COVER PAGE

COMPARISON OF NON-SURGICAL TREATMENT OPTIONS FOR CHRONIC EXERTIONAL COMPARTMENT SYNDROME (CECS)

NCT: 04409600

STUDY PROTOCOL v1.13

IRB APPROVED: 13 MAY 2024

UPLOADED TO CLINICALTRIALS.GOV DATE: 06 DEC 2025

EIRB Protocol Template (Version 1.13)

1.0 General Information

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

Comparison of Non-Surgical Treatment Options for Chronic Exertional Compartment Syndrome (CECS)

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

MIRROR Project 5 - Comparison of Non-Surgical Treatment Options for CECS
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

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

Yes

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add sites

2.1 List sites associated with this study:

Is Primary?	Site Name
◆	**P and R** - Walter Reed National Military Medical Center (WRNMMC)

3.0 ■ Assign project personnel access to the project

3.1 * Please add a Principal Investigator for the study:

Name	Role	Training Record
Leggit, Jeffrey Charles 2959460, Maryland	**Principal Investigator**	**View Training Record**

Responsibility

☐ Student
☐ Resident
☐ Site Chair
☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Name	Role	Training Record
Velasco, Teonette O	Associate Investigator	View Training Record

B) Research Support Staff

Name	Role	Training Record
Lucio, Whitley B	Research Coordinator	View Training Record
Ory, Rian Lyndzie, MS	Research Coordinator	View Training Record
Seales, Paul Evan, BS, MS, MD LCDR	Monitor	View Training Record

3.3 *Please add a Protocol Contact:

Name	Role	Training Record
Leggit, Jeffrey Charles 2959460, Maryland	Study Contact	View Training Record
Lucio, Whitley B	Study Contact	View Training Record
Ory, Rian Lyndzie, MS	Study Contact	View Training Record
Velasco, Teonette O	Study Contact	View Training Record

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):

Name	Role	Training Record
Helgeson, Melvin Dennis	Department Chair	View Training Record

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

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

5.0 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 results found

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.) Velasco, Teonette O Role on Protocol: Associate Investigator	Phone Number: 703-634-9457	Email Address: teonette.velasco.ctr@usuhs.edu	Associated Institution: The Geneva Foundation / WRNMMC
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
Name: (Last, First, M.I.) Lucio, Whitley B Role on Protocol: MIRROR Sr. Regulatory Affairs & Data Manager	Phone Number: 202-375-8831	Email Address: whitley.lucio.ctr@usuhs.edu	Associated Institution: The Geneva Foundation / USUHS

5.4 Will you have a Research Monitor for this study?

(•) Yes
( ) No
( ) N/A

Research Monitor Qualifications
Ensure the individual has expertise consistent with the nature of risk(s) identified within your study and is independent of the team conducting the research.

Research Monitor Role:

The Research Monitor is responsible for providing medical guidance and overseeing participant safety. They will review and keep abreast of Adverse Events and UPIRTSOs and determine their relatedness to the protocol. The Research Monitor will make recommendations

on changes to the informed consent process and study procedures based on review of study events. They have the authority to stop the research study if they have concerns for the safety and/or well-being of the research participants. The Research Monitor may withdraw individual study participants and take any other actions necessary to protect the rights and safety of the human subjects. The Research Monitor may discuss the protocol with study investigators, interview human subjects, and consult with others outside the protocol about the research. The Research Monitor will co-sign all new reportable events and continuing review reports. The Research Monitor will promptly report any observation or findings to the Institutional Review Board (IRB), Human Protections Administrator (HPA), or Institutional Official.

If applicable, you may nominate an individual to serve as the Research Monitor:

Selected Users
Paul Evan Seales, BS, MS, MD LCDR

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 USU Award Number: HU00011920011	: Research Development Testing and Evaluation (RDT&E) funds Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR)	836683

Total amount of funding:

836683

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:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
P&R	Uniformed Services University	Coordinating center	FWA00001628	05/04/2026	: IAIR	: WRNMMC IRB
Army	Alexander T. Augusta Military Medical Center (ATAMMC)	Performance site	FWA00017754	11/20/2028	: IAIR	: WRNMMC IRB
Army	Carl R. Darnall Army Medical Center (CRDAMC)	Performance site	FWA00026734	08/18/2028	: IAIR	: WRNMMC IRB
Army	Womack Army Medical Center (WAMC)	Data analysis	FWA00012834	03/14/2028	: IAIR	: WRNMMC IRB
Army	Madigan Army Medical Center (MAMC)	Performance site	FWA00003277	09/17/2026	: IAIR	: WRNMMC IRB
P&R	Walter Reed National Military Medical Center (WRNMMC)	Lead site	FWA00017749	03/11/2027		: WRNMMC 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 results found					

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

Chronic Exertional Compartment Syndrome (CECS), Gait Re-Training, Gait Analysis, Botulinumtoxin A, Military

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

Chronic exertional compartment syndrome (CECS) is a debilitating disorder affecting mostly an active population. The proposed pathophysiology is increased pressure in muscle compartments causing pain, paresthesia, and inability to tolerate exercise in the affected fascial compartment. CECS involves the lower extremities, primarily affects young active adults, and limits running and /or endurance activities. While the incidence of CECS in the general population is unknown, the prevalence in the military population has been found to be 0.49 cases per 1000 patient-years.[1,4,5,7]

The current standard for definitive treatment of CECS is surgical fasciotomy of the involved compartments. According to a 2016 systematic review, surgical intervention for CECS is successful in only 66% of those affected, with 13% of patients reporting complications from surgery, and 6% needing a repeat procedure.[5] A 2013 retrospective analysis of military members showed fasciotomy for CECS was successful in only 55% of those affected. Additionally, 28% were unable to return to full activity, 16% suffered surgical complications, and 6% underwent repeat fasciotomy. Of 661 participants, 106 were referred for medical discharge from the Armed Forces.[6] A 2014 military cohort found 22% of patients were medically discharged or had surgical revision at short-term to mid-term follow-up. Additionally, 28% of service members were unable to return to full duty and 45% experienced incomplete relief of symptoms.[4] Besides risks and complications, surgery also required a mean of 13 weeks to return to full activity when effective.[7,8,9]

Formalized gait retraining is an attractive alternative to fasciotomy. It aims to influence the effect of foot contact and running kinematics to reduce leg compartment pressures which relieves pain. Diebal et al. published a case series of 10 military members with CECS who underwent a Supervised Gait Retraining (SGR) program that emphasized forefoot running. At six-weeks and one-year post-intervention, running distance, pain, and performance all significantly

improved. This case series also showed significant patient satisfaction with patients reporting 98 or better on the single assessment numeric evaluation (SANE) and 92 or better on the lower leg outcome survey.[3] A 2015 prospective cohort study showed home-based gait retraining (HBGR) is an effective alternative to SGR while reducing time and invested resources.[10] Despite high rates of success in limited case studies, real world application of gait retraining has limitations. Many patients struggle to make and/or sustain adaptations in their running style. Some patients have severe pain with exercise which limits efforts at effective gait re-training.

A newer proposed treatment for CECS is the intramuscular administration of botulinumtoxin A (BoNT-A) into the muscles of the involved compartment(s). BoNT-A is FDA approved for intramuscular, intradetrusor, or intradermal use for muscle spasticity, migraine headaches, detrusor instability and severe forehead lines, lateral canthal lines, and glabellar lines in adults. A 2013 case series studying botulinum toxin injections for CECS demonstrated normalized intramuscular pressure up to nine months post-injection in 87.5% (14/16) of patients, and exertional pain was completely eliminated in 94% (15/16) of patients. Eleven patients experienced reduced muscle strength that was without functional consequences and transient resolving within 3 months. Only 1 of the 16 patients complained of new posterior leg pain that did not appear to be related to BoNT-A injections. There were no other adverse effects reported.[1] An additional 2016 case report showed effective pain and paresthesia relief from CECS after 1 set of injections for a recreational female athlete. In this report, the patient's symptoms resolved within 1 week. More importantly, she was able to return to full recreational activity within 4 weeks, with no return of symptoms throughout the 14 months of follow up without any weakness or adverse effect.[2]

Military sports medicine clinics at Fort Belvoir Community Hospital (FBCH) and the Uniformed Services University (USU) as well as the Department of Physical Medicine & Rehabilitation at Walter Reed National Military Medical Center WRNMMC) currently utilize BoNT-A (trade names BOTOX® or Xeomin®) injections for the non-surgical treatment of CECS. All of our performance sites currently offer BoNT-A (trade names BOTOX® or Xeomin®) injections as standard of care non-surgical treatment options for CECS.

An unpublished retrospective review of patients with CECS treated with BoNT-A at FBCH Sports Medicine Clinic from 2014 to 2017 provided data on twenty-nine patients who were treated with BoNT-A for CECS (Protocol title: "Intramuscular botulinum toxin A injections for chronic exertional compartment syndrome: A retrospective therapeutic case series" Reference#: 905663). Prior to treatment, none of the 29 patients were able to perform their desired activity and 24% were unable to run one mile without severe leg pain. After botulinum injections, these numbers improved to 66% and 72% respectively. Sixty-nine percent of the patients reported that they were satisfied or somewhat satisfied with their treatment, twelve patients continued to have sustained relief by the time they were contacted, and seven patients experienced a recurrence of symptoms. In those with recurrence, the mean duration of improvement was 7.8 months. Of note, 11 patients received both BoNT-A and fasciotomy during their treatment course. Only one patient reported a favorable response to fasciotomy and failure with BoNT-A, suggesting that BoNT-A injections might be predictive of success with fasciotomy.

While alternative strategies like gait retraining and BoNT-A injections have emerged, the amount of data that is currently available to guide treatment is significantly limited. Studies assessing gait retraining in the treatment of CECS are few in number and small in power, with the largest published US case series involving 10 or fewer patients. Likewise, studies assessing the effectiveness of BoNT-A injections have thus far only included small, non-controlled, non-blinded case series. Perhaps the reason for paucity of data is a relative rarity of cases of CECS occurring at any single location. Military databases have thus far provided some of the best evidence for evaluating the effectiveness of fasciotomy for CECS, in large part because of the increased incidence of CECS among military members. By performing an intervention study at multiple military treatment facilities, we have the ability to evaluate non-surgical options for CECS with high quality, high-powered, blinded protocols.

This study will be the first of its kind to utilize blinding and a control while analyzing BoNT-A injections for CECS in the military health system. It will also be the first to judge whether formal gait retraining is required for the successful non-operative treatment of CECS or if BoNT-A injections is sufficient as a stand-alone treatment. The information gained from this study has the potential to revolutionize the treatment of CECS and provide guidance to physicians caring for these patients all over the world.

9.3 Objectives/Specific Aims/Research Questions:

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

The long-term objective of this project is to simultaneously assess the effectiveness of non-surgical treatments, botulinumtoxin A (BoNT-A) injections and supervised gait retraining (SGR), in terms of pain control and ability to return to full duty among adult active duty service members suffering from lower extremity Chronic Exertional Compartment Syndrome (CECS), specifically of the anterior and/or lateral comparments.[1,2,3]

This study will determine if successful supervised gait retraining is required for the successful non-operative treatment of anterior and/or lateral CECS or if BoNT-A injections is sufficient as a standalone treatment. Furthermore, this study will determine if BoNT-A injections plus supervised gait retraining is better.

Study Treatment Groups:

- Group 1 - Home Based Gait Retraining (HBGR) and Normal Saline (placebo)
- Group 2 - Supervised Gait Retraining (SGR) and Normal Saline (placebo)
- Group 3 - BoNT-A + HBGR
- Group 4 - BoNT-A + SGR

Objective 1: Assess and compare the treatment efficacy of the below study treatment groups.

Hypothesis 1: BoNT-A injections will prove effective as a non-surgical treatment option for CECS.
Process for Hypothesis 1**:** Evaluate functional improvements in Group 3 as compared to Group 1 via the subjective and objective data variables described in protocol sections 10.1 & 10.2.

Hypothesis 2: Supervised Gait Retraining will prove effective as a non-surgical treatment option for CECS.
Process for Hypothesis 2**:** Evaluate functional improvements in Group 2 as compared to Group 1 via the subjective and objective data variables described in protocol sections 10.1 & 10.2.

Hypothesis 3: The use of both BoNT-A injections and supervised gait retraining will be more effective than either treatment alone. In adult active duty service members with CECS, the use of both BoNT-A injections and supervised gait retraining returns service members to full duty, including being able to complete their service-specific military physical tests, sooner and for sustained longer periods that SGR or BoNT-A injections alone.
Process for Hypothesis 3**:** Evaluate functional improvements in Group 4 as compared to Groups 2 & 3 via the subjective and objective data variables described in protocol sections 10.1 & 10.2. Assess the ability of all study groups to complete a 2-mile run and to compete their required service-specific physical fitness testing within the established standards at 8 weeks, 3 months, 6 months, and 12 months post-study injection.

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

Multi-site, single-blinded randomized placebo-controlled study

9.5 Target Population:

Describe the population to whom the study findings will be generalized

Adult military beneficiaries diagnosed with Chronic Exertional Compartment Syndrome (CECS)

9.6 Benefit to the DoD:

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

Chronic exertional compartment syndrome (CECS) may occur in the four compartments of the lower leg: anterior, lateral, superficial posterior, and deep posterior. CECS typically occurs in the anterior and/or lateral compartments and is commonly seen within the military and has been shown to result in both significant warfighter disability and degradation of the unit mission. Active duty military members represent a population with a significantly higher risk of CECS. Military members also face requirements for exercise training and fitness that are jeopardized by a condition that limits aerobic exercise and physical activity. Fasciotomy, the current standard definitive treatment, has significant limitations in terms of effectiveness and direct and indirect costs. Pooled data shows that 28-59% of military members with CECS who underwent fasciotomy were unable to return to full duty and approximately 20% ultimately required medical separation from the military.[1] Not included in these statistics was the loss of member productivity during appointments, procedures, and recovery time.

Given the significant impact of CECS on the military mission, there is strong interest and motivation to investigate less invasive and less costly alternatives to fasciotomy. Within the National Capital Region, military sports medicine physicians have been utilizing both Supervised Gait Retraining (SGR) and botulinumtoxin A (BoNT-A) injections for years. While results have been promising for both options, there is insufficient high-quality data to create treatment guidelines and protocols for other providers in the military who treat these patients.

Based on a retrospective review of 29 patients from Fort Belvoir Community Hospital who received BoNT-A injections for CECS, approximately two-thirds of these patients were able to return to their desired activity level. In addition, among 11 patients who eventually underwent both BoNT-A injections and fasciotomy, only 2 patients would recommend fasciotomy as the first intervention over BoNT-A. Additionally, 69% of the patients in this review expressed satisfaction with BoNT-A injections. Aside from self-limited weakness with ankle dorsiflexion, there were no significant adverse effects.[2] The next logical step is to study the effect of BoNT-A injections in a randomized, prospective, single-blinded, placebo- controlled fashion.

In our present era of constrained troop numbers and enhanced emphasis on deployment readiness for every military member, this study offers a unique opportunity to evaluate novel treatment options for a significant source of lost readiness and disease burden in the DoD. Additionally, the data from this study will be readily translatable to allied military and civilian athlete populations. Given the epidemiology of CECS, this study is likely only feasible in a tri-service, multi-centered military environment. Results have the promise to greatly influence treatment decisions and help physicians and warfighters maintain the readiness and physical prowess of the fighting force.

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

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).

Recruitment, Pre-Screening (before consent), Study Introduction & Consent:
Potential participants will be identified via three methods:

1. Under the HIPAA Preparatory to Research Provision, local study clinicians will review medical records of patients coming in to the Physical Medicine & Rehabilitation (PM&R), Orthopaedics, Physical Therapy (PT), and Sports Medicine clinics for suspected Chronic Exertional Compartment Syndrome (CECS) to identify prospective research participants for the purposes of seeking their authorization to participate/use their protected health information for this research study,

2. If a local healthcare provider identifies a potential participant seen in the PM&R, Orthopaedics, PT or Sports Medicine clinic for suspected CECS as part of regular clinical care, they may refer them to a member of the local research team (who will be located within the clinic or available via phone) for further discussion, and
3. Study flyers will be posted within the departments of PM&R, Orthopaedics, PT, and Sports Medicine.

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 initial eligibility in close collaboration with the patient's attending provider. Initial eligibility (see Section 12.5 Inclusion Criteria #1-5 & Section 12.6 Exclusion Criteria #1-8) will be confirmed using an Inclusion/Exclusion CRF (Appendix A). This Inclusion/Exclusion CRF does not record any PII/PHI.

If the potential participant meets initial 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.

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 and study brochure 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 completion of informed consent, 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), by an authorized local study team member and a unique study ID will be automatically generated. This coded study ID will be used on all research data collection forms in place of the participant's name, social security number, Department of Defense (DoD) ID, or other protected identifier. No PII will be entered into REDCap. Please see Appendix J for additional information on REDCap.

In order to document screen failures and refusals, the results of the Inclusion/Exclusion CRF will be entered into REDCap even if a patient doesn't consent to participate in the study. The Inclusion/Exclusion CRF does not record any PHI/PII.

In order to adhere to WRNMMC's recruitment policy, research activities (e.g., study introduction, consent conversations, etc.) will take place after the clinic visit has ended. Recruitment and consent conversations 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.

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, last four digits of their social security number, preferred phone number, email address, etc.).

With the exception of the Consent Form and HIPAA Authorization, 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) and separately from all other paper research forms. All remaining paper research forms will be identified using a 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 (post-consent), Demographics & Baseline Data Collection:

Formal Screening:
As part of standard of care, other concomitant causes of leg pain will be ruled out with a physical examination, relevant medical history review and lower leg magnetic resonance imaging (MRI).

As part of the formal screening procedures, the participant's CECS diagnosis will be confirmed via an intramuscular compartment pressure test. To do this, the participant will have an intramuscular compartment pressure (IMCP) test done in one area at each of their anterior and lateral leg compartments at rest and post exerting on a treadmill, stairs, marching, or any type of exertional activity that increases the participant's leg pain and/or symptoms. Once they have their leg pain or symptoms reproduced while running or completing the

offending exertional activity, they will then have repeat IMCP test done at 1 minute post exertion. The IMCP test is currently the diagnostic standard for CECS. The use of ultrasound imaging will be used to identify and mark the region of interest of the anterior and lateral leg compartments that will be tested. If a participant has had any of these procedures performed within the 6 months prior to study enrollment, the research team will review those results and not repeat procedures if the testing was adequate and acceptable for clinical standards.

Also as part of the formal screening procedures, participants will have their ankle brachial index (ABI) blood pressure taken on each side at their ankle, foot, and arm separately using a blood pressure cuff and Doppler instrument. Blood pressures will be taken at rest, then 1 minute within completing approximately 50 repetitions of bilateral heel raises. At rest, an ABI measurement of less than or equal to 0.90 or greater than or equal to 1.4 on either side will be excluded from the study and resume normal care with their referring provider. If their ABI post exertion decreases in value greater than 0.2 compared to baseline, limb pressures are decreased greater than 30 mmHg compared to baseline, or they meet the previous exclusion baseline criteria for their ABI, then the participant will be excluded from the study and resume normal care with their referring provider.

Any female participant will also be required to have a urine hCG test performed prior to study injection. If the urine hCG indicates the participant is pregnant, per stated inclusion/exclusion criteria, they will be formally withdrawn from the study and will resume normal care with their referring provider.

All of the formal screening procedures must be completed within 60 days post-study consent.

Demographics & Baseline Data Collection:
Prior to being randomized to a study arm beginning their assigned study treatment (saline or BoNT-A injection, SGR or HBGR), participants will complete a Demographics CRF (Appendix C) and a Baseline Data Collection CRF (Appendix D) which ask relevant medical and service history and demographic questions including: age, gender, body mass index (BMI), symptom duration and characteristics, treatment history, work status, military rank, branch of service, length of service, limited duty/profile status, occupational specialty, concomitant medical conditions, activities provoking symptoms, footwear characteristics and orthosis use, etc. The Baseline Data Collection CRF also includes the following measures and clinical tests: Balance Error Scoring System (BESS), Numeric Pain Rating Scale (NPRS), University of Wisconsin Running Injury and Recovery Index (UWRI), Single Assessment Numerical Evaluation (SANE), Patient Specific Functional Scale (PSFS), gait analysis using advanced wearable technology as part of a self-paced treadmill test until cessation or the successful completion of a two-mile run (whichever occurs first), and objective leg length discrepancy measurement, foot parameters, lower extremity strength, range of motion (ROM), and palpation testing. A gait analysis Data Collection CRF (Appendix R) will be used to collect some of the gait analysis from the advanced wearable technology and will be completed after the participant's visit.

Many of the baseline questionnaires and clinical tests utilized in this study are already performed as standard of care. Please see attached Data Collection Schedule (Appendix H) for additional details.

Overall, the total time to complete all screening and baseline activities will be a maximum of 5.5 hours.

Randomization:
Participants who meet final eligibility criteria (no other concomitant causes of leg pain, confirmed CECS diagnosis of the anterior and/or lateral compartments via intramuscular compartment pressure test and lower limb MRI, ABI between 0.90 and 1.40, and if applicable, negative pregnancy test) will be randomized to a study arm and their intervention dates (i.e. injection and/or supervised gait retraining) will be scheduled. Study injections (both placebo and BoNT-A) must occur within 60 days of randomization and ≥ 2 weeks post-intramuscular compartment pressure test. A computer-generated randomization program prepared by the study biostatistician will be used to assign participants uniformly across all four study arms.

Participants will be assigned to one of four treatment groups:

- Group 1 - Home Based Gait Retraining (HBGR) and Normal Saline (placebo)
- Group 2 - Supervised Gait Retraining (SGR) and Normal Saline (placebo)
- Group 3 - BoNT-A + HBGR
- Group 4 - BoNT-A + SGR

Study Intervention:

BoNT-A Injections:
Those randomized into a BoNT-A injections group (i.e., Group 3 or 4) will receive up to 2 injections per affected anterior and/or lateral compartment. Per standard clinical procedure, a solution of 25 units of Botulinum toxin, per 1 mL of normal saline will be used for each injection. Standard aseptic technique will be followed. Insertion into the correct compartment will be accomplished using ultrasound guidance. The anterior and/or lateral compartments will each be separated into thirds measuring from the tibial plateau to the head of the calcaneus. Injections will be given at approximately 1/3 the distance from the tibial plateau for the proximal injection and 2/3 the distance from the tibial plateau for the distal injection. Injections will only be given in the compartments that have elevated compartment pressure using the standard Pedowitz criteria: 1) a pre-exercise pressure greater than or equal to 15 mmHg, 2) a 1 minute post-exercise pressure of greater than or equal to 30 mmHg, or 3) a 5 minute post-exercise pressure greater than or equal to 20 mmHg.[12] If the lateral compartment is affected, a total of 50 units of botulinum toxin will be given. The proximal aspect of the peroneus longus and brevis is approximately 1/3 the distance from the tibial plateau and it will receive 25 units of botulinum toxin A. The distal aspect of the peroneus longus and brevis is approximately 2/3 the distance from the tibial plateau and this area will also receive 25 units of botulinum toxin A. If the anterior compartment is affected, a total of 50 units of botulinum toxin will be given; 25 units to the proximal anterior compartment and 25 units to the distal anterior compartment.[1,2]

Of note, CECS mainly affects the anterior and lateral compartments and is rarely seen in the superficial posterior or deep posterior areas; thus, the anterior and lateral compartments will be the focus of this study and patients with concomitant or isolated posterior compartment symptoms will not be included in this study. Participants who receive BoNT-A injections will be provided with a Post-Injection After Care Handout (Appendix O). The information provided to the participant after the injection are observed signs and/or symptoms that could occur with receiving either a BoNT-A or saline injection. This handout is not likely to expose the blinding of the injection that the participant receives as part of the study.

Saline Injections:
Those randomized into the normal saline groups will receive injections in the identical manner above, using the appropriate amount of solution (0.5 mL to 1 mL). The syringes will be prepared by the clinical research staff using standard sterile techniques, out of view of the participant to ensure appropriate blinding.

Study Injection Documentation (both groups):
All injections will be done under ultrasound guidance. The provider will use the ultrasound machine to identify bony landmarks of the tibial plateau and will then move the probe laterally towards the fibular head to identify the anterior and lateral compartments of the lower leg. Distally, the provider will identify the midway area between the fibular head and the tip of the lateral malleolus.

Study injection administration to the participant will be documented using a Treatment Documentation CRF (Appendix N). This Treatment Documentation CRF will be entered into REDCap. Study injection administration will also be documented in the participant's electronic medical record following standard procedures.

Supervised Gait Retraining (SGR):
The SGR course will focus on mid-forefoot strike, increasing their cadence while shortening their stride, and decreasing their peak ground reaction force. This program has been developed by physical therapists at West Point and the Army DPT program in Fort Sam Houston. This program uses group physical therapy sessions, lower extremity exercises, home exercise training drills, and advanced wearable technology to effectively change key gait parameters.

Supervised physical therapy sessions will be documented using a SGR Physical Therapy Documentation CRF (Appendix M). This SGR Physical Therapy Documentation CRF will be entered into REDCap. Study supervised physical therapy sessions will also be documented in the participant's electronic medical record following standard procedures. Participants in the SGR group(s) will also be sent home with a handout (Appendix L) explaining exercises that can/should be done from home to supplement their supervised physical therapy sessions.

Home Based Gait Retraining:
The HBGR will focus on increasing cadence, running softer and increasing endurance strength with exercises for the lower extremity. A handout (Appendix L) explaining desired exercises and gait retraining will be given to each participant with daily exercise instructions. Participants will be contacted weekly as a reminder to complete their home program.

For participants assigned to the HBGR group, their first (and only) study-related in-person physical therapy session and follow up communications will be documented using an HBGR Physical Therapy Documentation CRF (Appendix Q). This HBGR Physical Therapy Documentation CRF will be entered into REDCap. Their first (and only) study-related in-person physical therapy visit will also be documented in the participant's electronic medical record following standard procedures.

Both the SGR & HBGR Groups:
Initiation of physical therapy visits for both SGR and HBGR groups can be greater than or equal to 2 weeks post-injection. All participants (regardless of study arm) will be instructed to avoid other physical therapy and invasive treatments (including acupuncture) while participating in this study. Concomitant medications and therapies will be recorded at each follow up visit (Appendix M & Appendix Q). Participants will be free to participate in optional complimentary activities available to them as standard of care such as aquatics and yoga.

Follow Up Data Collection:
For all study groups, participants will complete a Follow Up Data Collection CRF (Appendix E) at 8 weeks (+/- 1 week), 3 months (+/- 2 weeks), 6 months (+/- 2 weeks) and 12 months (+/- 2 weeks) post-study injection and a Long Term Follow Up Data Collection CRF (Appendix F) at 24 months (+/- 4 weeks) post injection. The Follow Up Data Collection CRF and Long Term Follow Up Data Collection CRF both include the following measures: Numeric Pain Rating Scale (NPRS), University of Wisconsin Running Injury and Recovery Index (UWRI), Single Assessment Numerical Evaluation (SANE), Patient Specific Functional Scale (PSFS), and the Global Rate of Change (GROC). Additionally, patients will be asked about their ability to complete their service-specific military physical training requirements, running and activity leg symptoms, footwear characteristics and orthosis use, pertinent medical history, and treatment satisfaction at each follow-up time point.

At 8 weeks (+/- 1 week), 3 months (+/- 2 weeks), 6 months (+/- 2 weeks), and 12 months (+/- 2 weeks) post-injection, participants will undergo Balance Error Scoring System (BESS) testing, objective foot parameters, ankle strength, range of motion (ROM), ankle brachial index (ABI) blood pressure, and palpation tests, and a gait and run analysis using advanced wearable technology as part of a self-paced treadmill test until cessation or the successful completion of a two-mile run (whichever occurs first). A gait analysis Data Collection CRF (Appendix R) will be used to collect some of the gait analysis from the advanced wearable technology and will be completed after the participant's visit.

Participants will also be asked about involvement in non-study related activities and treatments including acupuncture/acupressure, aquatics, anti-inflammatory/pain medication, athletic taping, change in running shoes, chiropractor, dry needling, electrical stimulation, foot orthotics, gait retraining, ice pack/massage, massage, physical therapy, strengthening, stretching, yoga, and other treatments.

Intramuscular compartment testing of participant’s anterior and lateral compartments will be re-tested at 6 months (+/- 2 weeks) post-injection. The same compartments tested at baseline or at a previous test 6 months prior to consent of the study, will be recollected at the 6 month time point.

Results of the in-person clinical assessments and the intramuscular compartment testing will be recorded in the Follow Up Data Collection CRF.

Overall, the 8 week, 3 month, 6 month, and 12 month follow up activities will take approximately 2.5 hours each and the 24 month follow up activities will take approximately 30 minutes each.

If the participant has a change of duty station (permanent or temporary) and/or cannot make an in-person visit, the following will be collected using Appendix E, Follow Up Data Collection Sheet: relevant medical and service history and demographic questions including age, gender, body mass index, symptoms duration, location, and characteristics, treatment history, work status, military rank, branch of service, length of service, limited duty/profile days, occupational specialty, concomitant medical conditions, activities provoking symptoms, location of symptoms, footwear characteristics and orthosis use, etc., numeric pain rating scale (NPRS), University of Wisconsin Running Injury and Recovery Index (UWRI), Single Assessment Numerical Evaluation (SANE), Patient Specific Functional Scale (PSFS) will also be assessed. This may be collected with electronic mail, postal mail, and/or telephone communication with the participant.

Many of the activities in this study are performed regularly as part of standard of care for patients being seen for lower extremity CECS. Please see Appendix H: Data Collection Schedule for details on which activities are standard of care.

Study Completion:
Participants' study completion or withdrawal will be documented on the Study Completion CRF (see Appendix S).

Additional Considerations - COVID-19:
For as long as deemed clinically appropriate, there will be additional precautions in place to ensure the health and safety of research staff and research participants and to combat the spread of COVID-19. Research staff will closely follow all current local clinical guidelines regarding the use of PPE, hand washing, disinfecting of equipment, proper distancing, etc. Additionally, the study team will reduce the need for in-person research-specific visits when possible. For participants assigned to one of Standardized Gait Retraining (SGR) groups, some of their clinical follow ups during the physical therapy period may be conducted and documented as a video/telehealth encounter. For participants assigned in all groups, the 24-month follow up visit which requires no physical examination can be conducted remotely, meaning the participants can complete the questionnaires electronically, over the phone, or hard copy via mail all while remaining at home.

Study Blinding:
Participants will be blinded to assigned treatment arm (i.e., saline vs. BoNT-A injection) until 3 months post-injection.

Blinding will be revealed to the participants after all the components of the 3 month follow-up visit have been completed. Participants who are not satisfied with their treatment results and /or who are unable to complete a 2-mile run without producing pain and/or symptoms will be offered the option to receive BoNT-A injections and/or Supervised Gait Retraining if they had not received those active treatments.

At the 6 month follow-up visit, participants who are still not satisfied with their treatment results and/or still unable to complete a 2-mile run will be offered any remaining treatment option, including surgical fasciotomy which is offered as standard of care. Participants who express interest in surgical fasciotomy will be referred to an orthopaedic surgeon who will dictate and guide this treatment option. Further details and scheduling will be per the orthopaedic surgeon’s recommendations. Patients who cross over to alternative treatment options (including surgical fasciotomy) will remain in the study and will continue to follow up with the research team at the intervals listed above.

Data Entry:
With the exception of the Intake CRF which collects participant contact information, all coded research data 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 (USU). No PII will be entered into REDCap. See Appendix J for additional information on REDCap. See Appendix I for a PDF copy of the REDCap forms for this study.

Additional Info - MIRROR/USU:
This research study is being conducted as part of Musculoskeletal Injury Rehabilitation Research for Operational Readiness, formerly known as the Collaboratory for Musculoskeletal Injury Rehabilitation Research (CMIRR), 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 Department of Defense (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 Materiel Command (USAMRMC), 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 17 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. De-identified research data will shared MIRROR/USU and maintained indefinitely for possible use in future research.

There will be appropriate data sharing agreements in place between the data owner(s) (e.g., DHA for AHLTA) and the Walter Reed National Military Medical Center (WRNMMC), as well as the Uniformed Services University (USU) and all appropriate parties involved in the handling of data (e.g., The Geneva Foundation).

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 H).

The local study team will collect study data directly from the study participant, from their attending provider or, where applicable, from the participant's medical record (i.e., relevant medical and treatment history and relevant clinical notes) and record it on paper CRFs (see Appendixes A-F). Study completion will be documented (see Appendix S). The completed paper CRFs will serve as source documents for this study. Participants may also enter study data directly into REDCap using a coded survey link. In these cases, the completed eCRFs will be printed and stored in the participant's research files and serve as source documents. Other source documents include relevant laboratory results (i.e., hCG urine test) and relevant clinical notes which will be printed, redacted, and stored in the participant's research file.

With the exception of the Informed Consent Form, HIPAA Authorization, and 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.

The primary outcome will be functional improvement via statistical changes in the Balance Error Scoring System (BESS), University of Wisconsin Running Injury and Recovery Index (UWRI), Single Assessment Numerical Evaluation (SANE), Patient Specific Functional Scale (PSFS), Global Rate of Change (GROC), objective data from the gait and run analyses (e.g., average vertical load rate, cadence, foot pattern strike, etc.), ability to return to full active duty, and ability to complete a 2-mile run. Full active duty is defined as meeting all service specific requirements of physical training and ability to complete work duties with either no pain or pain that is tolerable as determined by the patient.

Secondary outcomes will include pain reduction according to the Numeric Pain Rating Scale (NPRS), ability to complete service specific military physical training requirements, and patient satisfaction. To assess patient satisfaction, patients will be asked if they were or were not satisfied with intervention at each follow up time point.

This will be an intention to treat study and additional data that will be collected via the Demographics CRF (Appendix C) and Baseline Data Collection CRF (Appendix D) includes:

- Standard Demographics (e.g., Age, Sex, military occupational specialty, height, weight, BMI, MOS)
- Length of military service
- Symptom duration (including length of limited duty, military profile)
- Previous Treatments
- Time to diagnosis

- Concomitant medical conditions
- Footwear characteristics and orthosis use
- Activities provoking symptoms, and perceived exertion (Borg) tolerance
- Duration of symptoms when present
- Performance on military fitness tests
- Ability to perform occupational related tasks
- Objective lower extremity strength, range of motion (ROM), ankle brachial index (ABI) blood pressure, palpation, leg length, foot parameters tests

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

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.

[x] Talking with MHS health care providers or MHS health plans about specific research participants
[ ] Obtaining MHS hard copy records specific to research participants
[x] 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
[x] 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
: ESSENTRIS	: Yes

PII-Only Systems:

MHS Information System	Requesting Data
No results found	

De-Identified Data & Other Systems:

Information System	Requesting Data
Other MHS System (May include PII and /or PHI) List other system here: MHS Genesis	: 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)	☐	☑	☐	☐	☐	☐
11. Health Plan Beneficiary Numbers (including DEERS ID, Electronic						

Data Interchange Personal Identifier (EDIPI) or Number (EDIPN))	☐	☐	☐	☐	☐	☐
12. Account Numbers	☐	☐	☐	☐	☐	☐
13. Certificate /License Numbers	☐	☐	☐	☐	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐	☐	☐	☐	☐
15. Device identifiers and serial numbers	☐	☐	☐	☐	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐	☐	☐	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐	☐	☐	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐	☐	☐	☐	☐
19. Full-face photographic images and any comparable images	☐	☐	☐	☐	☐	☐
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?

DoD ID numbers and SSNs are used to identify and locate patients in MTFs. For this study, the local study team will use both DoD IDs and the last 4 digits of SSNs to identify and track participants and their medical records within the individual enrolling hospital only. The full DoD ID and the last 4 digits of the participant's SSN will be recorded on the paper Intake CRF (Appendix B) alongside other contact information. The paper Intake CRF will be stored separately from all other paper research data alongside the signed Informed Consent Documents and HIPAA Authorizations in a locked cabinet inside of a locked room, only accessible by local personnel authorized by the PI. With the exception of the paper Intake CRF and the electronic Master List, the participant's SSN will not be recorded on any other paper CRFs, will not be entered into the electronic database, and will not be shared with other participating institutions.

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.

- [x] 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, from their attending provider or, where applicable, from the participant's medical record (i.e., relevant medical and treatment history (retrospective collection) and relevant clinical notes throughout duration of study participation (prospective collection) and record it on paper CRFs (see Appendixes A-F).

If for any reason a research participant is unable to physically come in for an in-person follow up visit, we will obtain as much data remotely (electronically, via phone, via mail or via medical record review) as possible.

The completed paper CRFs will serve as source documents for this study. Participants may also enter study data directly into REDCap using a coded survey link. In these cases, the completed eCRFs will be printed and stored in the participant's research files and serve as source documents. Other source documents include relevant laboratory results (i.e., hCG urine test) and relevant clinical notes which will be printed, redacted, and stored in the participant's research file.

Electronic Data Entry:
Following each research visit, a local study team member will review the paper CRFs for accuracy and completeness and then enter the collected non-personally identifiable data from the paper CRFs into REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a Department of Defense (DoD) server and maintained by the Uniformed Services University Information Technology (USU IT). No PII will be entered into REDCap. The information collected on the Intake CRF will not be entered into REDCap.

Please see Appendix J for additional information on REDCap.

Data Storage & Access:
With the exception of the Informed Consent Form, HIPAA Authorization, Intake CRF (Appendix B) 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, social security number, 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 will be stored separately from the coded paper research forms alongside the Informed Consent Forms and HIPAA Authorizations 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 Department of Defense (DoD) server and maintained by the Uniformed Services University Information Technology (USU IT). No PII will be entered into REDCap.

This coded electronic research data will only be accessible by local research staff designated and authorized by the Principal Investigator and authorized staff from Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR), formerly known as the Collaboratory for Musculoskeletal Injury Rehabilitation Research (CMIRR), which is based out of the Department of Physical Medicine & Rehabilitation at the Uniformed Services University (USU) and is serving as the data coordinating center for this research study. Staff from MIRROR/USU will not have access to the paper research records or any identifiable research data to include the Master List, the informed consent forms/HIPAA authorizations, or any other form of participant PHI/PII. 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.

There will be appropriate data sharing agreements in place between the data owner(s) (e.g., DHA for AHLTA) and the Walter Reed National Military Medical Center (WRNMMC), as well as the Uniformed Services University (USU) and all appropriate parties involved in the handling of data (e.g., The Geneva Foundation).

No recruitment will occur at Womack Army Medical Center (WAMC). The WAMC team will only conduct coded data analysis. Authorized WAMC study team members will analyze the coded gait data points obtained from each of the recruiting sites at the baseline, 8-week, 3-, 6-, and 12-month follow up time points. This coded gait data will be stored in a USU-hosted password protected cloud based storage service accessible only by authorized study team members. The WAMC team will analyze the gait data using MATLAB and the results will be stored in the same USU-hosted password protected cloud based storage service. No identifiable information will be used or transferred during this process. The WAMC team will not have access to the coded master lists from the participating sites at any time.

Authorized members of the local study team will create and maintain a separate electronic master list which matches unique study IDs with participant names. The electronic master list will be stored separately from the coded electronic research data in a secure, password protected Excel spreadsheet 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, the local IRB, 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 connecting unique study ID to participant identifiers will be destroyed within one year of study closure. Once the master list is permanently destroyed, the collected study data will be considered de-identified. The electronic de-identified research data will be maintained indefinitely as described in protocol section 10.15.

Is this a data repository?

○ Yes ◉ No

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.

Long Term Data Storage & Access:
The de-identified electronic dataset will be maintained by MIRROR/USU indefinitely or as long it is practicable to maintain.

De-identified electronic research data will be securely transmitted from local study teams to the MIRROR/USU via REDCap 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 Appendix J). DoD SAFE uses a TLS (Transport Layer Security) protocol when files are uploaded and downloaded.

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 Department of Defense (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.

There will be appropriate data sharing agreements in place between the data owner(s) (e.g., DHA for AHLTA) and the Walter Reed National Military Medical Center (WRNMMC), as well as the Uniformed Services University (USU) and all appropriate parties involved in the handling of data (e.g., The Geneva Foundation).

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

Data Withdrawal:
Because there will be no way to link an individual's identity to their specific research data, participants will not be able to withdraw their de-identified research data from storage.

Is this a data repository?

(•) Yes ( ) No

If Yes, provide the name of the Repository

USU OCIO REDCap

Who will have access to the Repository?

MIRROR core team, investigators, study team members, as applicable.

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.

What data type will be stored in the Repository?

- [ ] Protected Health Information
- [ ] Limited Data Set
- [x] De-identified Data

11.0 Statistical/Data Analysis Plan

11.1 Data Analysis Plan and 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 subgroup 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.

To maximize efficiency of the factorial study design, the clinical effectiveness of each treatment will be measured simultaneously using logistic regression analysis. Specifically, the regression model will include three binary independent variables, one for each treatment group, with group 1 (HBGR + NS) as the reference treatment. In this way, the group 3 coefficient (BoNT-A + HBGR) will correspond to the effect estimate of group 3 vs 1 (specific aim 1), the group 2 coefficient (SGR + NS) will correspond to the effect estimate of group 2 vs 1 (specific aim 2), and the group 4 coefficient (BoNT-A + SGR) will correspond to the effect estimate of group 4 vs either 2 or 3 (specific aim 3).

Missing Data and Outliers:

In keeping with statistical analysis standards in randomized controlled trials, data will be analyzed using complete-case, intention-to-treat (ITT) analysis—that is, we will analyze all study subjects who received treatment assignment and for whom we obtained sufficient outcome data.

Confounding Variables:
Clinical effectiveness will be studied using a factorial randomized design. Such designs are widely recognized to yield unbiased estimates by removing confounding between treatment and outcome when sufficiently powered.

11.2 Sample Size:

We are requesting to enroll up to 620 participants (155 per treatment group) across all performance sites in order to evaluate a final sample of 480 subjects (120 per treatment group) across all performance sites. Up to 125 of these participants will be enrolled at WRNMMC. Up to 125 of these participants will be enrolled at each of the other performance sites.

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

620

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

Across all performance sites, up to 620 participants will be uniformly randomized across the four treatment groups: Up to 155 participants in Group 1 - Home Based Gait Retraining (HBGR) and Normal Saline (placebo), up to 155 participants in Group 2 - Supervised Gait Retraining (SGR) and Normal Saline (placebo), up to 155 participants in Group 3 - BoNT-A + HBGR, and up to 155 participants in Group 4 - BoNT-A + SGR.

11.5 Please provide a justification for your sample size

Using a 2x2 factorial design and assuming success rates for passing the US Army 2-mile run test among control (saline/home based gait retraining), botulinumtoxin A (BoNT-A) injection, supervised gait retraining (SGR), and combined therapy (BoNT-A + SGR), respectively, are 15%, 80%, 50%, and 85%, we estimate that enrolling a grand total of at least 60 patients would yield 80% power to detect the effect of BoNT-A, enrolling a grand total of at least 120 patients would yield 80% power to detect the effect of SGR, and enrolling a grand total of at least 380 patients would yield 80% power to demonstrate the benefit of combined therapy (BoNT-A + SGR) vs. either therapy in isolation. If we can obtain complete data on more than 380 participants, then it will strengthen our power. We hope to have a final sample of 480 participants. Assuming roughly 20% attrition and accounting for screen failures, we are requesting to enroll up to 620 participants across all performance sites.

Power was estimated using Monte Carlo simulations assuming uniform randomization among four groups in the 2x2 factorial design, while testing for statistical significance simultaneously among the four groups of control, BoNT-A, SGR, and combined therapy using a generalized linear model. Statistical significance was indicated if the corresponding $p < 0.05$ per generalized linear model.

12.0 Participant Information

12.1 Subject Population:

Active duty service members aged 18-60 (inclusive) diagnosed with Chronic Exertional Compartment Syndrome (CECS) of their anterior and/or lateral compartments in their lower leg.

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
- [x] 18-24
- [x] 25-34
- [x] 35-44
- [x] 45-54
- [x] 55-64
- [ ] 65-74
- [ ] 75+

18-60 (inclusive)

12.3 Gender:

- [x] Male
- [x] Female
- [ ] Other

12.4 Special categories, check all that apply

- [ ] Minors /Children
- [ ] Students
- [ ] Employees - Civilian
- [ ] Employees - Contractor
- [ ] Resident/trainee
- [ ] Cadets /Midshipmen
- [x] 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	Active duty service member age 18-60 (inclusive).
2	Fluent in speaking and reading English
3	Unable to run 2 miles without producing pain and/or symptoms, including aching, burning, numbness, tingling, and/or weakness in the affected limb.
4	Has difficulty completing the running portion of their service specific physical training due to pain and/or symptoms in the affected limb.

5	Meets clinical diagnostic criteria for CECS of the anterior and/or lateral compartment(s) in the lower leg, per clinical exams (e.g., physical examination, intramuscular compartment pressure test (IMCP test needle testing), lower leg MRI, etc.).

12.6 Exclusion Criteria:

Order Number	Criteria
1	Prior Botulinum toxin injection(s) in the lower leg compartments of the affected limb.
2	Prior compartment release of the affected limb.
3	Recent (within the last 6 months) lower limb injury that needed medical intervention
4	Undergone formal gait retraining within the last 6 months.
5	Allergic to BoNT-A (trade names BOTOX® or Xeomin®)
6	Pregnant or breastfeeding.
7	Medical history and/or clinical exams (e.g., physical examination, intramuscular compartment pressure test, lower limb MRI, amyotrophic lateral sclerosis (ALS), myasthenia gravis, Lambert-Eaton Syndrome, or any neuromuscular junction disorders) indicate other more likely causes of leg pain and/or symptoms.
8	Ankle Brachial Index (ABI) blood pressure ≤ 0.90 or or >/= to 1.4 within the last 6 months. Post Exertion ABI is >0.2 or limb pressure decreases > 30 mmHg.

13.0 Recruitment and Consent

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

Potential participants will be identified via three methods:

1. Under the HIPAA Preparatory to Research Provision, local study clinicians will review medical records of patients coming in to the Physical Medicine & Rehabilitation (PM&R), Orthopaedics, Physical Therapy (PT), and Sports Medicine clinics for suspected Chronic Exertional Compartment Syndrome (CECS) to identify prospective research participants for the purposes of seeking their authorization to participate/use their protected health information for this research study,
2. If a local healthcare provider identifies a potential participant seen in the PM&R, Orthopaedics, PT or Sports Medicine clinic for suspected CECS as part of regular clinical care, they may refer them to a member of the local research team (who will be located within the clinic or available via phone) for further discussion, and
3. Study flyers will be posted within the departments of PM&R, Orthopaedics, PT, and Sports Medicine.

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 initial eligibility in close collaboration with the patient's attending provider. Initial eligibility (see Section

12.5 Inclusion Criteria #1-5 & Section 12.6 Exclusion Criteria #1-8) will be confirmed using an Inclusion/Exclusion CRF (Appendix A). This Inclusion/Exclusion CRF does not record any PII/PHI.

If the potential participant meets initial 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.

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 and study brochure 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 completion of informed consent, 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), by an authorized local study team member and a unique study ID will be automatically generated. This coded study ID will be used on all research data collection forms in place of the participant's name, social security number, Department of Defense (DoD) ID, or other protected identifier. No PII will be entered into REDCap. Please see Appendix J for additional information on REDCap.

In order to document screen failures and refusals, the results of the Inclusion/Exclusion CRF will be entered into REDCap even if a patient doesn't consent to participate in the study. The Inclusion/Exclusion CRF does not record any PHI/PII.

In order to adhere to WRNMMC's recruitment policy, research activities (e.g., study introduction, consent conversations, etc.) will take place after the clinic visit has ended. Recruitment and consent conversations 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.

13.2 Compensation for Participation:

Participants will not be financially compensated for their participation in this research study.

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):
Potential participants will be identified via three methods:

1. Under the HIPAA Preparatory to Research Provision, local study clinicians will review medical records of patients coming in to the Physical Medicine & Rehabilitation (PM&R), Orthopaedics, Physical Therapy (PT), and Sports Medicine clinics for suspected Chronic Exertional Compartment Syndrome (CECS) to identify prospective research participants for the purposes of seeking their authorization to participate/use their protected health information for this research study,
2. If a local healthcare provider identifies a potential participant seen in the PM&R, Orthopaedics, PT or Sports Medicine clinic for suspected CECS as part of regular clinical care, they may refer them to a member of the local research team (who will be located within the clinic or available via phone) for further discussion, and
3. Study flyers will be posted within the departments of PM&R, Orthopaedics, PT, and Sports Medicine.

If the potential participant meets initial 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. In order to adhere to WRNMMC's recruitment policy, research activities (e.g., study introduction, consent conversations, etc.) will take place after the clinic visit has ended.

Formal Screening (post-consent):
As part of standard of care, other concomitant causes of leg pain will be ruled out with a physical examination, relevant medical history review and lower leg magnetic resonance imaging (MRI).

As part of the formal screening procedures, the participant's CECS diagnosis will be confirmed via an intramuscular compartment pressure test. To do this, the participant will have an intramuscular compartment pressure (IMCP) test done in one area at each of their anterior and lateral leg compartments at rest and post exerting on a treadmill, stairs, marching, or any type of exertional activity that increases the participant's leg pain and/or symptoms. Once they have their leg pain or symptoms reproduced while running or completing the offending exertional activity, they will then have repeat IMCP test done at 1 minute post exertion. The IMCP test is currently the diagnostic standard for CECS. The use of ultrasound imaging will be used to identify and mark the region of interest of the anterior and lateral leg compartments that will be tested. If a participant has had any of these procedures performed within the 6 months prior to study enrollment, the research team will review those results and not repeat procedures if the testing was adequate and acceptable for clinical standards.

Also as part of the formal screening procedures, participants will have their ankle brachial index (ABI) blood pressure taken on each side at their ankle, foot, and arm separately using a blood pressure cuff and Doppler instrument. Blood pressures will be taken at rest, then 1 minute within completing approximately 50 repetitions of bilateral heel raises. At rest, an ABI measurement of less than or equal to 0.90 or greater than or equal to 1.4 on either side will be excluded from the study and resume normal care with their referring provider. If their ABI post exertion decreases in value greater than 0.2 compared to baseline, limb pressures are decreased greater than 30 mmHg compared to baseline, or they meet the previous exclusion baseline criteria for their ABI, then the participant will be excluded from the study and resume normal care with their referring provider.

Any female participant will also be required to have a urine hCG test performed prior to study injection. If the urine hCG indicates the participant is pregnant, per stated inclusion/exclusion criteria, they will be formally withdrawn from the study and will resume normal care with their referring provider.

Participants will be assigned to one of four treatment groups:

- Group 1 - Home Based Gait Retraining (HBGR) and Normal Saline (placebo)
- Group 2 - Supervised Gait Retraining (SGR) and Normal Saline (placebo)
- Group 3 - BoNT-A + HBGR
- Group 4 - BoNT-A + SGR

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 locally at each performance site. Documentation of consent will be recorded in the participant's medical record. No Legally Authorized Representatives will be utilized.

Potential participants will be identified via three methods:

1. Under the HIPAA Preparatory to Research Provision, local study clinicians will review medical records of patients coming in to the Physical Medicine & Rehabilitation (PM&R), Orthopaedics, Physical Therapy (PT), and Sports Medicine clinics for suspected Chronic Exertional Compartment Syndrome (CECS) to identify prospective research participants for the purposes of seeking their authorization to participate/use their protected health information for this research study,
2. If a local healthcare provider identifies a potential participant seen in the PM&R, Orthopaedics, PT or Sports Medicine clinic for suspected CECS as part of regular clinical

care, they may refer them to a member of the local research team (who will be located within the clinic or available via phone) for further discussion, and
3. Study flyers will be posted within the departments of PM&R, Orthopaedics, PT, and Sports Medicine.

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 initial eligibility in close collaboration with the patient's attending provider. Initial eligibility (see Section 12.5 Inclusion Criteria #1-5 & Section 12.6 Exclusion Criteria #1-8) will be confirmed using an Inclusion/Exclusion CRF (Appendix A). This Inclusion/Exclusion CRF does not record any PII/PHI.

If the potential participant meets initial 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.

Formal consent, as represented by the act of signing a dated, IRB approved consent statement for the study will only occur after confirming initial 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 Botulinum toxin injections, gait retraining and surgical fasciotomy. If desired, potential participants will be allowed to discuss the option of fasciotomy with a surgeon prior to deciding to participate in the study. Potential participants will also be reminded of the expectations placed on them if they enroll, including the blinded randomization and formal screening processes and the study follow up schedule.

The potential participant will be given a copy of the informed consent to read before, during, and /or after discussion of the informed consent with the Research Coordinator, Principal Investigator, Associate Investigator, or other authorized study team member. Sufficient time will be given to the potential participant to understand the study purpose, study procedures and 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 also 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.

Potential participants will also be given a Participation Timeline Handout (Appendix P) on the time commitments for each of the study arms that the participant could be randomized into. This handout will be explained to the participant to aid them in understanding their time commitment to the study. Once the participant has all of their questions about the time commitments satisfied, they will initial a line on the informed consent form confirming that they received this information.

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. 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 copy of a blank consent form and study brochure 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.

In order to adhere to WRNMMC's recruitment policy, research activities (e.g., study introduction, consent conversations, etc.) will take place after the clinic visit has ended. Recruitment and consent conversations 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.

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-physician study staff to prevent any misconception of coercion or undue influence.

In the event a reconsent is required, participants will be reconsented the next time they report to clinic for a research visit. For participants who have had a change of duty station and will not be returning to clinic in person, a letter may be sent to the participant through postal mail and/or electronic mail.

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

- (●) N/A
- ( ) 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 data collected up to the time of withdrawal if the data is necessary to maintain the integrity of the study. However, no further data will be collected after the date of withdrawal.

Participants may contact the study research coordinator or Principal Investigator to initiate the formal withdrawal process. Participants will be advised to follow-up with their personal provider if they chose to withdraw.

Withdrawal Without Participant Consent:
Participants will be removed from the study if they fail to meet the formal screening criteria outlined in protocol section 13.3.

Additionally, 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, if they fail to adhere to the protocol and/or therapy plan, or if they display inappropriate behavior towards study personnel.

The reason for any withdrawal/removal will be documented (see Appendix S).

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

With the exception of the injection itself, all of the study activities are regularly performed in a standard clinical environment as procedures and treatment for CECS of the anterior and/or lateral compartments in the lower leg, therefore the potential risks directly associated with study-specific activities and procedures are minimal. However, there are standard risks common with some of these procedures.

The potential side effects of Botulinum toxin A injections include: rare minor side effects of bleeding, pain, soreness, infection, transient general muscle weakness and muscular atrophy, flu-like symptoms, and even rarer transient breathing and swallowing difficulties which has the potential to cause death if not appropriately treated.

The potential side effects of saline injections include: pain, soreness, bleeding, and infection which are all very rare.

The potential side effects of IMCP needle insertion for intramuscular compartment pressure testing include: pain which is minimized with local anesthesia, soreness, minor local bleeding, and the rare incidence of infection.

The potential risks for balance screening, physical objective measurements, physical performance based testing, gait retraining, standard gait analysis, self-paced treadmill test, and lower strengthening and stretching exercises include: physical discomfort (increased pain and reduced activity level), soreness, possible chronic or acute musculoskeletal injury, overuse or a fall.

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 precautions will be taken to minimize the above-mentioned risks. Standard clinic protocols will be followed to reduce the risks of infections and related complications.

To minimize the risk to participants, once they receive their injection, a waiting period of at least 15 minutes will occur at the clinic. This waiting period is to observe for any side effects that may occur due to the injection. The participant will also be given an after care injection handout. In order to safeguard participants, providers will use ultrasound guidance to identify the locations of the anterior and lateral compartments of the lower leg. Expected soreness may occur from the study injection procedures which may impact the start of physical therapy visits to 2 weeks post injection. Providers will be trained on all study procedures. All of this will provide consistent delivery of treatment to the targeted areas and minimize risk to the participant.

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, social security number, DoD ID, or other similar identifier. All available measures allowed by law will be taken by research staff to protect participant confidentiality. See protocol section 14.3 for additional information.

All participants will be evaluated for adverse events at each follow-up visit and concomitant medications and treatments will be documented. All adverse events, regardless of severity, will be reported to the Principal Investigator and Research Medical Monitor. The Research Medical Monitor will review all adverse events. 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 (Appendix B) 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, social security number, DoD ID, or other protected identifier.

At WRNMMC, paper research forms and source documents will be stored in a locked cabinet inside of a locked room within the Department of Physical Medicine & Rehabilitation (America Bldg. 1st Floor), accessible only by local research staff designated and authorized by the Principal Investigator. The paper Intake CRF which records participant contact information will be stored separately from the coded paper research forms alongside the Informed Consent Forms and HIPAA Authorizations 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 Department of Defense (DoD) server and maintained by the Uniformed Services University Information Technology (USU IT). No PII will be entered into REDCap. The Intake CRF will not be entered into REDCap.

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

The electronic Master List, the Intake CRF, and all research data and forms (both paper and electronic) will only be accessible by authorized local study staff, the local DoD research office, the WRNMMC Department of Research Programs (DRP), 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.

Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR) which is based out of the Department of Physical Medicine & Rehabilitation 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. Staff from MIRROR/USU will not have access to the paper research records or any identifiable research data including the electronic Master List, the informed consent forms/HIPAA authorizations, information recorded on the Intake CRF, or any other participant PHI/PII. There will be appropriate data sharing agreements in place between the data owner(s) (e.g., DHA for AHLTA) and Walter Reed National Military Medical Center as well as the Uniformed Services University (USU) and all appropriate parties involved in the handling of data (e.g., The Geneva Foundation).

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, social security number, 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 date (e.g., group means) where appropriate. Participants will not 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 a participant will benefit from participation in this study because as with any treatment intervention, there is a potential for no relief of CECS symptoms in their anterior and/or lateral compartment(s). However, potential benefits include a relief of symptoms, avoidance of surgical fasciotomy, and return to full active duty status.

Study results may help to improve future rehabilitative care for musculoskeletal injuries in the military population and have a positive impact on force readiness.

14.5 Privacy for Subjects:

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

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.

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.

Because our participants are active duty military personnel, information regarding the participant's 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 and Research Medical Monitor 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 and Research Medical Monitor will review and sign adverse event logs/reports, protocol deviation logs/reports, and continuing reviews/annual progress reports.
4. If there is concern about the welfare of enrolled participants, the PI and/or Research Medical Monitor 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 Research Medical Monitor (if applicable) 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 providers will monitor the progress and health of the participants alongside our Research Monitor. 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 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:

All adverse events (AEs), regardless of severity, will be reported to the Principal Investigator and Research Medical Monitor. The Research Medical Monitor 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 and the Research Monitor 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 and the Research Monitor 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 occurring in subjects enrolled at WRNMMC 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 that was previously known or recognized in the protocol will be reported to the IRB and Research monitor via telephone or email within 24 hours 24 hours of discovery and a complete written report via eIRB will follow within 5 business days.

Expected adverse events 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.

Because this is a multi-center study, a summary of adverse events study-wide will be included with the CR.

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 will be promptly reported to the local IRB via telephone or email within 24 hours of discovery and a complete written report will follow within 5 working days. The investigator is required to make the determination whether the deviation meets the criteria for an unanticipated problem involving risks to subjects or others. The IRB Chair or IRB staff member shall also make the determination if the protocol deviation meets the definition of an unanticipated problem involving risks to participants or others. If the IRB Chair or IRB Staff member determines and documents that the deviation is an unanticipated problem involving risks to subjects or others or the deviation resulted from serious or continuing noncompliance, the IRB staff member shall place the deviation on the agenda of the next available IRB meeting for review. If the IRB Chair or IRB Staff member determines and documents that the deviation is not an unanticipated problem involving risks to subjects or others, the IRB Chair or staff member shall acknowledge the submission and complete the review through an administrative review procedure.

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 Section 10.1 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?

- [x] Drugs
- [ ] Dietary Supplements
- [ ] Biologics
- [ ] Devices
- [ ] N/A

18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:

- [ ] Are drug(s) in this research being used in accordance to the approved labeling?
- [x] Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

View Details	Drug Name	FDA Approved	A new drug or a new use of an already approved drug:	IND Number
⊟	**Trade Drug Name:** Botox **Generic Drug Name:** **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	Botox
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Allergan
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	N/A - please see section below for exemption rationale.
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	BotulinumtoxinA injections are already currently used in the sports medicine clinics at Fort Belvoir Community Hospital (FBCH) and the Uniformed Services University (USU) as well as in the Dept. of Physical Medicine & Rehabilitation (PM&R) at Walter Reed National Military Medical Center (WRNMMC) for the non-surgical treatment of CECS. Additionally, our use of BoNT-A in this study does not require an IND because it meets all of the required exemption criteria outlined by the FDA: 1) The drug we propose to use is currently lawfully marketed in the United States. 2) This study/investigation is not intended to be reported to the FDA as a well-controlled study. This study is also not intended to support neither a new indication of this drug nor a change to the current labeling of this drug. 3) This study does not intend to support a significant change in advertising for the drug. 4) Although this drug is not currently explicitly approved for the treatment of CECS, it is

	currently FDA approved for injection into extremity musculature for other medical conditions. We will be using this drug following a similar dosing guideline, using a similar route of administration, and in a population that it is already FDA approved for. Our intended procedures do not significantly increase the risks associated with the use of this drug. 5) This study will be conducted in compliance with the requirements for review by our IRB board. 6) This study is not intended to promote or commercialize this drug product.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	N/A
Dose Range:	50-100 units per limb
Frequency:	one time
Route of administration:	injection
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	N/A - the source is an FDA licensed facility
Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared:	The BoNT-A will be prepared by a trained physician or nurse. Four syringes using 25 units of BoNT-A and 1 mL of normal saline will be prepared per limb.
Indication(s) under Investigation:	BoNT-A (trade name BOTOX, generic name onabotulinumtoxinA) is currently FDA approved for injection into extremity musculature for other medical conditions (i. e. muscular hypertrophy/spasticity). We are investigating its usage for chronic exertional compartment syndrome.
Where will the drug be stored	Within a locked cabinet in a Dept. of Physical Medicine & Rehabilitation procedure room
Drug Storage Restrictions (including temperature, etc.):	Unopened vials of BoNT-A (trade name BOTOX, generic name (onabotulinumtoxinA) will be stored in a refrigerator set for 2°C to 8°C or 36°F to 46°F.
Administration Instructions:	Standard aseptic technique will be followed. Insertion of the correct compartment will be accomplished using ultrasound guidance. The anterior and lateral compartment will be separated into thirds measuring from the tibial plateau to the head of the calcaneus. Injections will be given at approximately 1/3 the distance from the tibial plateau for the proximal injection and 2/3 the distance from the tibial plateau for the distal injection. Injections will only be given to compartments that have elevated pressures. If the lateral compartment is affected, the peroneus longus and brevis muscles will receive 25 units proximally and 25 units distally, for a total of 50 units, of BoNT-A. If the anterior compartment is affected, a total of 50 units of BoNT-A will be given: 25 units at the proximal region and 25 units at the distal region.
Possible Untoward Effects, Their Symptoms & Treatment:	The potential side effects for BoNT-A (trade name BOTOX, generic name onobotulinumtoxinA) include: rare minor side effects of bleeding, pain, infection, transient general muscle weakness and muscular atrophy, flu-like symptoms, and even rarer transient breathing and swallowing difficulties which has the potential to cause death if not appropriately treated.

Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	Potential excessive BoNT-A (trade name BOTOX, generic name onobotulinumtoxinA) drug effect may produce neuromuscular weakness with a range of symptoms and should be medically treated immediately and may require hospitalization. In the event of an overdose, an antitoxin is available through contact with the local and state health departments to the CDC. The antitoxin will not reverse any effects that have occurred prior to the antitoxin administration.
Contraindications and Interactions, If Known:	Individuals who have known hypersensitivity to BoNT-A (trade name BOTOX, generic name onobotulinumtoxinA) or its ingredients/components and individuals that have a presence of infection at the site of injection.
Investigators Authorized to Prescribe:	Dr. Jeffrey Leggit

⊟	**Trade Drug Name:** Xeomin **Generic Drug Name:** **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	Xeomin
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Merz Pharmaceuticals
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	N/A - please see section below for exemption rationale.
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	botulinumtoxinA injections are already currently used in the sports medicine clinics at Fort Belvoir Community Hospital (FBCH) and the Uniformed Services University (USU) as well as in the Dept. of Physical Medicine & Rehabilitation (PM&R) at Walter Reed National Military Medical Center (WRNMMC) for the non-surgical treatment of CECS. Additionally, our use of BoNT-A in this study does not require an IND because it meets all of the required exemption criteria outlined by the FDA: 1) The drug we propose to use is currently lawfully marketed in the United States. 2) This study/investigation is not intended to be reported to the FDA as a well-controlled study. This study is also not intended to support neither a new indication of this drug nor a change to the current labeling of this drug. 3) This study does not intend to support a significant change in advertising for the drug. 4) Although this drug is not currently explicitly approved for the treatment of CECS, it is currently FDA approved for injection into extremity musculature for other medical conditions. We will be using this drug following a similar dosing guideline, using a similar route of administration, and in a population that it is already FDA approved for. Our intended procedures do not significantly increase the risks associated with the use of

	this drug. 5) This study will be conducted in compliance with the requirements for review by our IRB board. 6) This study is not intended to promote or commercialize this drug product.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	N/A
Dose Range:	50-100 units per limb
Frequency:	One time
Route of administration:	Injection
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	N/A - the source is an FDA licensed facility
Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared:	The BoNT-A will be prepared by a trained physician or nurse. Four syringes using 25 units of BoNT-A and 1 mL of normal saline will be prepared per limb.
Indication(s) under Investigation:	BoNT-A (trade name Xeomin, generic name incobotulinumtoxinA) is currently FDA approved for injection into extremity musculature for other medical conditions (i.e. muscular hypertrophy/spasticity). We are investigating its usage for chronic exertional compartment syndrome.
Where will the drug be stored	Within a locked cabinet in a Dept. of Physical Medicine & Rehabilitation procedure room
Drug Storage Restrictions (including temperature, etc.):	Unopened vials of BoNT-A (trade name Xeomin, generic name incobotulinumtoxinA) will be stored at room temperature 20°C to 25°C (68°F to 77°F).
Administration Instructions:	Standard aseptic technique will be followed. Insertion of the correct compartment will be accomplished using ultrasound guidance. The anterior and lateral compartment will be separated into thirds measuring from the tibial plateau to the head of the calcaneus. Injections will be given at approximately 1/3 the distance from the tibial plateau for the proximal injection and 2/3 the distance from the tibial plateau for the distal injection. Injections will only be given to compartments that have elevated pressures. If the lateral compartment is affected, the peroneus longus and brevis muscles will receive 25 units proximally and 25 units distally, for a total of 50 units, of BoNT-A. If the anterior compartment is affected, a total of 50 units of BoNT-A will be given: 25 units at the proximal region and 25 units at the distal region.
Possible Untoward Effects, Their Symptoms & Treatment:	The potential side effects for BoNT-A (trade name Xeomin, generic name incobotulinumtoxinA) include: rare minor side effects of bleeding, pain, infection, transient general muscle weakness and muscular atrophy, flu-like symptoms, and even rarer transient breathing and swallowing difficulties which has the potential to cause death if not appropriately treated.
Potential or Actual Antidotes for Excessive or Adverse Drug	Potential excessive BoNT-A (trade name Xeomin, generic name incobotulinumtoxinA) drug effect may produce neuromuscular weakness with a range of symptoms and should be medically treated immediately and may require hospitalization. In the event of an overdose, an antitoxin is

Effect:	available through contact with the local and state health departments to the CDC. The antitoxin will not reverse any effects that have occurred prior to the antitoxin administration.
Contraindications and Interactions, If Known:	Individuals who have known hypersensitivity to BoNT-A (trade name Xeomin, generic name incobotulinumtoxinA) or its ingredients/components and individuals that have a presence of infection at the site of injection.
Investigators Authorized to Prescribe:	Dr. Jeffrey Leggit

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

N/A

BotulinumtoxinA injections are already currently used in the sports medicine clinics at Fort Belvoir Community Hospital (FBCH) and the Uniformed Services University (USU) as well as in the Dept. of Physical Medicine & Rehabilitation (PM&R) at Walter Reed National Military Medical Center (WRNMMC) for the non-surgical treatment of CECS.

Additionally, our use of BoNT-A in this study does not require an IND because it meets all of the required exemption criteria outlined by the FDA:

1. The drug we propose to use is currently lawfully marketed in the United States.
2. This study/investigation is not intended to be reported to the FDA as a well-controlled study. This study is also not intended to support neither a new indication of this drug nor a change to the current labeling of this drug.
3. This study does not intend to support a significant change in advertising for the drug.
4. Although this drug is not currently explicitly approved for the treatment of CECS, it is currently FDA approved for injection into extremity musculature for other medical conditions. We will be using this drug following a similar dosing guideline, using a similar route of administration, and in a population that it is already FDA approved for. Our intended procedures do not significantly increase the risks associated with the use of this drug.
5. This study will be conducted in compliance with the requirements for review by our IRB board.
6. This study is not intended to promote or commercialize this drug product.

18.5 Sponsor (organization/institution/company):

☐ N/A

If applicable, provide sponsor contact information:

Jeffrey C. Leggit, MD, CAQSM
Walter Reed National Military Medical Center
Uniformed Services University
(301) 295-9460
jeff.leggit@usuhs.edu

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

○ Registration is not required
○ Registration pending

◉ Registration complete

"NCT" number:

NCT04409600

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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2. Baria, M. R., and J. L. Sellon. "Botulinum Toxin for Chronic Exertional Compartment Syndrome." *Clinical Journal of Sport Medicine* (2016): 1.
3. Diebal AR, Gregory R, Alitz C, Gerber JP. Forefoot Running Improves Pain and Disability Associated with Chronic Exertional Compartment Syndrome. *The American Journal of Sports Medicine* 40.5 (2012):1060-1067.
4. Dunn, J. C., and B. R. Waterman. "Chronic Exertional Compartment Syndrome of the Leg in the Military." *Clinics in Sports Medicine* 33.4 (2014): 693-705.
5. Campano, D., J. A. Robaina, N. Kusnezov, J. C. Dunn, and B. R. Waterman. "Surgical Management for Chronic Exertional Compartment Syndrome of the Leg: A Systematic Review of the Literature." *Arthroscopy: The Journal of Arthroscopic & Related Surgery* 32.7 (2016): 1478-486.
6. Waterman, B., et al. "Surgical Treatment of Chronic Exertional Compartment Syndrome of the Leg." *The Journal of Bone and Joint Surgery*, 95.7 (2013): 592-596.
7. Schepsis, A. A., D. Martini, and M. Corbett. "Surgical Management of Exertional Compartment Syndrome of the Lower Leg: Long-term Followup." *The American Journal of Sports Medicine* 21.6 (1993): 811-17.
8. Slimmon, D., K. Bennell, P. Brukner, K. Crossley, and S. N. Bell. "Long-Term Outcome of Fasciotomy with Partial Fasciectomy for Chronic Exertional Compartment Syndrome of the Lower Leg." *American Journal of Sports Medicine* 30.4 (2002): 581-88.
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11. Aweid, O., A. Del Buono, P. Malliaras, H. Iqbal, D. Morrissey, N. Maffulli, and N. Padhiar. "Systematic Review and Recommendations for Intracompartmental Pressure Monitoring in Diagnosing Chronic Exertional Compartment Syndrome of the Leg." *Clinical Journal of Sport Medicine* 22.4 (2012): 356-70.
12. Pedowitz, R. A., A. R. Hargens, S. J. Mubarak, and D. H. Gershuni. "Modified Criteria for the Objective Diagnosis of Chronic Compartment Syndrome of the Leg." *The American Journal of Sports Medicine* 18.1 (1990): 35-40.

20.2 Abbreviations and Acronyms:

ABI - Ankle brachial index
AE - Adverse Events
AHLTA - Armed Forces Health Longitudinal Technology Application

ALS - Amyotrophic lateral sclerosis
ATAMMC - Alexander T. Augusta Military Medical Center
BESS - Balance Error Scoring System
BMI - Body Mass Index
BoNT-A - botulinumtoxin A
Borg - Perceived exertion tolerance
CECS - Chronic Exertional Compartment Syndrome
CMIRR - Collaboratory for Musculoskeletal Injury Rehabilitation Research
CRDAMC - Carl R. Darnall Army Medical Center
CRF - Case Report Form
DEERS - Defense Enrollment Eligibility Reporting System
DHA - Defense Health Agency
DoD - Department of Defense
DPT - Department of Physical Therapy
FBCH - Fort Belvoir Community Hospital
FDA - Food and Drug Administration
GROC - Global Rate of Change
HBGR - Home Based Gait Retraining
hCG - Human chorionic gonadotropin
HIPAA - Health Insurance Portability and Accountability Act
HPA - Human Protections Administrator
IMCP - Intramuscular Compartment Pressure
IRB - Institutional Review Board
ITT - Intention-to-treat
JPC - Joint Program Committees
MAMC - Madigan Army Medical Center
MHS - Military Health System
MIRROR - Musculoskeletal Injury Rehabilitation Research for Operational Readiness
MOS - Military Occupational Specialty
MRI - Magnetic Resonance Imaging
MSI - Musculoskeletal injury
MTF - Military Treatment Facility
OCIO - Office of the Chief Information Officer
PHI - Protected health information
PII - Personally identifiable information
PM&R - Physical Medicine & Rehabilitation
PPE - Personal protective equipment
PSFS - Patient Specific Functional Scale
PT - Physical Therapy
REDCap - Research Electronic Data Capture
ROM - Range of motion
SAE - Serious Adverse Events
SAFE - Secure access file exchange
SANE - Single Assessment Numerical Evaluation
SGR - Supervised Gait Retraining
SSL - Secure Sockets Layer
TLS- Transport Layer Security
UPIRTSO - Unanticipated Problems Involving Risks to Subjects or Others
USU - Uniformed Services University
USUHS - Uniformed Services University of the Health Sciences
USU IT - Uniformed Services University Information Technology
UWRI - University of Wisconsin Running Injury and Recovery Index
WAMC - Womack Army Medical Center
WRNMMC - Walter Reed National Military Medical Center