

**Utilizing Photobiomodulation Therapy for Treatment of Lower
Extremity Stress Fractures in Military Training Settings**

Protocol approved 3 March 2023

NCT05843864

EIRB Protocol Template (Version 1.2)

1.0 General Information

***Please enter the full title of your study:**

Utilizing Photobiomodulation Therapy for the Treatment of Lower Extremity Stress Fractures in a Military Training Setting

***Please enter the Protocol Number you would like to use to reference the protocol:**

Photomedicine Project 12: PBMT for Treating Stress Fractures at Training
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

Yes

Does this protocol involve the use of animals?

☐ Yes ☒ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary
Dept?

Department Name



P and R - Brooke Army Medical Center (BAMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Parsons, Nathan A, DSc MAJ

Select if applicable

☐ Student

☐ Site Chair

☐ Resident

☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Golden, Andrew Phillip

Associate Investigator

Rhon, Daniel I, DPT, DSc, PhD

Associate Investigator		
B) Research Support Staff		
Callas, Mariah Johanna Research Coordinator Dunn, Nathan M Research Coordinator Farias, Athena M Research Coordinator Foster, Kaitlyn S Research Coordinator Greenlee, Tina A, Ph.D. Kinesiology Research Coordinator Johnston, Brian C, DPT Research Coordinator Lucio, Whitley B Research Coordinator Metzger, Elizabeth C Research Coordinator Ory, Rian Lyndzie, MS Research Coordinator Roberts, Jennifer Susan Research Coordinator		
3.3 *Please add a Protocol Contact:		
Callas, Mariah Johanna Dunn, Nathan M Farias, Athena M Foster, Kaitlyn S Greenlee, Tina A, Ph.D. Kinesiology Johnston, Brian C, DPT Lucio, Whitley B Metzger, Elizabeth C Ory, Rian Lyndzie, MS Parsons, Nathan A, DSc MAJ Rhon, Daniel I, DPT, DSc, PhD Roberts, Jennifer Susan The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).		
3.4 If applicable, please select the Designated Site Approval(s):		
Wiesenthal, Alison Claire <i>Department Chair</i> Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).		

4.1 * What department(s) will be associated with this protocol?

Physical Medicine & Rehab

4.2 * Is the IRB of record for this study an IRB/HRPP that does NOT use EIRB? If Yes, complete the application according to the IRB/HRPP Determination.

If your Projects or Protocols are under the oversight of another IRB that does use EIRB, stop this submission and contact the core site and request an invitation as a performing site.

If your Project or Protocol is now being submitted for the first time to an IRB that does use EIRB, continue with this application and answer the questions to be reviewed by the IRB.

Answering yes means the board of record is an IRB that does NOT use EIRB.

☐ Yes ☒ No

4.3 * Is this protocol research, expanded access, or humanitarian use device?

☒ Yes ☐ No

4.4 * What type of protocol is this?

- ☐ Behavioral Research
- ☒ Biomedical Research
- ☒ Clinical trial (FDA regulated)
- ☐ Educational Research
- ☐ Expanded Access
- ☐ Humanitarian Use Device (HUD)
- ☐ Psychosocial Research
- ☐ Oral History
- ☐ Other

4.5 Are you conducting this project in pursuit of a personal degree?

☐ Yes ☒ No

4.7 * Is this human subjects research? (As defined by 32 CFR 219) Human subject means a living individual about whom an investigator (whether professional or student) conducting research:
(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

☒ Yes ☐ No

4.8 * Do you believe this human subjects research is exempt from IRB review?

☐ Yes ☒ No

Personnel Details

5.1 Does the Principal Investigator have a Permanent Change of Station (PCS) Date or Estimated Institutional Departure Date (EIDD)?

☐ Yes ☒ No

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

No records have been added

5.3 Are any Contractors or Subcontractors involved in this study? If yes, please list them and describe their role.

☒ Yes ☐ No

Name: (Last, First, M.I.) Ory, Rian L Role on Protocol: MIRROR Regulatory Affairs Manager	Phone Number: 909-904-5034	Email Address: rian.ory.ctr@usuhs.edu	Associated Institution: The Geneva Foundation / USUHS
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Name: (Last, First, M.I.) Metzger, Elizabeth C Role on Protocol: MIRROR Photomedicine Scientistic Program Manager	Phone Number: 252-562-2419	Email Address: emetzger@genevausa.org	Associated Institution: The Geneva Foundation / USUHS
Name: (Last, First, M.I.) Rhon, Daniel I, DPT, DSc, PhD Role on Protocol:	Phone Number: 253-293-0154	Email Address: daniel.rhon2.ctr@health.mil	Associated Institution: The Geneva Foundation / USUHS

Associate Investigator			
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Name: (Last, First, M.I.) Roberts, Jennifer S Role on Protocol: Research Coordinator	Phone Number: 210-464-3868	Email Address: jennifer.s.roberts12.ctr@health.mil	Associated Institution: The Geneva Foundation / BAMC

5.4 Will you have a Research Monitor for this study?

- ☐ Yes
☒ No
☐ N/A

6.0 Data/Specimens

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

- ☐ Yes ☒ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
: Other USUHS Award Number HU00011920056	Research Development : Testing and Evaluation (RDT&E) funds Photomedicine	300000

Total amount of funding:

300000

7.2 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?

- ☐ Yes ☒ No

All personnel engaged in research must complete and attach a Conflict of Interest (COI) form.

8.0 Study Locations

8.1 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

- ☒ Yes ☐ No

8.2 Study Facilities and Locations:

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Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
Army	Brooke Army Medical Center	Lead site	FWA00004092	06/16 /2025	☐ : ☒ IAIR	☐ : ☒ RHC - C IRB
P&R	Uniformed Services University	Coordinating center	FWA00001628	05/04 /2026	☐ : ☒ IAIR	☐ : ☒ RHC - C IRB

Other:

Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added					

8.3 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

☐ Yes ☒ No

8.4 Is this an OCONUS (Outside Continental United States) study?

☐ Yes ☒ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

☐ Yes ☐ No

9.0 Study Details

9.1 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

Lower extremity Bone Stress Injuries, Photobiomodulation, military population, Photomedicine, Bone Stress Injuries

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

Musculoskeletal injuries remain the primary reason for outpatient visits and non-deployable and limited duty status amongst Active-Duty Service Members (ADSMs) (Molloy). Bones Stress Injuries (BSIs) are the strongest predictor of basic training drop out in some branches (Reis), and primary reason for lost duty days and recycling during training (Cowan). This injury is estimated to affect up to 5-10% of Service Members within the first few training months (Reis, Lee, Waterman, Kandouni, Wentz, Wood) and can take over 100 days to heal as compared to other common training injuries (e.g., sprains) that may only take 20 days or less (Knapik). Of note, BSIs occur on the magnitude of 10x-15x more often in trainees than in ADSMs (Molloy 2020). Financially, BSIs cost the military an estimated 100 million USD annually in trainees alone (Cowan). Overall, BSIs are costly and decrease readiness, as this injury reduces ADSMs ability to perform necessary military duties.

In military and athletic populations, most BSIs (70-90%) are in the lower extremity, with tibial and metatarsal fractures accounting for roughly half of all BSIs (Kahanov, Waterman). Traditional treatment for low-risk tibial and metatarsal BSIs includes correcting nutritional deficiencies and abnormal biomechanics, elevating and icing, cross-training (swimming/cycling), ensuring proper footwear, prescribing acetaminophen for pain, implementing strength and flexibility rehabilitation, and encouraging weight management. The primary treatment pathway includes initially decreasing activity followed by a gradual increase until return to function, guided by symptomatology reduction. In high-risk fractures (e.g., non-union, anterior tibial cortex), surgical intervention may be needed (Patel). With traditional care, metatarsal and tibial BSI symptomatology can differ greatly, due to several factors, including health care seeking, with an average duration of 2-8 weeks after diagnosis; return to duty typically takes 4-8 weeks but may take up to 22 weeks (Wood). Outcomes are also varied (Kiel), and recurrence is common, presenting in approximately 25% of cases (Rizzone, Beck). Ultimately, trainees are often out of the fight as they heal from this injury. Promising, innovative treatment pathways, along with prevention efforts, need to be employed to return trainees to the fight sooner, reduce recurrence, and increase successful outcomes.

Photobiomodulation therapy (PBMT) involves applying non-ionizing forms of light from sources including lasers, LEDs, and broadband light, in the visible and near infrared spectrum, to the body to enhance performance, stimulate healing, modulate recovery, and improve health. It is postulated that PBMT increases proliferation of osteoblasts and differentiation, ultimately positively contributing to bone regeneration through increased osteocyte presence (Bayat). Animal studies indicate that PBMT increases bone strength (Tajali). A recent systematic review found that PBMT positively influences bone regeneration via a biostimulatory effect by increasing necessary osteoid matrix components and the expression of proliferating genes for bone proteins (Escudero). PBMT also reduces inflammation in a manner that is equivalent in magnitude to non-steroidal anti-inflammatory drugs (NSAIDs) (Bjorodal), a needed component in healing; NSAIDs, however, are associated with increased fracture risk due to their compound competing with necessary acids for binding sites on enzymes that are initiators of bone formation (Fedgo). Overall, bench side research provides potential explanations for the biological mechanisms of PBMT enhancing bone healing.

In human trials, PBMT has shown to be a promising therapy for reducing pain and increasing functionality during healing of fractures (Neto). In treating distal radius fractures after cast removal, PBMT was found to decrease consumption of analgesic medication and night pain during a home-based exercise program (Saebo, 2022). Pre-cast removal, PBMT also reduced night pain and improved range of motion and pinch and grip strength (Saebo, 2021). A prospective randomized trial found that use of PBMT in tibial BSI treatment resulted in earlier symptom resolution and pain free ambulation, and decreased recurrence, as compared to placebo (Chauchan). Taken as a whole, PBMT is an encouraging avenue for treatment of lower extremity BSIs. Moreover, Special Forces and athletic populations are utilizing this cutting-edge therapy to enhance muscle recovery during training (Ailioaie). There, however, is a gap in understanding the effectiveness of using PBMT to treat BSIs in a military training setting. This study will address this need, which could ultimately provide a treatment avenue that keeps more Service Members in the fight and increases overall military readiness.

This study will investigate the effectiveness of providing photobiomodulation therapy in addition to standard of care in the treatment of tibial and metatarsal BSIs in a military training setting. Participants will be randomized into two groups: 1) standard of care with sham photobiomodulation therapy and 2) standard of care combined with photobiomodulation therapy.

The need to address BSIs is particularly relevant in Army Advanced Individual Training (AIT), a training setting where rates of BSIs are anecdotally high. This relative increased incidence is postulated to be due to this training occurring on the heels of basic combat training (BCT), where recruits may appear without a baseline fitness/activity level that is necessary to meet training demands. Thus, increase in activity may occur rapidly, producing risk for injury. Trainees at BCT may not endorse these injuries during Army BCT due to fear of being dismissed from training. It is likely the trainees develop BSIs during BCT and then postpone this endorsement until AIT,

which occurs immediately after BCT, and where they are then screened for these injuries. ADSMs may then also feel more secure in their positions, thus feeling more able to endorse this symptomology without fear of training dismissal. Additionally, AIT allows for more autonomy than BCT, making the conduct of research more feasible. Taken as a whole, AIT is a prime location to conduct BSI research that may provide participant and military benefit.

9.3

Objectives/Specific Aims/Research Questions:

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

This study will investigate the effectiveness of providing photobiomodulation therapy in addition to standard of care in the treatment of tibial and metatarsal bone stress injuries in a military training setting.

Participants will be randomized into two groups:

- 1) standard of care with sham photobiomodulation therapy, and
- 2) standard of care combined with photobiomodulation therapy.

Aim 1: Assess return to duty and completion of Advanced Individual Training (AIT) cycle in the PBMT treatment group as compared to the sham PBMT treatment group at the 4-month follow up (prior to graduation/departure).

Aim 2: Evaluate differences in pain and functional status at the 3-week, 6-week, and 4-month follow up time points.

9.4 Study Design:

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

Single-blind Randomized Control Trial

9.5 Target Population:

Describe the population to whom the study findings will be generalized

Active-Duty Service Members, Academies requiring similar activity (e.g., police, intelligence agencies)

9.6 Benefit to the DoD:

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

BSIs are the strongest predictor of drop out in basic training in some branches, and primary reason for lost duty days and recycling during training. BSIs are estimated to affect up to 5-10% of Service Members within the first few training months, reducing their ability to perform necessary military duties. In trainees, BSIs occur 10-15X more often than ADSMs. Symptomatology can last for months, outcomes are varied, and reoccurrence happens in up to a fourth of those treated; some Service Members never return to duty. This study will examine a potential treatment avenue, that keeps more Service Members in the fight and increases overall military readiness.

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

Study activities will occur at Fort Sam Houston within AIT training units. Participants must be current AIT students/trainees. Study activities, including recruitment, will occur at the Soldiers in Training Clinic or other applicable treatment areas.

Recruitment, Pre-Screening (before consent), Study Introduction & Informed Consent:

Potential participants will be identified via four methods:

1. Under an approved Partial HIPAA Waiver, local study team members will review medical records of patients coming to the Soldiers in Training (SIT) Clinic, where AIT students present for medical needs. Authorized study team members will pre-screen for individuals seeking care for suspected BSIs to identify prospective research participants for the purposes of seeking their authorization to participate/use their protected health information for this research study.
2. Patients may self-refer to participate in the study. Interested potential participants will be able to contact a member of the study team via phone or email. Potential participants who contact the study team directly will be instructed to access the SIT Clinic or their applicable health care provider (e.g., primary care provider or physical therapist) for a physical exam and BSI diagnosis, or confirmation of BSI diagnosis.
3. Direct referral from local healthcare providers in SIT Clinic, and other applicable departments/ clinics at Brooke Army Medical Center (BAMC) such as Primary Care (including Army Patient Centered Medical Home, Family Medicine, Internal Medicine Clinic), and Pain Management.
4. Mass briefs of incoming classes for AIT. Every effort will be made to ensure there is not undue coercion, such as ensuring that there is not the presence of instructors or Command. Briefs will not be performed by any study team member in a military uniform. (Please see Appendix W Mass Recruitment Brief)

If a potential participant expresses interest in learning more about the research study, a member of the research staff will briefly introduce the study, express the voluntary nature of participation, assess interest in participating, and screen the potential participant for eligibility. Eligibility will be determined in person using the Inclusion/Exclusion Case Report Form (CRF; Appendix A). Additionally, the potential participant may be provided with a study brochure and/or flyer (Appendices U-V).

Pre-screening conversations may also take place over the phone using the Screening Script (Appendix L). Potential participants that meet initial eligibility per the Screening Script and express interest in participating will be asked to come to clinic to complete an Inclusion/Exclusion CRF to confirm eligibility with an authorized study team member.

If the potential participant meets initial eligibility criteria as determined by the Inclusion/Exclusion CRF and expresses interest in participating in the study, an authorized study team member will initiate the formal consent discussion and, if applicable, obtain informed consent. No instructors will be present during the consent process. The study team member will clearly indicate that choosing to participate, or not, does not have an effect on student status and thus graduation from AIT.

If a potential participant would like additional time to review the consent form, study procedures, risks and benefits, etc., they will be provided with a consent form to take home and, if applicable, they may return to clinic at a later date to have any and all remaining questions answered and to finish the consent process.

Following screening, the results of the Inclusion/Exclusion CRF will be entered into REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a DoD server and maintained by the Uniformed Services University Information Technology (USU IT), and a unique study ID will be generated.

Participants that consented to participate in this study will be added to a master list (Appendix N), that will be used to match the participants unique study ID with their name, Department of Defense (DoD) ID, date of birth (DOB), and contact information. The master list will be stored in a password-protected electronic document on a Common Access Card (CAC)-enabled server; only on-site study team members will have access to this file. This coded study ID will be used on all research data collection forms in place of the participant's name, social security number,

DoD ID, or other protected identifier. No Protected Health Information (PHI)/Personally Identifiable Information (PII) will be entered into REDCap. Please see Appendix Q for additional information on REDCap.

The research team will also maintain a separate password-protected electronic screening log (Appendix M) containing DoD ID number and eligibility/ineligibility status of all individuals that are screened. The screening log will be electronically maintained in a secure folder on a secure drive, accessible only by authorized users. This screening log is needed to avoid any duplicative screening of individuals and to track screen failures. Screening IDs will not be the same as Study IDs.

Contact Information Data Collection (post-consent):

Immediately following consent, the participant will complete an Intake CRF (Appendix B). The Intake CRF will collect participant contact information (full name, DoD ID number, preferred phone number, email address, etc.).

With the exception of the Consent Form and HIPAA Authorization Form, the Intake CRF is the only paper research form that will contain participant identifying information. It will be stored with the signed consent forms (in a locked cabinet inside of a locked room), separated from all other paper research forms. All other paper research forms will be identified using the participant's unique study ID and not by participant name, social security number, DoD ID, or other similar identifier. The Intake CRF will not be entered into REDCap.

Formal Screening, Demographics, & Baseline Data Collection:

Formal Screening:

Urine Pregnancy Test: As part of the formal screening procedures, consented participants that are females of child-bearing age and capacity will have their final eligibility status confirmed via urine hCG pregnancy test. If participants do not meet this eligibility criteria, they will be formally withdrawn from the study.

Diagnostic Imaging: As part of the formal screening procedures, consented participants' final eligibility status will be confirmed via diagnostic magnetic resonance imaging (MRI). If imaging was completed within one month prior to study enrollment, the previous images may be utilized. If diagnostic images are required, imaging will be ordered by an authorized medical provider. The results of the diagnostic images will determine if the participant meets final eligibility criteria (i.e., clinical diagnosis of metatarsal or medial tibial bone stress injury/stress fracture) and should continue with the study intervention. If participants do not meet this eligibility criteria, they will be formally withdrawn from the study. Direct identifiers may be removed from the diagnostic MRI and labelled using only the participant's assigned participant ID. These coded images will be securely stored and uploaded to the Teleray data platform. More information regarding Teleray is listed in Protocol Sections 10.14-10.15.

Formal screening and confirmation of final eligibility status will be completed prior to study randomization.

Demographics & Baseline Data Collection:

Prior to being randomized to a study treatment group, participants will complete a Demographics CRF (Appendix C) and a Baseline Data Collection CRF (Appendix D). These questionnaires collect relevant data including: personal demography, military and employment demography, injury demography, and medical history. Baseline outcome measures that will be assessed include the LEFS and the Defense and DVPRS with Supplemental Questions.

Functional Assessments:

- Participants will be asked to complete a hopping test in the clinic. Participants will be asked to perform up to 10 hops on their respective study leg(s). At the conclusion of the test, participants will be asked to rate their pain using the DVPRS basic.
- A study team member will also conduct a percussion test by directly and indirectly palpating the injured area. The study team member will use 2-3 fingers to firmly tap up and down on the injury area. This process will be completed 3-4 times. At the conclusion of the test, participants will be asked to rate their pain using the DVPRS basic. Results will be recorded on the Baseline Data Collection CRF (Appendix D).

Fitzpatrick Skin Phototype: A study team member will indicate the participant's Fitzpatrick Skin Phototype. Results will be recorded on Appendix D.

Randomization:

Participants that meet all final eligibility criteria will be randomized to a study arm using a computer-generated randomization model prepared by the study biostatistician, to assign participant 1:1 across both study arms (either PT + sham PBMT or PT + PBMT).

Study Treatments (PT + sham PBMT, PT + PBMT):

All participants will be blinded to the study arm they are assigned to and will be unblinded at the conclusion of their final study visit.

Participants will be asked to refrain from using perfumes or plant extracts (e.g., St John's Wort) in the treatment areas, as this can increase photosensitivity.

If a participant has not been placed on profile at the time of consent, a profile may be written by the study medical provider to ensure limitation of activities, as appropriate.

Standardized Home Exercise Program

All participants will be instructed to follow a standardized Return to Running Program (Appendix O) as a research procedure.

Standard of Care (SOC) Physical Therapy (PT)

All participants will complete a standard PT program to address individual strength, mobility, and flexibility deficits in both proximal and distal muscle groups. The provider may also use other modalities to address distal issues, and may include relative rest, elevation, ice, and, when appropriate, cross-training (swimming/cycling). These procedures are standard of care for management of BSIs.

The PT treatment received as standard of care is not a study-specific research procedure; however, PT care provided/received will be tracked on a Chart Review CRF (Appendix H) in order to monitor treatment fidelity.

Study Intervention (PBMT v. Sham)

Participants will complete three in-person visits each week, for a maximum of six weeks, to receive their assigned study treatment. Treatment visits will be terminated if a participant is cleared by a healthcare provider to return to duty (RTD).

Photobiomodulation Therapy (PBMT) Arm:

Participants assigned to the PBMT arm will receive PBMT in addition to SOC PT and the return to run program.

The device that will be used to deliver PBMT is the Omnilux Plus 830, which is a Class II FDA cleared medical device (see Appendix S for more information on the Omnilux Plus 830). PBMT will be provided by study team members that receive appropriate device training.

PBMT will be delivered using the Omnilux Plus 830 nm panels in treatment mode, with an output wavelength of 830 +/-5 nm. The device will be placed at 1-8 cm (ideally 2-5 cm) from the surface of the injury. The device will be folded around the targeted area (see Figures 1 & 2). The Omnilux Plus 830 has multiple adjustable points and five panels that can be independently activated, allowing for targeting of the specific treatment area. The device will be set at 30-50 J /cm² for 10-16 minutes. Participants will then be instructed to rest for 5 minutes after the treatment.

Sham PBMT Arm:

The sham PBMT arm will receive sham PBMT in addition to SOC PT and the return to run program.

Sham PBMT will be provided by a trained study team member. Sham PBMT will be delivered in the same manner as indicated for the PBMT process above, but the device will stay in standby mode; the treatment mode will not be turned on. Sham PBMT treatment is expected to last 10-16 minutes. Participants will then be instructed to rest for 5 minutes after the treatment.

The inclusion of sham PBMT will ensure all participant treatment procedures remain the same, with the exception of the emission of photons (active treatment), thus, allowing for contribution of any differences between groups to be credited to the use of PBMT. As infrared light is not visible to the naked eye, the only visible difference between treatment and standby modes is the presence of a few tiny amber lights (these lights are on during treatment mode).

Follow-Up Data Collection:

Participants will complete follow-up data collection procedures, either up to 4 months, or until graduation/dismissal from training, whichever comes first.

Daily Assessments:

All activities, including additional exercises and running will be recorded by the participant in a daily activity log (Appendix E). The activity log will be completed for the duration of the study, or until they are cleared for RTD by a healthcare provider. The activity log will be collected weekly.

Weekly Assessments:

Once a week, a study team member will follow-up with the participant to:

- ensure they are completing the return to run (walk-to-run) program and activity log,
- administer the DVPRS with supplemental questions, and
- assess for adverse events.

Weekly follow-up data will be recorded on Appendix F. This follow-up visit can be completed in-person or remotely.

The 3-week, 6-week, and 4-month follow-up data will be recorded on Follow-Up Data Collection CRF (Appendix G), which will include Patient reported outcome measures (PROMs), hopping and percussion tests, and adverse event (AE) assessment. Follow-up diagnostic MRI will be completed at the 6-week and 4-month follow-up visits.

RTD status will be assessed weekly during the 6-week treatment period and at the 4-month follow-up visit utilizing the Medical Operational Data System (MODS).

Finally, a medical record chart review will be completed at the 4-month follow-up visit to ensure that all PT visit information is recorded in study documentation (Appendix H). Typically, a blood draw is completed as standard of care at or around the time of injury diagnosis in this injured population. Results of the blood draw (e.g., vitamin D/iron levels, date of test, etc.) will be extracted from the medical record and recorded on Appendix H. A study visit is not required on behalf of the participant.

Data may be captured in person or remotely (e.g., entered directly into REDCap using a personalized coded link with no log-in required, verbally over the phone with a study team member, etc.). Reminder phone calls, texts, and/or emails will be sent to participants at their preferred contact method indicated on the Intake Form (Appendix B).

An overview of study timepoints, treatments, and outcome measures can be found in the Data Collection Schedule (Appendix J) and Study Flow Diagram (Appendix K).

Missed Appointments and Study Removal:

If a participant misses a scheduled appointment, they will be contacted to reschedule in order to maintain the treatment plan of their assigned study treatment group. In the event that a participant misses an appointment, study staff will make one attempt to reschedule each day on three separate days (for three total attempts to reschedule).

Data Entry:

With the exception of the Intake CRF which collects participant contact information, all coded research data will be entered into REDCap. No PII will be entered into REDCap. See Appendix Q for additional information on REDCap.

Diagnostic MRIs will be uploaded to Teleray.

Additional Info - MIRROR/USU:

This research study is being conducted as part of Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR), which is based out of the Department of Physical Medicine & Rehabilitation (PM&R) at the Uniformed Services University (USU).

MIRROR is focused on advancing musculoskeletal injury (MSI) rehabilitative care within the military healthcare system in order to reduce the burden MSIs have on military readiness and to ultimately enhance the operational capabilities of the armed forces. MSIs affect approximately 800,000 service members annually and result in 25 million days of limited duty. These conditions are the primary reasons for medical discharge/downgrade and result in 34% of medical evacuations from theatre. MIRROR was developed as a means to study risk factors of common MSIs, generate prevention strategies, optimize treatments, and establish return-to-duty criteria that is based on scientific evidence rather than case-specific clinical judgment alone.

MIRROR involves interdisciplinary and inter-service partnerships, the DoD, and several major academic medical centers. To ensure military mission focus and scientific relevance, MIRROR is guided by a steering committee composed of members from the Joint Program Committees (JPCs) at the U.S. Army Medical Research and Development Command (USAMRDC), military operational leaders, and experts in musculoskeletal medicine from the military and civilian communities. MIRROR aims to be the world's leader in military relevant musculoskeletal injury care research.

Currently, research projects are being deployed at more than 20 military and civilian treatment facilities nationwide.

MIRROR/USU is serving as a Coordinating Center for this study and will also be providing remote regulatory support. Staff from MIRROR/USU will not interact with human subjects and will not have access to the paper research records or any identifiable research data to include the Master List, the Informed Consent Documents/HIPAA Authorizations, or any other form of participant PHI /PII. Deidentified research data will be shared with MIRROR/USU and maintained indefinitely for possible use in future research.

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.

Please see attached Data Collection Schedule (Appendix J).

The local study team will obtain the information necessary to complete the study CRFs (see Appendices A-I) from several sources including the participant's medical record (i.e., relevant medical and treatment history and relevant clinical notes), clinical evaluations, from their attending provider(s), and directly from the participant (including in person, via mail or email, or over the phone).

With the exception of the Intake CRF (Appendix B) which collects contact information, all paper CRFs will be identified using a unique study ID only, and not by the participant's name, social security number, DoD ID, or other protected identifier.

PROMs:

- Defense and Veteran's Pain Rating Scale (DVPRS) with supplemental questions will capture pain weekly; the single-item DVPRS basic will be assessed after the percussion and hopping tests.
- Lower Extremity Functional Scale (LEFS) will capture functional status

Functional Assessments:

- Hopping Test
- Percussion Test

Appendix A Inclusion Exclusion CRF:

Verifies that the potential participant meets eligibility criteria for participation in this research study.

- Inclusion/Exclusion Criteria
- Documentation of Informed Consent

- Formal Screening (Diagnostic MRI)
- Final Eligibility Status
- Randomization documentation

Appendix B Intake CRF:

Obtains sufficient contact information in order to locate and track the participant during study participation.

Appendix C Demographics CRF:

Characterizes the participant's demographics and relevant medical and work history. This information may have a significant effect on functional and clinical outcomes.

- Personal Demography
- Military & Employment Demography
- Injury Demography
- Study-Specific Demography

Appendix D Baseline Data Collection CRF:

Collects relevant baseline research data.

- Medical History
- LEFS
- DVPRS with Supplemental Questions
- Current Military & Work Status
- Fitzpatrick Skin Phototype (a rating of susceptibility to skin damage from ultraviolet (UV) radiation)
- Percussion Test (with DVPRS basic)
- Hopping Test (with DVPRS basic)
- Diagnostic MRI Results

Appendix E Activity Log CRF:

Collects relevant research data to assess daily activity and return to activity from intervention start to 4-month follow-up to RTD.

Appendix F Weekly Follow-Up Data Collection CRF:

Collects relevant follow-up research data weekly from intervention start to 6-week follow-up or RTD.

- Intervention Adherence
- AE Assessment
- RTD Status
- DVPRS with Supplemental Questions

Appendix G Follow-Up Data Collection CRF:

Collects relevant follow-up research data.

- Supplement Assessment
- LEFS
- DVPRS with Supplemental Questions
- Current Military & Work Status (*4-Month Follow-Up only*)
- AIT Status (*4-Month Follow-Up only*)
- Percussion Test (with DVPRS basic)
- Hopping Test (with DVPRS basic)
- Diagnostic MRI Results (*6-Week & 4-Month Follow-Up only*)
- Intervention Adherence
- RTD Status
- AE Assessment

Appendix H Chart Review CRF:

Documents the completion and standardization of chart review procedures at study completion.

- PT/ Medical Care Resource Utilization
- AE Assessment
- RTD Status

- Lab Results

Appendix I Study Completion CRF:

Documents participant study completion status.

- Study Completion Status
- AE Assessment
- Protocol Deviation (PD) Assessment

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

☒ Yes ☐ No

10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA.PrivacyBoard@mail.mil for assistance. 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, I am an MHS workforce member
☐ No, I am not an MHS workforce member

Are you an MHS business associate?

- ☐ Yes, I am an MHS business associate
☒ No, I am not an MHS business associate

10.5 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

10.6 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)

10.7 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

10.8 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

10.9 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:

MHS Information System	Requesting Data
AHLTA	☐ Yes
CHCS	☐ Yes

PII-Only Systems:

MHS Information System	Requesting Data
No records have been added	

De-Identified Data & Other Systems:

Information System	Requesting Data
Other MHS System (May include PII and/or PHI) List other system here: Genesis	☐ Yes
Other MHS System (May include PII and/or PHI) List other system here: MODS	☐ Yes

10.10 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

10.11 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.
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.

Direct and Indirect Identifiable Data Elements	DHA Hard Copies	DHA Data Elements to be Accessed	DHA Data Elements Verbal	Extracted DHA Digital Data	Downloaded DHA Digital Data	Non-DHA Hard Copies or Digital
1. Names	☐	☒	☐	☐	☐	☐
2. Postal address with only town, city, state, and zip code	☐	☐	☐	☐	☐	☐
3. Postal address with all geographic subdivisions smaller than state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code	☐	☒	☐	☐	☐	☐

from all such geographic units containing 20,000 or fewer people is changed to 000						
4. Dates including all elements (except year) directly related to an individual, including birthdate, admission date, discharge date, and date of death	☐	☒	☐	☐	☐	☐
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	☐	☐	☐	☐	☐	☐
6. Telephone Numbers	☐	☒	☐	☐	☐	☐
7. Fax Numbers	☐	☐	☐	☐	☐	☐
8. Email Addresses	☐	☒	☐	☐	☐	☐
9. Social Security Numbers	☐	☐	☐	☐	☐	☐
10. Medical Record Numbers (MRN) (including record ID)	☐	☐	☐	☐	☐	☐

20. Any other unique identifying number, characteristic, or code (including non-military provider IDs)	☐	☒	☐	☐	☐	☐
21. Free Text Fields	☐	☐	☐	☐	☐	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used.

Due to guidelines stated within DoDI 1000.30, Reduction of SSN Use within DoD, the reduction or elimination of SSN usage must occur wherever possible. If SSNs are required to complete the project, the PI must provide a justification and explanation as to why a substitution cannot be used.

For example:

- If alternatives to SSN (e.g., EDIPNs or pseudo person IDs) are sufficient in other instances, will those alternatives to SSN usage be sufficient to respond to Congressional inquiries and /or Senior DoD stakeholders inquiries?
- Are alternatives to SSN used first?
- Are those alternatives to SSN insufficient to combine data from multiple data sources? Is the issue that some individuals do not possess alternatives ID numbers and SSN is the only way to identify them?

N/A

a. Will you receive or obtain health information?

Note: If you indicate you are not receiving health information, the answer must be consistent with the DHA data source. For a non-health information data request, if you are a non-MHS employee or non-MHS business associate, you may not access an information system that has PHI or LDS. For both MHS and Non-MHS employees and MHS business associates, you may **NOT** include data elements in the above table on: 1) lines 10 or 11, 2) line 21 if the free text field comes from a PHI or LDS system, and 3) lines 12, 13, or 18 if the account numbers, certificate and license numbers, biometric data, or any other data elements are health information created or received by an MHS health care provider, health plan, or business associate in relation to the physical or mental health or condition of an individual or payment for health care.

- ☒ Yes, I will receive or obtain health information
- ☐ No, I will not receive or obtain health information

b. If no data elements were checked in the above table, is it possible that the requested DHA data is or will be identifiable because of any unique data elements, triangulation, or small cell size?

☒ Data elements were checked in the above table, STOP HERE.

NOTE: A unique data element includes any unique features that alone are not identifiable but that could be used to identify an individual within the context of other information, such as any type of code (such as diagnosis or procedural), rank of general or admiral, gender, or race. Triangulation means using different data elements that when combined can be used to identify an individual, such as including the above lists of unique data elements in a data set. Determining whether an individual is identifiable through triangulation requires consideration of all data elements in combination. Within the military, the use of rank and/or diagnosis code, procedural codes, or any other code that changes on a predictable basis, increases the possibility

of identification. Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Department of Defense Manual 6025.13, Medical Quality Assurance and Clinical Quality Management in the Military Health System MHS, provides that the threshold for de-identifying data within the MHS requires a cell size of three, but also states that the de-identification standards must meet the DoD implementation of the HIPAA Privacy Rule. Centers for Medicare and Medicaid also gives guidance on small cell size stating that no data cell less than 11 may be published or displayed. However, the Office for Civil Rights' OCR, which is the official regulatory office for the HIPAA Privacy Rule, provides that OCR does not designate a universal value for small cell size in accordance with the de-identification standard; instead, the cell size should be set at a level that is appropriate to mitigate risk of identification by the anticipated recipient of the data set. This means that a cell size of 3 or 11 may not meet the HIPAA Privacy Rule requirements if the cell size level does not appropriately mitigate risk of identification by the anticipated recipient of the data set.

Note: If dates are altered as a means of de-identifying the data, diagnosis and procedural codes need to be rolled-up or collapsed. If dates are provided "as time between events," the roll-up is not necessary.

- ☐ Yes, the DHA data will become identifiable
- ☐ No, the DHA data will not become identifiable

10.12 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

10.13 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

If yes, please check which one.

- ☐ HIPAA Authorization
- ☐ HIPAA Waiver (Full or Partial)
- ☒ Other (please provide copies when uploading Other Study Documents)

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.)

Data Capture Methods:

The local study team will collect study data directly from the study participant (including in person, via mail or email, or over the phone), from their attending provider(s), clinical evaluations or, where applicable, from the participant's medical record (i.e., relevant medical and treatment history and relevant clinical notes) and record it on study CRFs. (See Appendices A-I).

The completed CRFs will serve as source documents for this study. Other source documents include relevant clinical notes, imaging, and/or test results which, if applicable, will be redacted and stored in the participant's research file.

Participants may also enter their coded data directly into REDCap using a personalized survey link (no log-in required). In these cases, the completed REDCap questionnaire(s) will be printed and added to the participant's research record as a source document.

Electronic Data Entry:

Following each research visit, a local study team member will review any completed paper CRFs for accuracy and completeness and then enter the collected non-personally identifiable data from the paper CRFs into REDCap. Please see Appendix Q for additional information on REDCap.

Coded diagnostic MRIs will also be uploaded to Teleray, more information is outlined below.

Data Storage & Access:

With the exception of the Informed Consent Form, HIPAA Authorization, Intake CRF, and electronic Master List, all research data (both paper and electronic) will be identified using a unique study ID only, and not by the participant's name, date of birth, DoD ID, or other protected identifier.

Paper research forms and source documents will be stored in a locked cabinet inside of a locked room.

Coded diagnostic MRIs will be uploaded to Teleray. Teleray ensures that all accounts stored in Microsoft Azure's self-healing network with advance security protocols enabled and is only located in the USA Secure Connection: The sessions established are secure (with secured tokens that are regenerated). Random AES keys are generated by clients at the beginning of the media connection and, to increase security, additional keys are generated periodically throughout the session. Teleray employs Transport Layer Security (TLS) to encrypt video data. The core protocols used are Secure Real-time Transport Protocol (SRTP) for media traffic encryption and Datagram Transport Layer Security (DTLS)-SRTP for key negotiation, both of which are defined by the Internet Engineering Task Force (IETF). The endpoints use Advanced Encryption Standard (AES) cipher with 256-bit keys to encrypt audio and video, and Hash-based Message Authentication Code- Secure Hash Algorithm 1 (HMAC-SHA1) to verify data integrity. No PHI/PII will be entered into TeleRay. Access to the coded data uploaded to Teleray will be controlled and managed by the local BAMC research team.

The coded electronic research data for this study will be stored in REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a DoD server and maintained by the USU IT. No PHI/PII will be entered into REDCap.

This coded electronic research data will be accessible by authorized staff from MIRROR which is based out of the Department of PM&R at USU and is serving as the data coordinating center for this research study. Access to the electronic coded research data will be governed strictly on an individual-by-individual basis within REDCap. Individual data access as well as privileges will be clearly delegated, audited, and monitored by MIRROR/USU. Staff from MIRROR/USU will not have access to the paper research records or any identifiable research data.

The local study team will maintain a separate electronic master list which matches unique study IDs with participant identifying information. The electronic master list will be stored separately from the coded electronic research data in a secure, password protected document on a computer and network that requires CAC access and will only be accessible by local research staff.

All research data and forms (both paper and electronic) will only be accessible by authorized study staff, authorized staff from MIRROR/USU (coded data entered into REDCap and Teleray

only, as described above), the IRB of record, the local research office (if applicable), and applicable governmental agencies as part of their duties and in accordance with federal law. These duties include making sure that research participants are protected.

Informed Consent Forms and HIPAA Authorizations will be maintained for a period of 6 years following study closure and then securely shredded. Paper research forms will be maintained for a period of 5 years following study closure and then securely shredded. The master list and screening log will be destroyed at study closure. The electronic coded research data will be maintained indefinitely as described below in protocol section 10.15.

Is this a data repository?

☐ Yes ☒ No

If Yes, provide name of the Repository.

N/A

Who will have access to the Repository?

N/A

What data type will be stored in the Repository?

- ☐ PHI
☐ LDS
☐ De-identified Data

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 recontacted 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.

Consent for Future Use:

The Informed Consent Form for this research study states that de-identified research data will be shared with MIRROR/USU and maintained indefinitely for possible use in future research. By consenting to participate in this research study, participants agree to allow us to maintain their de-identified research data indefinitely for possible use in future research.

Participants will not be given the option to opt out of us retaining their de-identified research data indefinitely for possible future use. The consent form states, "If you do not want your deidentified data collected as part of this research study to be kept for use in future research studies, you should not sign this consent form."

Long Term Data Storage & Access:

The de-identified electronic dataset will be maintained by MIRROR/USU and the study team indefinitely or as long as it is practicable to maintain.

The de-identified data uploaded to Teleray will be maintained by the local research team indefinitely, or as long as it is practical to maintain, and while funding is allotted for this service.

De-identified electronic research data will be securely transmitted from local study teams to the MIRROR /USU via REDCap, Teleray, or the DoD SAFE application (or other comparable safe data sharing system implemented by the local site and/or the US Army/DHA). REDCap utilizes Secure Sockets Layer (SSL) in addition to other safeguards on its web server to maintain secure communication with end-users (see Appendices Q-R). DoD SAFE uses a TLS protocol when files are uploaded and downloaded. Teleray employs TLS to encrypt video data. The core protocols used are SRTP for media traffic encryption and DTLS-SRTP for key negotiation, both of which are

defined by the IETF. The endpoints use AES cipher with 256-bit keys to encrypt audio and video, and HMAC-SHA1 to verify data integrity.

Once received, the electronic de-identified research data will be stored within an encrypted, access controlled, password protected electronic data capture and management system housed on a DoD-compliant server.

Access to the de-identified research data will be governed strictly on an individual-by-individual basis within the secure electronic data capture and management system. Individual data access as well as privileges will be clearly delegated, audited, and monitored by MIRROR/USU. Any future research using retained data will require a research protocol to be approved by an Institutional Review Board or other authorized official responsible for protecting human subjects of research.

Any future research using retained data will require a research protocol to be approved by an Institutional Review Board or other authorized official responsible for protecting human subjects of research.

Data Withdrawal from Storage:

Participants may request to have their data withdrawn at any time before their personal identifiers have been removed. Once their data has been de-identified, it will be impossible for the researchers to locate their specific study data.

Is this a data repository?

☒ Yes ☐ No

If Yes, provide the name of the Repository

(1) USU OCIO REDCap (2) Teleray

Who will have access to the Repository?

(1) USU OCIO REDCap: study investigators, study team members, and MIRROR core team members, as appropriate. Access to the de-identified research data will be governed strictly on an individual-by-individual basis with the secure electronic data capture and management system. Individual data access as well as privileges will be clearly delegated, audited, and monitored by MIRROR/USU.

(2) Teleray: study investigators, study team members, and MIRROR core team members, as appropriate. Access to the de-identified research data will be maintained/delegated by the local research team on an individual-by-individual basis.

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

Descriptive statistics will report location and scale in terms of mean and standard deviation for normally distributed variables, median and interquartile intervals for ordinal metric variables, and in terms of proportion and size for categorical variables. Descriptive statistics will be reported for baseline demographic and clinical characteristics at an overall level and by initial treatment group.

Outliers will be removed if determined to be erroneous based on relevant clinical expertise. Confounding will be principally controlled by randomization. In regards to the treatment of missing data within our proposed analyses: all patients in the study with partial or complete data will be included in hierarchical/mixed-level modeling; patients without both the baseline and final follow-up data point will be excluded from sensitivity analyses; patients removed from the study prior to the four-month follow-up will be excluded from survival analysis.

Methods to be used for the Primary Aim (Aim 1): Survival analysis will be used to evaluate return to duty between treatment arms with censoring beyond 4 months.

Methods to be used for the Secondary Aims (Aim 2): Longitudinal hierarchical/multilevel models with random effects will be used to evaluate differences between treatment arms across all collected time points for the relevant outcome measure (e.g., MRI, functional and pain scores, and self-reported measures). Sensitivity analyses will be conducted predicting change in measures at the final follow-up (4 months) relative to baseline, and will use linear generalized additive models.

Hypothesis tests will be two-tailed and statistical significance will be considered at the putative threshold ($\alpha=0.05$). Any secondary P-values will be subject to a false discovery rate adjustment in keeping with best statistical practices. Multilevel models will incorporate random effects to account for repeated measures, using distribution families and link functions appropriate for the outcomes of interest, determined using QQ plots analyzed for best model fit. All statistical analyses will be performed using the R Programming language.

11.2 Sample Size:

After adjusting for screen failures and attrition, we are requesting to enroll up to 122 (61 per arm) participants across one performance site in order to evaluate a final sample of 82 (41 per arm).

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

122

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

Up to 122 participants will be randomized across the PBMT and sham PBMT treatment arms (61 participants per arm).

11.5 Please provide a justification for your sample size

41 patients in each treatment group (82 patients total) will achieve 90% power to detect an effect size of 13. 36 patients in each treatment group (72 patients total) will achieve 90% power to detect an effect size of 14. Effect size is defined as the average improvement in days to return to duty within the PBMT treatment group relative to the sham treatment group, with statistical significance defined as $\alpha = 0.05$. We are requesting to enroll up to 122 total patients (approximately 61 per treatment arm), for a final sample of 82 (41 per treatment arm) after accounting for attrition and screen failures. Power was calculated using repeated Monte Carlo Markov Chain simulations predicting days to return to duty between treatment and control groups, and sourced assumptions of mean and spread from Miller et al, 2018.

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

Descriptive statistics will report location and scale in terms of mean and standard deviation for normally distributed variables, median and interquartile intervals for ordinal metric variables, and in terms of proportion and size for categorical variables. Descriptive statistics will be reported for baseline demographic and clinical characteristics at an overall level and by initial treatment group.

Survival analyses will be used for time-to-event analyses. Hierarchical/multilevel models with random effects will be used to evaluate non-time-to-event measures over time points collected.

Sensitivity analyses within secondary aims will predict change in measures collected at the final follow-up relative to baseline, and will use linear generalized additive models.

Hypothesis tests will be two-tailed and statistical significance will be considered at the putative threshold ($\alpha=0.05$). Any secondary P-values will be subject to a false discovery rate adjustment in keeping with best statistical practices. Multilevel models will incorporate random effects to account for repeated measures, using distribution families and link functions appropriate for the outcomes of interest, determined using QQ plots analyzed for best model fit. All statistical analyses will be performed using the R Programming language.

12.0

Participant Information

12.1 Subject Population:

DEERS-eligible adults (between the ages of 17-64, inclusive), active-duty service members within Fort Sam Houston AIT training units, diagnosed with tibial or metatarsal BSIs

12.2 Age Range:

Check all the boxes that apply. If the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- ☒ 0-17
- ☒ 18-24
- ☒ 25-34
- ☒ 35-44
- ☒ 45-54
- ☒ 55-64
- ☐ 65-74
- ☐ 75+

17-64 (inclusive)

12.3 Gender:

- ☒ Male
- ☒ Female
- ☐ Other

12.4 Special categories, check all that apply

- ☐ Minors /Children
- ☐ Students
- ☐ Employees - Civilian
- ☐ Employees - Contractor
- ☒ Resident/trainee
- ☐ Cadets /Midshipmen
- ☒ Active Duty Military Personnel
- ☐ Wounded Warriors
- ☐ Economically Disadvantaged Persons
- ☐ Educationally Disadvantaged Persons
- ☐ Physically Challenged (Physical challenges include visual and/or auditory impairment)

- ☐ Persons with Impaired Decisional Capacity
- ☐ Prisoners
- ☐ Pregnant Women, Fetuses, and Neonates
- ☐ Non-English Speakers
- ☐ International Research Involving Foreign Nationals - Headquarters Review is necessary

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

12.5 Inclusion Criteria:

Order Number	Criteria
1	DEERE Eligible
2	Between ages of 17-64 (inclusive) years old
3	Currently an ADSM in any of the US Armed Forces
4	Currently completing AIT training at Fort Sam Houston and at least 6 weeks prior to graduation
5	Clinical diagnosis of metatarsal or medial tibial bone stress injury/stress fracture (including both unilateral and bilateral) by a healthcare provider based on accepted diagnostic criteria and diagnostic imaging confirmation (may be evaluated during formal screening procedures)
6	Able to read and understand English language for consent purposes
7	Able to commit to study intervention and follow-up during time at AIT training

12.6 Exclusion Criteria:

Order Number	Criteria
1	Anterior tibial bone stress injury/ fracture
2	5th metatarsal stress injury/ fracture
3	Non-union bone stress injury/fracture
4	Received dry needling within the past 4 weeks
5	Received Platelet Rich Plasma (PRP) injection, corticosteroid injection, or prolotherapy within the past 3 months
6	Diagnosis of neuropathy affecting sensation to pain
7	Current or chronic sciatica (lumbosacral radiculopathy) resulting in chronic or intermittent lower extremity pain, numbness, or tingling (all below the knee)
8	Current or previous diagnosis of eating disorder (e.g., bulimia nervosa, anorexia nervosa, disordered eating, or other eating disorder not specified)
9	Diagnosis of porphyria (light induced allergy) or photosensitive eczema

10	Diagnosis of autoimmune disease (e.g., Lupus)
11	Albinism
12	Current use of anti-inflammatory steroids due to increased risk of BSI with the past two weeks
13	Current use of medications associated with sensitivity to heat or light in the past five days (e.g., amiodarone, chlorpromazine, doxycycline, hydrochlorothiazide, nalidixic acid, naproxen, piroxicam, tetracycline, thioridazine, voriconazole)
14	Previous or current (within the past 2 years) use of Depo Provera
15	Current use of pacemaker
16	Tattoo in the area of treatment due to sensitivity to PBMT
17	Concurrent participation in another research study receiving treatment for metatarsal or medial tibial bone stress injury/stress fracture
18	Currently pregnant or plan to become pregnant during intervention period (safety of PBM not established in pregnancy)
19	Current diagnosis or symptoms of amenorrhea (≥ 6 months without a menstrual period) or oligomenorrhea (only 4-9 menstrual periods in a year)

13.0

Recruitment and Consent

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

Please see Study Procedures Section 10.1

Potential participants will be identified via four methods:

1. Under an approved Partial HIPAA Waiver, local study team members will review medical records of patients coming to the SIT Clinic, where AIT students present for medical needs. Authorized study team members will pre-screen for individuals seeking care for suspected BSIs to identify prospective research participants for the purposes of seeking their authorization to participate/use their protected health information for this research study.
2. Patients may self-refer to participate in the study. Interested potential participants will be able to contact a member of the study team via phone or email. Potential participants who contact the study team directly will be instructed to access the SIT Clinic or their applicable health care provider (e.g., primary care provider or physical therapist) for a physical exam and BSI diagnosis, or confirmation of BSI diagnosis.
3. Direct referral from local healthcare providers in the SIT Clinic, and other applicable departments/ clinics at BAMC such as Primary Care (including Army Patient Centered Medical Home, Family Medicine, Internal Medicine Clinic), and Pain Management.
4. Mass briefs of incoming classes for AIT. Every effort will be made to ensure there is not undue coercion, such as ensuring that there is not the presence of instructors or Command. Briefs will not be performed by any study team member in a military uniform.

An appropriate Partial HIPAA Waiver Application has been uploaded with this submission.

The local research team will keep a separate electronic screening log containing DoD ID number, ineligible/eligible, and date screened. This log will be password protected and stored in a secure folder on a secure drive accessible only by authorized local research staff. This log is needed to

avoid any duplicative screening of those that are screen failures. This reduces burden on potential participants, providers, and study team and ensures the study team will not screen the same person twice or examine records for eligibility criteria when screen status is already established.

With increased awareness and acknowledgement of the vulnerability of the AIT trainee population, recruitment and consent conversations will be provided by non-uniformed personnel /study team members, without the presence of AIT instructors, in order to prevent undue coercion. Initial recruitment discussions will stress the voluntary nature of study participation. No uniformed study personnel will interact with the study recruits during the recruitment and/or consent process.

13.2 Compensation for Participation:

Participants will be compensated with a \$50 gift card for completing the log (at 4-months or RTD, whichever occurs first). Gift cards will be stored on-site and distributed by local research staff.

In accordance with the DHA-AI 3200.01 indicates active-duty service members may receive compensation for the completion of a daily health diary when completed off-duty. In accordance with DHA-AI 3200.01 the following definitions of on-duty and off-duty will apply to active duty-service member study participants:

- An individual is on-duty when they are expected or required to perform the duties of their assigned job or position.
- An individual is off-duty if the individual is not scheduled to perform any work that may arise during the period.

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

This study has two screening phases: 1) Pre-screening based on initial inclusion/exclusion criteria (before informed consent) and 2) a formal screening phase to determine eligibility for randomization to intervention arm (after informed consent).

Pre-Screening (before consent):

If a potential participant expresses interest in learning more about the research study, a member of the research staff will briefly introduce the study, express the voluntary nature of participation, assess interest in participating, and screen the potential participant for eligibility.

Eligibility will be determined using the Inclusion/Exclusion CRF (Appendix A).

Individuals who do not meet Inclusion/Exclusion criteria will be encouraged to continue to seek care with their primary care provider and/or direct access at SIT.

If the potential participant meets eligibility criteria as determined by the Inclusion/Exclusion CRF and expresses interest in participating, an authorized study team member will initiate the formal consent discussion and, if applicable, obtain informed consent. See protocol section 13.4 for additional information on the consent process.

Pre-screening conversations may also take place over the phone using the Screening Script (Appendix L). Potential participants who meet initial eligibility per the Screening Script and express interest in participating will be asked to come to clinic to complete an Inclusion/Exclusion CRF to confirm final eligibility with an authorized study team member prior to providing informed consent.

Formal Screening (post-consent):

As part of the formal screening procedures, all consented participants will complete diagnostic imaging, if applicable, to confirm diagnosis of metatarsal or medial tibial bone stress injury /stress fracture (including both unilateral and bilateral). If diagnostic imaging was completed within one month of study enrollment, those images may be used to confirm study 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.

Are you requesting a waiver or alteration of informed consent?

☐ Yes ☒ No

Please explain the consent process:

Consent will be obtained in accordance with principles of Belmont Report and Common Rule guidelines.

The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the signed consent form will be given to the participant and the original will be stored in a locked cabinet inside of a locked office. No Legally Authorized Representatives will be utilized.

Formal consent, as represented by the act of signing a dated, IRB approved consent statement for the study will only occur after confirming eligibility using the Inclusion/Exclusion CRF, a thorough review of what is involved in the study, and after all questions have been answered.

Potential participants will be provided information regarding all available study treatments and reminded of the expectations placed on them if they enroll, including the blinding and randomization processes.

The potential participant will be given a copy of the informed consent document to read before, during, and/or after discussion of the informed consent with the Research Coordinator (RC), Principal Investigator (PI), Associate Investigator (AI), or other authorized study team member. Sufficient time will be given to the potential participant to understand the study purpose, study procedures, time commitments, potential risks and benefits, and the types of health information that will be accessed, collected, and used by the research team if they agree to participate in the study.

Questions can be raised by the potential participant at any time during the consent discussion and at any time during the conduct of the study. The potential participant will be instructed that their participation is completely voluntary and that they may withdraw from the study at any time without penalty. Their decision to participate or to not participate, or to withdraw from the study after consent, will not affect their access to health care that they are otherwise entitled to and it will not affect their military position.

The authorized study team member present during the consent conversation will confirm that the potential participant has no additional questions before deciding to provide consent.

Every effort will be made to eliminate the perception of authority, which is a particularly important consideration when recruiting active-duty study participants. When applicable, the study investigators will be in scrubs or civilian clothes instead of uniform and will introduce themselves as doctor rather than their military rank. Some potential participants may be patients of the study PI or AI. In these cases, the consent conversation will be initiated by non-clinician study staff to prevent any misconception of coercion or undue influence.

Informed consent and HIPAA authorization will be obtained in person.

In the event that there are significant new findings regarding the therapy that may affect participants' willingness to continue in the study, an information sheet will be provided to all current and past participants. The informed consent document will be amended for future participants.

Following completion of informed consent, the results of the Inclusion/Exclusion CRF will be entered into REDCap, and a unique study ID will be generated. This coded study ID will be used on all research data collection forms in place of the participant's name, DoD ID, or other protected identifier. Study IDs will be different from Screening IDs. No PII will be entered into REDCap.

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
☐ Propose ombudsman

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

Participant Withdrawal:

Participants may withdraw from the study at any time without penalty. Participants will be informed that withdrawal will not affect their access to health care that they are otherwise entitled to and it will not affect their military position.

If a participant withdraws from the study, we may retain and analyze all coded/de-identified data collected up to the time of withdrawal if the data is necessary to maintain the integrity of the study. Participants may contact the study research coordinator/assistant or Principal Investigator in writing to formally withdraw from the study. At the time of study withdrawal, researchers will seek to obtain written confirmation from the participant to clarify if researchers may continue to collect health information for study purposes. If the participant withdraws from the study, but does not revoke their HIPAA Authorization, no further data will be collected directly from the participant; however, the study team may continue to obtain relevant information from the participant's health care record at the four-month follow-up time point to capture health care utilization and profile status. If a participant chooses not to allow researchers to continue to collect their health information after their study withdrawal, then no further data will be collected for the participant.

Participants will be advised to follow-up with their personal physician if they choose to withdraw.

Withdrawal Without Participant Consent:

A participant may be withdrawn from the study without their consent if remaining in the study might be dangerous or harmful to them. Participation may also be stopped if the military mission requires it, if they lose their right to receive medical care at a military hospital, if the study is canceled, or if they display inappropriate behavior towards study personnel.

14.0 Risks and Benefits

14.1 Risks 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 potential risks directly associated with study-specific activities and procedures are minimal.

Diagnostic Imaging:

The risks of the MRI in this study are no different than those for any other clinical MRI scan. MRI scanners tend to be small, and some participants may experience anxiousness from being in the confined space. Additionally, MRI scanners produce loud noises and heat than can cause harm if adequate protection isn't used. Persons with certain medical implants should not undergo an MRI or may require special conditions.

Physical Therapy:

Possible risks associated with physical therapy treatment include: worsening of pre-existing conditions, continued and/or increased pain that may limit activities, no improvement in mobility or strength, soreness, or failing during and/or injury from physical therapy exercises and/or performance-based tests. However, these are risks related to physical therapy, which the individual would likely be getting even if not enrolled in the study, and not risks associated with study participation.

Photobiomodulation Therapy:

The risks associated with PBMT are minimal. PBM treatment is used by a variety of healthcare practitioners for painful clinical conditions. Mild discomfort may be experienced during the treatment, the treatment should not be "hot", but participants should notify the study team member if they feel any uncomfortable warming. Individuals with neuropathies or difficulty distinguishing changes in skin temperature are at higher risk. Potential research-related risks include damage to eye structures, headaches post-procedure, uncomfortable skin heating or erythema/redness, which are both very rare.

Data Collection:

Additionally, any time information is collected for a study, there is a small risk of breach of confidentiality.

14.2**Measures to Minimize Risks 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

All available measures to minimize risks will be taken in accordance with standard clinic protocols. The risks associated with diagnostic imaging will be mitigated by using trained professionals that follow industry standards for minimizing these risks.

Protective eyewear will be worn by all participants and study team members during PBMT and sham PBMT treatment sessions to avoid potential eye damage.

Along with the Laser Safety Officer (LSO), the PI will ensure that the treatment space meets all regulatory requirements for utilization of a treatment laser, including appropriate signage and use of laser blocking screens to absorb any potential scatter/refraction of light outside of the treatment area.

In the rare occurrence that participants experience uncomfortable warmth over the treatment area during PBMT, the treatment will be modified or stopped.

In order to protect participant confidentiality, research data will be identified using a unique study ID only, and not by participant name, date of birth, DoD ID, or other similar identifier. All available measures allowed by law will be taken by research staff to protect participant confidentiality. Secure data storage and management procedures have been put in place to minimize risk and all research team members with authorized access will be trained in these procedures. See protocol section 14.3 for additional information

All participants will be evaluated for adverse events at each follow-up visit. All adverse events, regardless of severity, will be reported to the Principal Investigator. Adverse events will also be reported according to the guidelines stated in Protocol Section 16.

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

Upon consenting for the study, participants will be assigned a unique study ID. With the exception of the Informed Consent Form, HIPAA Authorization, Intake CRF, and electronic Master List, all research data (both paper and electronic) will be identified using this unique study ID only, and not by the participant's name, date of birth, DoD ID, or other protected identifier.

Paper research forms and source documents will be stored in a locked cabinet inside of a locked room, accessible only by local research staff designated and authorized by the Principal Investigator. The paper Intake CRF which records participant contact information, Informed Consent Forms and HIPAA Authorizations will be stored separately from the coded paper research forms in a locked cabinet inside of a locked room, accessible only by authorized local research staff.

The coded electronic research data for this study will be stored in REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a DoD server and maintained by the USU IT. The local study team will manage the storage and upload of ultrasound in Teleray, which is an encrypted and access controlled data platform. No PHI/PII will be entered into REDCap or Teleray. See Appendix R for additional information on REDCap.

The local study team will maintain a separate electronic Master List which matches the unique study IDs with participant identifying information. The electronic Master List will be stored separately from the coded electronic research data in a secure, password-protected electronic document on a computer and network that requires CAC access.

All research data and forms (both paper and electronic) will only be accessible by authorized study staff, the IRB of record, the local research office, and applicable governmental agencies as part of their duties and in accordance with federal law (except as stated in the next paragraph). These duties include making sure that research participants are protected.

MIRROR, which is based out of the Department of PM&R at the Uniformed Services University (USU), is serving as the data coordinating center for this research study. As such, authorized staff from MIRROR/USU will have access to the coded research data that is entered into REDCap. Authorized staff from MIRROR/USU will not have access to the electronic Master List, the paper research records, or any participant PHI/PII.

Any research data shared with an approved agency for review will be linked only to the participant's unique study ID and not with the personal identity of the participant (i.e., name, DOB, DoD ID, address, phone number, etc.). If the research data is used in scholarly presentations or journal articles, the investigators will protect the anonymity of individual participants and report only aggregate data (e.g., group means) where appropriate.

Participants will not be individually identified in any publication or presentation of research results.

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

We cannot guarantee that participants will benefit from participation in this research study, but information gained may help providers better manage treatment of BSIs in future patients. The aim of this study is to improve recovery of BSIs. It is expected that all treatment arms will help stress fracture recovery, but the addition of PBMT could help speed up the recovery process.

BSIs are the strongest predictor of drop out in military training and are estimated to effect one in ten Service Members, reducing their ability to perform necessary military duties. In military and athletic populations, most BSIs (70-90%) are in the lower extremity, with tibial and metatarsal fractures accounting for roughly half of all BSIs. With traditional PT, stress fracture symptomatology can last for months, outcomes are varied, and reoccurrence happens in up to a third of those treated; some Service Members never return to duty. This may also provide better /faster treatment pathway(s) for BSIs in the AD, larger physically active populations, and other training environments (e.g., police academies and intelligence agencies). A more effective treatment pathway can help keep more ADSMs in the fight, ultimately contributing to overall military readiness.

14.5

Privacy for Subjects:

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

When possible, recruitment, consent conversations, and follow-up research activities will take place in a private setting (e.g., closed clinic room, investigator's office, etc.) to minimize the potential opportunity to be overheard or inadvertently witnessed. Information being collected will be limited to only the minimum amount of data necessary to accomplish the proposed research.

No uniformed service members, supervisors, or instructors will be present during recruitment and consent discussions.

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

There is the possibility incidental findings could reveal information the participant would not otherwise be aware of. In cases where the participant could possibly benefit medically or otherwise, the participant will be notified and, when appropriate, so will their primary care provider. Research representatives will not share incidental and unexpected findings with anyone else unless required by law.

In cases involving military personnel, information regarding their health may be required to be reported to appropriate medical or command authorities to ensure the proper execution of the military mission, including evaluation of fitness for duty.

Although unlikely, incidental findings could impact a participant's future ability to receive health or life insurance, as is the case with all medical care. Incidental findings may also make the participant feel anxious.

15.0

Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

☒ DSMP

☐ DSMB

- ☐ Both
- ☐ Not Applicable

A DSMP should describe the plan to monitor the data to verify that the data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored, and the frequency of monitoring. It should also include the plan to ensure the safety of subjects

Participant Safety Monitoring Plan:

To ensure the safety of participants the PI will:

1. Monitor the conduct of the protocol per the approved study plan and ensure protection of human participants. This may involve periodic review of medical records and/or research files of enrolled participants.
2. Review and keep abreast of adverse events and protocol deviations that occur during the research.
3. The PI will review and sign adverse event logs/reports, protocol deviation (PD) logs /reports, and continuing reviews (CR)/annual progress reports.
4. If there is concern about the welfare of enrolled participants, the PI will stop the research study in progress, remove individual participants from a study, and take whatever steps necessary to protect the safety and well-being of research participants until the IRB can assess the situation.
5. Ensure that all study team members keep current required human subjects research trainings which require renewal every 3 years.

If an adverse event or protocol deviation occurs, it will be evaluated by the Principal Investigator and appropriate actions will be taken as outlined in Section 16.0 Reportable Events. In the case of an emergency, first responders will be called. In order to address the challenge of early identification of an increased risk of a known adverse event, all adverse event data will be tracked and evaluated.

On-site physicians will monitor the progress and health of the participants alongside our Principal Investigator. Participants can elect to withdraw from the study at any time. Participants may also be taken out of the study at any point if a research provider (or one of their treating providers) determines that it is no longer safe for them to continue with the study. If a participant elects to drop out of the study or is withdrawn for safety reasons, they will resume standard of care treatment with their assigned health provider(s).

Data Monitoring Plan:

Data will be collected and stored in both paper CRF and electronic format as described previously in protocol section 10.14 Data Management. In addition to data quality and data validation checks done continually by REDCap for electronic format data, authorized MIRROR staff will perform routine checks of the coded electronic data entered into REDCap and Teleray to ensure that data has been properly input and that data entry is consistent with expected values. The local PI will ensure that paper research forms and the electronic Master List are completed and securely stored in accordance with stated protocol procedures.

Please see protocol Section 14.3 Confidentiality Protections and 14.5 Privacy for Subjects for additional information regarding how we will protect participant privacy and confidentiality throughout this study.

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.**

Consult with the research office at your institution to ensure requirements are met

- Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)
- 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 research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

AEs/SAEs/UPIRTSOs:

The study overall is considered to be minimal risk for study participants, defined as not substantially above what would be encountered in everyday life including provision of routine medical care for the condition of BSIs. Potential risks are preventable by ensuring that appropriate and rigorous screening procedures are in place, and risk mitigation procedures (e.g., wearing appropriate eye protection) are utilized. Based on clinical use of this technology, and reports from other research studies, the risk of expected adverse events is low.

However, all reportable events, regardless of severity, will be reported to the Principal Investigator. The Principal Investigator will review all adverse events.

All Serious Adverse Events (SAEs) that are unexpected and related, or possibly related, to study participation will be reported to the IRB via telephone or email within 24 hours of discovery and a complete written report via EIRB will follow within 5 business days.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs) will be reported to the IRB via telephone or email within 24 hours of discovery and a complete written report via EIRB will follow within 5 business days.

Unexpected (but not serious) adverse events (AEs) occurring in subjects which, in the opinion of the PI, are related or possibly related to study participation AND places subjects or others at a greater risk of harm than was previously known or recognized in the protocol will be reported to the IRB via telephone or email within 24 hours of discovery and a complete written report via EIRB will follow within 5 business days.

Expected AEs/SAEs and AEs/SAEs that are not related or not possibly related to study participation will be tracked by the local study team using an Adverse Event Tracking Log and reported to the IRB at the time of continuing review or, if applicable, at study closure.

Continuing Review (CR) Progress Reports are generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

Protocol Deviations:

All protocol deviations, both major and minor, will be reported to the Principal Investigator. The Principal Investigator will review all protocol deviations.

Major protocol deviations, as determined by the Principal Investigator, will be promptly reported to the IRB via telephone or email within 24 hours of discovery and a complete written report will follow within 5 working days.

Minor protocol deviations will be tracked by the local study team using a Protocol Deviation Log and reported to the IRB at the time of continuing review or, if applicable, at study closure. Follow up visits that occur outside of the windows stated in protocol will be considered minor protocol deviations.

17.0

Equipment/non-FDA Regulated Devices

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

☐ Yes ☒ No

18.0

FDA-Regulated Products

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

- ☐ Drugs
- ☐ Dietary Supplements
- ☐ Biologics
- ☒ Devices
- ☐ N/A

18.3 Device Details:

- ☒ Are device(s) in this research being used in accordance to the approved labeling?
- ☐ Are device(s) in this research being used in a manner other than its approved labeling?

When adding a device indicate in the details section of the device if the use is either used in accordance to the approved labeling or in a manner other than it's approved labeling

View Details	Device Name
	Omnilux Plus 830 nm
Manufacturer/Supplier of Device	Omnilus
Where will the Devices Be Stored	In the research area, Soldiers in Training Clinic
Will Devices be supplied at no Cost	No
Is this a HUD (HDE)	No
HDE Number	N/A
Who holds the IDE	N/A
IDE details	N/A

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

The PI will be responsible for reporting any unanticipated adverse effects and unanticipated problems to the FDA.

18.5 Sponsor (organization/institution/company):

- ☒ N/A

If applicable, provide sponsor contact information:

19.0

Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- ☐ Registration is not required
- ☒ Registration pending
- ☐ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- ☒ Registration is not required
- ☐ Registration pending
- ☐ Registration complete

20.0

References and Glossary

20.1 References:

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20.2 Abbreviations and Acronyms:

Active-Duty (AD)
Active-Duty Service Members (ADSMs)
Advanced Encryption Standard (AES)
Advanced Individual Training (AIT)
Adverse Event (AE)
Armed Forces Health Longitudinal Technology Application (AHLTA)
Associate Investigator (AI)
Basic Combat Training (BCT)
Bone Stress Injury (BSI)
Brooke Army Medical Center (BAMC)

Case Report Form (CRF)
Centimeter (cm)
Common Access Card (CAC)
Composite Health Care System (CHCS)
Continuing Review (CR)
Datagram Transport Layer Security (DTLS)
Date of Birth (DOB)
Defense and Veterans Pain Rating Scale (DVPRS)
Defense Enrollment Eligibility Reporting System (DEERS)
Defense Health Agency (DHA)
Defense Health Agency Administrative Instruction (DHA-AI)
Department of Defense (DoD)
Electronic Medical Record (EMR)
Federalwide Assurance (FWA)
Food and Drug Administration (FDA)
Hash-based Message Authentication Code- Secure Hash Algorithm 1 (HMAC-SHA1)
Health Insurance Portability and Accountability Act (HIPAA)
Human Research Protection Office (HPRO)
Institutional Agreement for Institutional Review Board Review (IAIR)
Institutional Review Board (IRB)
Intention-to-Treat (ITT)
Internet Engineering Task Force (IETF)
Investigational Device Exemption (IDE)
Joint Program Committee (JPC)
Joules (J)
Laser Safety Officer (LSO)
Lower Extremity Functional Scale (LEFS)
Magnetic Resonance Imaging (MRI)
Medical Operational Data System (MODS)
Megahertz (MHz)
Military Health System (MHS)
Musculoskeletal Injury (MSI)
Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR)
Nanometer (nm)
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Patient Reported Outcome Measures (PROM)
Personally Identifiable Information (PII)
Photobiomodulation (PBM)
Photobiomodulation Therapy/Treatment (PBMT)
Physical Medicine & Rehabilitation (PM&R)
Physical Therapy (PT)
Platelet Rich Plasma (PRP)
Principal Investigator (PI)
Probability (P)
Protected Health Information (PHI)
Protocol Deviation (PD)
Quantile-Quantile (QQ)
Research Coordinator (RC)
Research Electronic Data Capture (REDCap)
Return to Duty (RTD)
Secure Access File Exchange (SAFE)
Secure Real-time Transport Protocol (SRTP)
Secure Sockets Layer (SSL)
Serious Adverse Event (SAE)
Soldiers in Training (SIT)
Standard of Care (SOC)
Transport Layer Security (TLS)
Ultraviolet (UV)
Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO)
Uniformed Services University (USU)
Uniformed Services University Information Technology (USU IT)
Uniformed Services University of the Health Sciences (USUHS)
United States Army Medical Research and Development Command (USAMRDC)