer be eligible for such research-related treatment and will be advised to contact their personal physician to discuss medical treatment for their condition.
Withdrawing consent to participate in this research will not fully revoke the HIPAA Authorization Form to use/disclose protected health information. To make that revocation, participants must send a letter to the principal investigator as discussed in the HIPAA Authorization Form.
The Principal Investigator of this research study may terminate participation in this research study at any time if he determines this to be in a participant's best interest, or if a participant is unable to comply with the procedures required, or if they no longer meet eligibility criteria.

14.0 Risk and Benefits

14.1 Risk of Harm

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

The following are some foreseeable risks:

Prescribed Exercise Program: Participants may experience fatigue, muscle soreness, exhaustion, and/or an injury from exercising as a result of engaging in the prescribed physical fitness exercises. We do not anticipate that these risks are more than what this population experiences in their regular fitness routines.

Neurocognitive Assessment: Neurocognitive assessments are designed to be challenging in order to capture peak performance. Subjects may experience frustration and anxiety over performance as they proceed through the assessment.

Physiological Assessments: Physiological assessments are designed to be challenging in order to capture physiological condition. Subjects may experience anxiety, fatigue, nausea, dizziness, skin rash and/or irritation from sensors on wearable devices. Risks of the mock CFT include: muscle strain from overuse of a specific muscle, lower back pain due to poor form, and the chance of dehydration or heat exhaustion on hot days

Warfighter Performance Assessment: work performance evaluation may be a sensitive topic for this population. Participants will be asked during the consent process if they give permission for the study team to contact their direct supervisor. If participants do not want their supervisor contacted, then the M-ADL will not be administered. If participants are okay with supervisors being contacted the supervisors will fill out a blank survey and return it to the researchers. Participants will not see their supervisors responses, and supervisors will not see any of the participant's study data.

Symptom Measures: In order to create a complete picture of symptoms and external factors affecting recovery we will administer measures that ask for personal information such as

emotional state, combat exposure, and childhood experiences. Due to the sensitive nature of the questions, subjects may experience some discomfort while completing these measures.
Breach of Confidentiality: Anytime sensitive information is collected, there is always a possibility for that data to be lost, stolen, or mishandled, which may lead to a breach of participant information confidentiality.

14.2 Measures to Minimize Risk of Harm (Precautions, safeguards)

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

Participants will be instructed to stop exercising for that day if they experience an increase in current symptoms (by 2 points on a 0-10 scale) or onset of two new symptoms of concussion while exercising at home. Also, if participants experience a prolonged or severe increase of concussion-related symptoms during exercise, they should not perform the prescribed exercises and contact their doctor.

Additionally, steps will be taken to ensure participant comfort. Study evaluations will be conducted in comfortable, quiet, and clean testing rooms at the Intrepid Spirit Center. Study personnel will be sensitive to patient discomfort and offer breaks and encouragement when needed and when appropriate.

If participants do not wish for their supervisors to be contacted regarding their job performance through the administration of the M-ADL, participants may opt out of this portion of the research.

If subjects require emergency care for any reason related to the study the NHCP is accessible on base. Adverse events will be reported to the Principal Investigator and IRB within 5 days, as per governing regulations.

14.3 Confidentiality Protections (for research records, data and/or specimens)

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

Although complete confidentiality cannot be guaranteed in any research study, our team will implement several strategies to ensure confidentiality of participant information. First, a "master-list" roster of consented participants will be maintained electronically in its own password-protected spreadsheet stored on a secured (restricted-access) shared directory. This master list will include the personal identifiers described above, as well as the FITBIR GUID described above. This master list is the only location where personal identifiers of participants will be stored. Other study records and data will be kept electronically in a password-protected database completely separate from the master list. Hard copies of data collection forms will be stored in a locked filing closet inside of

an office with restricted access. All study records and data will be identified only by the Subject ID. The only individuals with access to the master list and to study records/data will be the PI and research personnel approved to work on the project. Lastly, representatives from agencies we report to (DoD, Sponsor, IRB, etc.) as well state and local authorities will be granted access to review study records, accompanied by the PI, if requested with a specific reason(s) for access.

14.4 Potential Benefits

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society. If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

Subjects will have the opportunity to participate in a physical exercise program to potentially help ameliorate their symptoms. At the study's conclusion they will have the option to receive feedback regarding their performance on the neuropsychological assessments. Subjects will also have the knowledge that they are contributing to a research effort seeking to improve quality of life for people struggling with symptoms like theirs.

14.5 Privacy for Subjects

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

In order to maximize privacy during recruitment, only providers or study team members, who already have access to patient health records, will approach potential research participants.

When a patient indicates interest in learning more about study participation, their contact information be shared with study staff. This will also ensure the privacy of those who do not express interest in participating.

The consent process will take place in an office with a closed door separate from the rest of the clinic to ensure subject privacy and encourage participants to voice any questions or concerns they have. In the case of remote consent, staff will try to ensure that participants are in a private location and that distractions are minimized.

During treatment sessions, participation in research will not be disclosed in the gym areas, and participants will have the same privacy measures in place as any patient being treated at the Intrepid Spirit Center. During pre- and post- treatment evaluations, study data will be collected in a quiet, private location.

14.6 Incidental or Unexpected Findings

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject. Participants will be

informed if researchers discover an incidental finding. Depending on the type of incidental finding, we may contact participants by phone, and in the case of a potential serious emergency, the researcher will inform the participant right away.

The participant does not have the option to decline receiving information about an incidental finding. Information about incidental findings will be given to the participant's care provider or participants will be referred to an appropriate doctor for further evaluation. The costs for any care that will be needed to diagnose or treat an incidental finding will not be paid for by this research study.

In the event of any adverse events and/or unanticipated problems, study staff will report to the IRB immediately.

15.0 Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB). **– NOT APPLICABLE**

16.0 Reportable Events

16.1 Reportable Events: Consult with the research office at your institution to ensure requirements are met. Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event.

Expected adverse events will be logged when reported and kept with the study records. Expected adverse events for this study include headache, anxiety, fatigue, nausea, dizziness, skin rash and/or irritation, and breach of confidentiality. Due to the nature of this patient population, we believe that the likelihood of experiencing these physical/psychological symptoms to be fairly high; however, we anticipate that the severity of symptoms will be low. We expect that the symptoms will subside shortly after testing and/or exercising, and do not anticipate any long term effects. Because of the precautions we will take to secure patient information, we believe that the likelihood of a breach of confidentiality is low. Unfortunately, if a breach occurs, leaked information will not be recoverable. When an investigator or study personnel become aware of such an adverse event, the event will be documented and the Principal Investigator will be notified immediately.

In the event of Unanticipated Problems (UP), and Serious Adverse Events (SAE), the Principal Investigator will notify the IRB and the DCoE HRPP Office; furthermore, IRB determination documentation (when available) will be forwarded to the DCoE HRPP. AEs and UPs will be submitted within 5 days of occurrence to NMCSD and within 10 days to the DCoE HRPP Office. All SAEs will be submitted within 24 hours of the event to both institutions. Additionally, should the protocol be modified, terminated, or extended, it will be reported to regulatory bodies at NMCSD and DCoE HRPP. Protocol Deviations, Adverse Events and unanticipated problems will be summarized and reviewed quarterly to determine if changes need to be made to the protocol or consent form.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

The current study will utilize the following non-FDA regulated devices.

1. Exercise wearable device – this wearable will be used to accurately measure blood oxygen levels, body temperature, heart rate and HRV and other physiological metrics.

2. Korr Cardio Coach Plus - This VO_2max machine will be used to capture participants' VO_2 during exercise to determine the amount of oxygen used during intense exercise.

3. Bertec Balance Master - This vestibular machine is designed to assess and treat balance impairments following an mTBI.

18.0 FDA-Regulated Products

18.1 *Will any drugs, dietary supplements, biologics, or devices be utilized in this study?*
DEVICES

18.3 *Device Details***: Are device(s) in this research being used in accordance to the approved labeling?**

This product has FDA clearance and is not currently regulated under an IND or IDE. For the purposes of this study, this device is not being evaluated but rather used as a tool to provide additional information on brain changes during the exercise protocol.

18.4 Reporting requirements for FDA-regulated research under IND and IDE:
Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

18.5 *Sponsor (organization/institution/company):* **N/A**

19.0 Research Registration Requirements

19.1 *ClinicalTrials.gov Registration* – **Registration Pending**

19.2 *Defense Technical Information Center Registration (Optional)* – **Registration Pending**

20.0 References and Glossary

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20.2 Abbreviations and Acronyms

American Hospital Services Group (AHSG)
Autonomic Nervous System (ANS)
Brain Derived Neurotrophic Factor (BDNF)
Certified Strength and Conditioning Specialist (CSCS)
Cerebral Blood Flow (CBF)
Cerebral Blood Flow Velocity (CBFV)
Checklist of Military Activities of Daily Living (M-ADL)
Concussion Management Clinic (CMC)
Cooperative Research and Development Agreement (CRADA)
Federal Interagency Traumatic Brain Injury Research (FITBIR)
Food and Drug Administration (FDA)
Delis-Kaplan Executive Function System Color Word (DKEFS CW)
Delis-Kaplan Executive Function System Trail Making (DKEFS TM)
Defense Health Agency (DHA)
Department of Defense (DoD)
Department of Health and Human Services (DHHS)
Department of Social Services (DSS)
General Dynamics Information Technology (GDIT)
Global Deficit Scores (GDS)
Global Unique Identifier (GUID)
Heart Rate Variability (HRV)
High Frequency (HF)
Hopkins Verbal Learning Test-Revised (HVLT-R)
Institutional Review Board (IRB)
Intrepid Spirit Center (ISC)
Joint Commission on Accreditation of Healthcare Organizations (JCAHO)
Low Frequency (LF)
Legally Authorized Representatives (LAR)
Marine Corps Base Camp Pendleton (MCBCP)
Marine Corps Combat Fitness Test (CFT)
Maximal Oxygen Consumption (VO2 max)
Middle Cerebral Artery (MCA)
Mild Traumatic Brain Injury (MTBI)
Military Treatment Facilities (MTFs)
National Institute of Neurological Disorders and Stroke (NINDS)
National Institute of Health (NIH)
National Research Action Plan (NRAP)
Naval Hospital Camp Pendleton (NHCP)
Naval Medical Center San Diego (NMCSD)
Neurobehavioral Symptoms Inventory (NSI)

Negative Temperature Coefficient (NTC)
National Intrepid Center of Excellence (NICoE)
Office of Human Research Protections (OHRP)
Office of Research Protections (ORP)
Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID)
Paced Auditory Serial Addition Test (PASAT)
Patient Health Questionnaire (PHQ)
Personally Identifiable Information (PII)
Primary Care Manager (PCM)
Protected Health Information (PHI)
Return to Duty (RTD)
Service Members (SMs)
Stretching Control Group (SCG)
Sub-symptomatic Adaptable Exercise Treatment (SAET)
Symbol Digit Modalities Test (SDMT)
Traumatic Brain Injury Center of Excellence (TBICoE)
Traumatic Brain Injury (TBI)