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Botulinum for Chronic Exertional Compartment Syndrome

PROTOCOL FOR NON-EXEMPT RESEARCH INVOLVING HUMAN SUBJECTS

Title:	Comparison of Botulinum Toxin to Fasciotomy in Treatment of Chronic Exertional Compartment Syndrome
IRB #:	FWH20170037H

Principal Investigator (PI)	Rank / Civ Rating	Branch	AD/DoD Civ/ Ctr/Civilian	Dept/Base	Phone #	E-mail
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The research relevance of this protocol focuses on:					
☐	**Diagnosis**	☑	**Treatment**	☐	**Medical Utilization/Managed Care**
☐	**Prevention**	☐	**Medical Readiness**	☐	**Other:**

FOR 59 MDW PERSONNEL ONLY			
CONFLICTS OF INTEREST:	**Do you or any of your research staff have a potential conflict of interest to disclose?** If unsure, read the below statement before proceeding.	☐ Yes	☑ No
If you answer YES above, you must complete the *59 MDW Form 14 – Financial Conflict of Interest Disclosure* for each individual reporting a conflict and send it via **encrypted** email to the COI Manager for an official determination **BEFORE PROCEEDING** with this protocol application. The 59th Medical Wing Conflict of Interest Office can assist you with any questions you may have regarding conflicts of interest and the COI disclosure process. Contact the COI Manager with questions or for additional guidance at: 210-292-5885 or 59mdw.st.hrpp@us.af.mil.			

Does the research fall under the purview of any other departments or committees?	**Yes**	**No**
Radiation Safety Committee		☑
Institutional Biosafety Committee or Biosafety Officer		☑
AFMSA Officer of Research and Technology Applications (ORTA)		☑
59 MDW/SGARB Resource Management Office		☑

1. LOCATION AND SPONSOR

Collaborating Facilities: N/A
AF Sites Seeking Regional IRB:
Scott AFB Family Medicine Clinic, at 3 St. Elizabeth's Blvd, Suite 4000, O'Fallon IL 62269/ Trevor Brue, DO (512) 508-4094
Study Sponsors: N/A

2. RESEARCH PLAN

Purpose of Study:
Chronic exertional compartment syndrome (CECS) is a debilitating condition that causes elevation in compartment pressure, which can restrict patients from work and exercise. Typical treatment is to relieve compartment pressure though surgery. While surgery is effective for 66% of patients, it comes with increased risk and typically takes at least 8-13 weeks for full return to activity. One unproven alternative for pain relief is the use of botulinum toxin, a paralyzing agent. Botulinum toxin injections into the affected area in the lower extremities have been shown in limited trials to be a potentially cost effective way to relieve pain and return patients to full activity faster. Therefore, we will investigate the feasibility of a simple outpatient one time injection regimen for the treatment of CECS. We think botulinum toxin injections will be a potentially cost-effective, low-risk alternative to surgery in reducing pain and returning patients to full activity.
Hypotheses, Research Questions, or Objectives:

In adult military patients with confirmed CECS by intramuscular pressure (IMP) needle measurements, botulinum toxin injections may be a non-inferior effective alternative to surgical fasciotomy in reduction of pain and ability to return to full activity. Therefore, the goals of this project are 1) To determine the long term efficacy of botulinum toxin injections in CECS. 2) Compared with current data and previous studies, is botulinum toxin injections non-inferior to current treatment regimens for overall pain control and return to full activity.

Significance:

Currently, the only definitive treatment option for CECS is surgical fasciotomy. A simple outpatient procedure would save time, money, and potentially decrease recovery time and improve quality of life. An injection in place of surgery would also limit the chances of surgical complications and need for repeat surgical interventions.

Military Relevance:

CECS comes at significant cost to the military in terms of medical rehabilitation, surgery, and time lost. Additionally, those suffering from CECS are often non-deployable and unable to fully participate in all necessary activities, thus requiring waivers to be retained in the military. By finding a cost effective alternative to fasciotomy, with limited side effects, we hope to bring treatment costs of CECS down and to also allow soldiers to return to full activity faster and without restriction.

Background and Review of Literature:

The long term objective of this project is to validate botulinum toxin injections as a non-inferior treatment option for pain control and ability to return to full activity for adult military members suffering from lower extremity Chronic Exertional Compartment Syndrome (CECS), when compared to surgical fasciotomy.[1,2] CECS is a debilitating disorder in which pressure in muscle compartments increases with exercise and resolves with rest. This causes pain, paresthesia, and inability to tolerate exercise. CECS mainly afflicts the lower extremities, below the knee, but upper extremity CECS has also been reported. CECS mainly affects young active adults. At risk groups include males, active duty military members, and athletes, both professional and recreational.[1,3,4,5]

The current standard for definitive management and treatment of CECS is surgical fasciotomy. 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. Definition of success varied across studies, but included patient satisfaction, lack of surgical revision, and full return to activity.[4] Besides risks and complications, surgery also required a mean of 13 weeks to return to full activity when effective.[5,6,,7] A 2011 Cohort showed 81% overall patient satisfaction with the procedure, but noted best results from fasciotomy were young participants <23 years old, who underwent isolated anterior compartment release. Satisfaction was defined as being pain free or significantly improved on a 5 point pain scale, varying from pain free to worse.[8] A smaller 2014 retrospective chart review of elite athletes with CECS showed fasciotomy was initially successful in 85% with a mean return to elite activity of 10.4 weeks. However, 30.8 % had a return of symptoms within the follow-up period.[9]

Likewise, conservative treatment options yield mixed results. A systematic review in May of 2016 showed massage, gait changes, chemodenervation, and ultrasound-guided (USG) fascial fenestration had few adverse effects, but long term results and efficacy were unknown and unverified.[10] Another newer therapy, minimal incision fasciotomy was effective for returning patients to previous level activity in 94% of patients after 36 months follow up in a prospective trial. Though improved final outcome from regular surgical intervention, average return to activity and return to sport was 8 and 13 weeks respectively. [11]

Military personnel comprise a specific patient population for whom outcomes and return to full duty is important for continued service and deployment. A 2014 military cohort found women, junior enlisted service members, and the Army soldier experienced the highest incidence of CECS. There was also an association between increasing age and CECS incidence. The study also found 78% of patients were free from medical discharge or revision after surgery at short-term to mid-term follow-up. However, 28% of service members were unable to return to full duty and 45% experienced incomplete relief of symptoms. In a similar United Kingdom military study, only 47% of subjects' symptoms improved after surgery.[3] Additionally, a 2014 retrospective review of one United States tertiary military facility showed a return to full military duty in only 41% of patients who underwent elective fasciotomy for CECS. In that study, 78% of patients remained in the military and 71% reported satisfaction with the operative outcome.[12]

Treatment of CECS with botulinum toxin injections has shown effective and long term relief in initial studies. An initial case series; from November 2013; showed that a single series of injections at the proximal and distal end of the affected muscle was effective in relieving pain and decreasing intramuscular pressure up to the 9 months of follow up in 94% of patients. Sixty-nine percent of those participants did have a decrease in strength, which did not affect overall motor function with treatment, but no other adverse effects.[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] However; current studies regarding dosage and long term recovery are limited. This study aims to further investigate effectiveness of dose dependent botulinum toxin injections to relieve pain and discomfort of CECS, time to return to full activity, long term effects of this intervention, and prevention of surgical fasciotomy.

Bibliography:

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10. Irion, Val, R. A. Magnussen, T. L. Miller, and C. C. Kaeding. "Return to Activity following Fasciotomy for Chronic Exertional Compartment Syndrome." *Eur J Orthop Surg Traumatol European Journal of Orthopaedic Surgery & Traumatology* 24.7 (2014): 1223-228.
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3. RESEARCH DESIGN AND METHODS

Research Design and Methods:

The study will be a prospective cohort pilot study designed to compare Active Duty patients, 18 years of age or older, with CECS undergoing two different treatment interventions. The first arm will be patients receiving investigational botulinum toxin injections. The second arm will be patients who undergo the standard of care surgical fasciotomy. Both arms will be evaluated for pain relief with the universal pain scale and lower extremity functional index (LEFI) surveys at pre-treatment and again at one, three, and six months post-treatment. At the six month follow up, subjects will be asked the Satisfaction Survey (in-person, via Survey Monkey or Google Forms). Clinical data that will be analyzed for research purposes in both groups include age, sex, height, weight, body mass index, time to diagnosis, minutes of exercise prior to onset of symptoms, minutes of rest before relief of symptoms, LEFI and pain on the Universal Pain Assessment Tool.

In addition, we will be conducting a retrospective review from July 1, 2016 through June 30, 2017 of patients who have been diagnosed with CECS and have undergone surgical fasciotomy. They will be asked to recall their symptoms both before and six months after their surgery, in order to complete the LEFI and Universal Pain Assessment Tool (in-person, via Survey Monkey or Google Forms). They will also be asked if they were satisfied with their treatment. A HIPAA Waiver Request will be used to access medical records and contact these individuals, followed by each subject being verbally consented to participate in the study prior to completing the LEFI and universal pain scale surveys (in-person, via Survey Monkey or Google Forms). If the subjects refuse to be consented, then no data will be gathered from the subjects or their medical records.

a. Interventions and Observations:

If CECS is diagnosed by intramuscular pressure (IMP) elevation, patients will be offered Botulinum toxin injection regimen into the affected compartment or referral to orthopedic surgeon for a possible surgical fasciotomy. Patients will be provided information regarding both Botulinum toxin injections and fasciotomy. Patients will be allowed to discuss fasciotomy with a surgeon prior to making a decision to participate in the study, if desired. Potential side effects of Botulinum toxin injection include possible bleeding, pain, infection, general muscle weakness, muscular atrophy, flu-like symptoms, breathing and swallowing difficulties and death. Potential side effects of fasciotomy include surgical site pain, bleeding, recurrence of symptoms, scarring, muscle weakness, nerve damage, hematoma, need for repeat operation, infection, reactions to anesthesia (e.g. anaphylaxis), blood clot, muscle wasting (atrophy), and death. These will be explained to participants during the consent discussion.

For those diagnosed with CECS and desire Botulinum toxin injections, they will receive 2 injections per affected compartment. Up to 50 units of Botulinum toxin will be injected into the proximal and distal portions of the compartment for a maximum total dose of 100 units.[1,2] A solution of 100 units of Botulinum toxin per 2 mL of normal saline will be used for all injections. Standard sterile technique will be followed. Insertion in to the correct compartment will be accomplished using general landmarks. The 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. If the lateral or deep posterior compartment is affected, a total of 50 units Botulinum toxin will be given, 25 units per injection. If the anterior or superficial posterior compartment is affected, a total of 100 units Botulinum toxin will be given, 50 units per injection. Of note, CECS mainly affects the anterior and lateral compartments and is rarely seen in the superficial posterior or deep posterior areas.

For those diagnosed with CECS and desire surgical fasciotomy, the team will discuss the fasciotomy procedure and risks as mentioned above. For the procedure, the patient will be placed under general anesthesia and then linear incisions will be made into the affected compartment releasing the underlying fascial layer, reducing the pressure of the compartment. The entire procedure will be accomplished in a sterile fashion. Further details and scheduling will be per the orthopedic surgeon's recommendations.

After the initial Botulinum toxin injection regimen or fasciotomy, patients will be assessed at 1 month, 3 months, and 6 months with the LEFI and universal pain scale. Primary outcome will be pain reduction. Adequate pain reduction will be rated as less than 3 on the universal pain scale. Secondary outcomes will include return to full activity and patient satisfaction. Full activity is defined as able to run 1.5 miles and complete work duties with either no pain or pain that can be ignored. To assess patient satisfaction, patients will be asked if they were or were not satisfied with the Botulinum toxin injections at the 6 month visit.

b. Setting:

The study will be carried out in the 375 MDOS outpatient O'Fallon Family Medicine Residency Clinic located at 3 St. Elizabeth's Blvd, Suite 4000, O'Fallon, ILThe clinic is also part of a family medicine residency program. All counseling, injections, and follow-up will be done in the family medicine clinic. All standard of care tests for pre-screening of subjects will be performed at the Scott Air Force Base medical group radiology and laboratory facilities. These tests include blood tests, X-rays, physical exam and intramuscular compartment pressure readings.

c. Date(s):

For the prospective portion of the study for patients receiving Botulinum toxin injections, expected timeframe for data collection is April 2017 through April 2020.

For the retrospective portion of the study, we will review medical results and pain assessments from patients who had a surgical fasciotomy during the time period of July 1, 2016 through June 30, 2017.

d. Subjects:

Patients will be active duty military adults, 18 years of age or older, who have clinical signs and symptoms of chronic exertional compartment syndrome in any muscular compartment of the lower leg. All patients referred to the sports medicine clinic for leg pain will be screened for possible inclusion into the study, following standard of care clinical tests. After an initial standard of care evaluation, if CECS is suspected, each subject will be asked to participate in the study and will be formally consented by a member of the research team.

Other exertional causes of leg pain will be ruled out by a standard of care clinical examination (general, orthopedic, neurologic, and functional) and supporting workup. This will include plain radiographs of the knee, tibia, fibula, and ankle on the affected side of the lower extremity. Any patient with an abnormal finding not consistent with CECS, such as a stress fracture, will be ruled out from participating in the research study. Patients will have tried conservative treatment for at least 2 months prior to compartment testing to include rest, stretching, ice, and NSAIDs. All patients reporting lower extremity pain will be examined by a physician on the study team to confirm CECS under the direct supervision of Dr. Brue.

Intramuscular pressure in lower leg compartments will be obtained by IMP needle insertion (standard of care) into all four compartments of both lower legs before and after exercise. Infection risk will be decreased by sterilizing the puncture site with chlorhexidine swabs. Pain will be decreased by injecting 0.5 mL of 1% lidocaine with epinephrine superficially to anesthetize the skin. Pressure will be transmitted to a pressure transducer for measurement in mm Hg. The exercise portion will be standardized by having patients run on the same treadmill with enough speed until their symptoms begin. After symptoms begin, the patient will be asked to continue running until he or she cannot tolerate, at which time the exercise will be stopped and the patient will lie supine for repeat intramuscular pressure measurements. Definitive diagnosis of CECS will be based on intramuscular pressure elevations according to Pedowitz et al. This includes 1) a pre-exercise pressure greater than or equal to 15 mm Hg and 2) a 1-5 minute post-exercise pressure of greater than or equal to 30 mm HG.[13, 14]

e. Inclusion/Exclusion Criteria:

Inclusion Criteria	• Adult ages 18-65 • Active duty military • Unable to run 1.5 miles without producing symptoms, including aching, burning, numbness, tingling, or weakness in the affected limb • Failed conservative treatment over a period of 2 months, including trial of rest, NSAIDs, icing, and stretching routine • Meets standard of care clinical diagnostic intramuscular compartment pressure criteria for CECS, based on standardized IMP needle testing. See below for testing protocol and criteria.
Exclusion Criteria	• Prior Botulinum toxin injections into the affected limb • Prior compartment release of the affected limb • Pregnant or becomes pregnant during the study • Standard of care clinical exams indicating other more likely causes of leg pain

f. Source of Research Material:

Will you be using <u>private information</u> in this study?		☐ No – Only using publically available information ☑ Yes –
If Yes,	☑ protected health information (PHI) held by a covered entity	
	☐ other types of private information	Describe:
	☐ research information (non-PHI) that is not publically available (i.e., student records)	Describe:

Use of <u>identifiers</u> with private information

Identifiers to be Used?	**Column A** Looked at by research team	**Column B** Recorded on enrollment log, subject list, or key list	**Column C** Recorded on data collection tool (survey, spreadsheet, etc.)	**Column D** Recorded on specimen containers	**Column E** Shared w/ others not on research team	**Column F** Stored after study ended

NONE	☐	☐	☐	☐	☐	☐
Names	☑	☑	☑	☐	☐	☐
Study codes linked to individuals' identities using a key only accessible by the researcher		☐	☐	☐	☐	☐
Addresses	☐	☐	☐	☐	☐	☐
Dates (except year)	☑	☑	☑	☐	☐	☐
Ages over 89	☐	☐	☐	☐	☐	☐
Phone/Fax Numbers	☑	☑	☑	☐	☐	☐
E-mails	☐	☐	☐	☐	☐	☐
- SSNs - Scrambled SSNs - last four of SSN	☑ Specify: Last 4 SSN	☑ Specify: Last 4 SSN	☑ Specify: Last 4 SSN	☐ Specify:	☐ Specify:	☐ Specify:
Numbers: - Medical record # - Account # - Certificate/license # - Health plan beneficiary # - Vehicle identifier/serial # - License plate # - Device identifier/serial #	☑ Specify: Medical record #	☑ Specify: Medical record #	☑ Specify: Medical Record #	☐ Specify:	☐ Specify:	☐ Specify:
Web URLs or IP addresses	☐	☐	☐	☐	☐	☐
- Biometric Identifiers, including finger/voice prints - Full-face photo images and comparable images	☐ Specify:	☐ Specify:	☐ Specify:	☐ Specify:	☐ Specify:	☐ Specify:
Any other pre-existing unique identifying number, characteristic, or code	☐	☐	☐	☐	☐	☐

Coding Plan?	
☐ Not applicable, no identifiable information will be collected	
Describe the method that will be used to create and assign unique study codes to data.	Patients will be identified using their initials and last four of their SSN.
Describe the method that will be used to create and assign unique study codes to specimens.	☑ N/A, not collecting specimens Describe:
What is the format of the key?	☐ Paper ☑ Electronic
Who will have access to the key?	Only principal investigators
Where will the key be stored and how will it be protected?	Location(s): The key will be stored in principal investigator's locked office in a locked drawer. Confidentiality measures: All electronic information will be stored on a secure network with a double password protected document
Complete the table.	

Source of Research Material per Participant (Procedures)	# Routine Care	# Research Driven	# Total Procedures
X-rays, blood samples	1	0	1
Intramuscular compartment pressure readings	1	0	1
Lower extremity functional index	1	3	4
Universal Pain Scale	1	3	4
Satisfaction survey	0	1	1
Urine Pregnancy Test	0	1	1

g. Instrumentation:

The Stryker Intra-compartmental pressure monitor will be used for the standard of care diagnosis of compartment syndrome.

4. HUMAN SUBJECT PROTECTION

Recruitment and Consent Processes:

All patients referred to the sports medicine clinic for leg pain will be screened for possible inclusion into the study, following standard of care clinical tests. After an initial standard of care evaluation, if CECS is suspected, each subject will be tested for compartment syndrome using standard of care clinical tests. If they are diagnosed with CECS, they will be asked to participate in the study and will be formally consented by a member of the research team.

Other exertional causes of leg pain will be ruled out by a standard of care clinical examination (general, orthopedic, neurologic, and functional) and supporting workup. These tests will include plain radiographs of the knee, tibia, fibula, and ankle on the affected side of the lower extremity. Any patient with an abnormal finding not consistent with CECS, such as stress fracture, will be ruled out from participating in the research study. Patients will have tried conservative treatment for at least 2 months prior to compartment testing to include rest, stretching, ice, and NSAIDs. All patients reporting lower extremity pain will be examined by one of the study physicians to confirm CECS, under direct supervision of Dr. Brue.

Consent Processes:

How will you consent subjects to participate in the research?	X	Will obtain consent **without a signature**	☑ Telephone	*Submit Form F – HIPAA and Consent Waiver and Alteration Form.*
			Is the information collected for the study health information?	☑ Yes, *submit Form F – HIPAA and Consent Waiver and Alteration Form.*
	X	Will **exclude** some of the required elements of consent in the consent form, information sheet, or consent process		*Submit Form F – HIPAA and Consent Waiver and Alteration Form.*

Prospective Subjects: Informed Consent and HIPAA Authorization will be sought in advance from each prospective subject and appropriately documented in accordance with 32 CFR 219.117. Potential subjects will be notified about the study either through posted advertisements or by their primary care provider. Investigators will provide a written copy of the Informed Consent (ICD) and HIPAA Authorization (HIPAA) to the subject. The subject may decline to participate without prejudice. At the subject's discretion, they may take the ICD and HIPAA home to discuss further prior to making a decision. If the subject consents, a copy of the ICD and HIPAA will be given to them. No vulnerable populations are included in this research study. Subjects who cannot provide ICD and HIPAA will not be allowed to patriciate. No Legally Authorized Representatives will be utilized. Some patients may be patients of the PI or AI, however, they will have the study staff recruit their patients to prevent any misconception of coercion or undue influence.

Retrospective Subjects: Each subject will be verbally consented over the phone using the Telephone Consent prior to being asked any questions. The subject may decline to participate without prejudice. An approved HIPAA waiver is being utilized.

Recruiting Service Members	Will you be recruiting service members in a group setting?	☐ Yes	☑ No

Participation Compensation:

☑	Subjects will not be paid for participation in this study.

Assent Process: N/A

Benefits:

Potential benefits will be a relief of symptoms, avoidance of surgery, and return to full activity in the military setting.

Risks:

Procedural risks for an IMP needle insertion for intramuscular pressure testing may include pain, bleeding, and infection. There is a potential for no relief of CECS symptoms with either treatment intervention. Potential side effects of Botulinum toxin injections include possible pain, bleeding, infection, general muscle weakness, muscular atrophy, flu-like symptoms, breathing and swallowing difficulties and death. Potential side effects of fasciotomy include surgical site pain, bleeding, recurrence of symptoms, scarring, muscle weakness, nerve damage, hematoma, need for repeat operation, infection, reactions to anesthesia (e.g. anaphylaxis), blood clot, muscle wasting (atrophy), and death.

Costs: N/A

Safeguards for Protecting Information:

The research consents will be stored in a locked cabinet in a locked room. Medical records will be annotated with ICD-10 code Z00.6 to reflect the subject's participation in a research study. All research data including patient demographics will be kept in an electronic database, which will be encrypted, double password protected and the access will be restricted. The research data will be coded and any links to identifiable data will be destroyed as soon as the Final Report Approval has been obtained from the IRB.

Data and Specimen Storage Plan

How will coded or identifiable data/specimens be stored?		
X	Paper data, including completed consent forms	The research data will be coded to mask the identity of the individual. They will be kept in a locked cabinet in a locked office.
X	Electronic data	All research data will be kept in an electronic database, which will be encrypted, double password protected and the access will be restricted.
X	SSNs, Scrambled SSNs, or last four of SSNs	
X	Long-term storage (following completion of the study and inactivation of IRB approval)	Once a Final Report has been approved by the IRB, all patient identifiers will be removed. The anonymized research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval. The de-identified subject data, signed ICD and HIPAA documents, and the Regulatory Binder will be housed 3 years after the final report has been approved by the IRB.

Safeguards for Protecting Subjects Relative to Reasonably Expected Risks:

The subjects are not expected to experience any physical discomfort, psychological distress, or long term significant behavioral effects from their PHI being included in this study. The risk of invasion of private information is minimal as few identifiers will be used and will be protected, and any PHI will only be viewed by the investigators. Additionally, the data would not embarrass or disadvantage the participants if confidentiality were violated.

Categories of subjects: None

Clinical Care:

All subjects will receive standard care for any illness or disease found during the course of this study. At no time will this study preclude them from receiving any treatment for diseases related or unrelated to the study.

Injury Compensation: N/A

Data Safety Monitoring	☑ N/A – none of the situations listed above apply

5. ALTERNATIVES

Alternatives:
Alternatives to participation in the study are continued conservative management to include rest, stretching, icing, and anti-inflammatory medications. Other options are to proceed with standard of care surgical fasciotomy or to do nothing.

6. DATA ANALYSIS

Data Analysis:
Head-to-head comparison of patients undergoing or who have undergone standard of care surgical fasciotomy and investigational Botulinum toxin injections will be analyzed. Measures addressed will be pain severity, return to full activity, Lower Extremity Function index, and patient satisfaction over the course of pre-treatment, post-treatment, and 1, 3, 6 month follow-up visits. A power analysis, shown below, was completed for this pilot study. Assuming equal sample sizes of groups, 2-tail alpha of .05, power=.8, and 67% of fasciotomy group will have no pain (i.e. pain < 3).[4] 1. 75% of injection group, no pain - n=1008 total 2. 80% of injection group, no pain - n=360 total 3. 85% of injection group, no pain - n=176 total 4. 90% of injection group, no pain - n=98 total 5. 95% of injection group, no pain - n=60 total As CECS is an infrequent diagnosis, this pilot study will have difficulty over the course of the year to obtain enough sample size for statistical significance. However, the hope is to obtain a promising trend and eventually expand the study to obtain significance pending initial results.

Outcome Measures:
For the prospective portion of the study, the primary outcome will be pain reduction from either a standard of care surgical fasciotomy or an investigational Botulinum toxin treatment regimen. Adequate pain reduction will be rated as less than 3 on the universal pain scale. Secondary outcomes will include return to full activity and patient satisfaction. Full activity is defined as being able to run 1.5 miles and complete work duties with either no pain or pain that can be ignored. To assess patient satisfaction, patients will be asked if they were or were not satisfied with their surgical fasciotomy or their Botulinum toxin injections during their 6 month follow-up visit. For the retrospective portion of the study, the same measures will be addressed for subjects who have undergone a standard of care surgical fasciotomy, but only on a pre- and post-treatment basis.

Sample Size Estimation/Power Analysis:
The expected sample size for the prospective portion of the study is 15. The expected sample size for the retrospective review is 10.

Statistical Analysis:
The primary measure to be analyzed will be comparing pre- and post-treatment pain for each of the two treatment regimens using the universal pain scale. Additionally, participants will be evaluated for return to duty, overall patient satisfaction, and the Lower Extremity Functional Index will be compared pre- and post-treatment. The study team will complete the statistical analysis.

Number of Subjects:				
	# Planned to Enroll	# Enrolled	# Planned to Complete Study	TOTAL

Number of Subjects at Scott AFB	15	0	15	15

Number of Data Records Entered into the Study:				
	# Planned to Enroll	# Enrolled	# Planned to Complete Study	TOTAL
Number of Subjects at Scott AFB	10	0	10	10

7. STUDY DURATION

Duration of Study:
Approximate duration of the study: 2 years

8. LOCAL AND EXTERNAL SUPPORT SERVICES

Describe the plan for training personnel who are not part of the research team and will be administering intervention(s).	☑ Not applicable – no training of non-study personnel required

9. INTRAMURAL (GME) AND EXTRAMURAL FUNDING SUPPORT

Intramural (GME) and Extramural Funding Support: None

10. DRUGS, BIOLOGICS, DIETARY SUPPLEMENTS, AND MEDICAL DEVICES

Does the study plan dictate the use of any of the following?		
A drug	☑ Yes	☐ No
A biologic	☐ Yes	☑ No
A compound intended to affect structure or any function of the body	☐ Yes	☑ No
A dietary supplement or substance *generally recognized as safe* that will be used to diagnose, cure, mitigate, treat, or prevent disease	☐ Yes	☑ No
A medical device	☐ Yes	☑ No

10A. List all drugs covered by an **Investigational New Drug (IND)** from the **FDA** (approved or submitted)				
Name of Drug	**Dose(s) directed by protocol**	**Route(s) of administration**	**IND Number or Date Submitted**	**IND Holder (Sponsor)**
Botulinum Toxin	50-100u	IM	134278/Exempted	

10B. List all **FDA approved drugs** being **used in accordance with FDA approved labeling**		
Name of Drug	**Dose(s) directed by protocol**	**Route(s) of administration**
☑ N/A, no FDA approved drugs being used according to the labeling		

10C. List all **FDA approved drugs used for an unapproved use ("off-label")**		
Name of Drug	**Dose(s) directed by protocol**	**Route(s) of administration**
Botulinum Toxin	50u per injection	IM to treat CECS

10D. List all **biologics, compounds and dietary supplements**
☑ N/A, no biologics, compounds and dietary supplements
10E. List all devices covered by an **Investigational Device Exemption (IDE)** from the **FDA** (approved or submitted)
☑ N/A, an IDE has not been submitted to or approved by the FDA
10F. List all **FDA approved devices used for an unapproved use ("off-label")**
☑ N/A, no FDA approved devices being used "off-label"
10G. List all **unapproved devices.**

☑ N/A, no unapproved devices	
10H. Device Storage Location(s):	

Is this research an "applicable clinical trial" which must be registered on ClinicalTrials.gov?
x Yes, Local Investigator registered the trial NCT03339921

Use of a placebo in place of standard therapy:		
Is a placebo being used in place of standard therapy?	☑ No	☐ Yes

11. MEDICAL RESEARCH AREA

☐ Analytical Chemistry	☑ Anatomy	☐ Anesthesiology	☐ Biochemistry
☐ Cardiovascular Surgery	☐ Cardiology	☐ Cell Biology	☐ Dentistry
☐ Dermatology	☐ Dietetics	☐ Electrophysiology	☐ Endocrinology
☐ Emergency medicine	☐ Gastroenterology	☐ General Surgery	☐ Hematology
☐ Histology	☐ Immunology/Allergy	☐ Infectious Disease	☐ Microbiology
☐ Molecular Biology	☐ Neonatology	☐ Neurology	☐ Neurosurgery
☐ Nursing	☐ OB/GYN	☐ Occupational Medicine	☐ Occupational Therapy
☐ Oncology	☐ Ophthalmology	☐ Oral/Maxillofacial Surgery	☐ Orthopedics
☐ Pathology	☐ Pediatrics	☐ Pharmacology	☐ Physical Therapy
☐ Mental Health	☐ Radiology/Imaging	☐ Urology	☐ Wellness
☑ Other:	Sports Medicine, Musculoskeletal		

12. ATTACHMENTS

1. Form A, Signature Sheet
2. Form A-2, Study Personnel Listing
3. Form D, Informed Consent Document
4. HIPAA and Consent Waiver and Alteration Form
5. Form O, Use of a an Investigational Drug in Research
6. Universal Pain Scale
7. Lower Extremity Functional Index (LEFI)
8. Form E, HIPAA Authorization Document
9. FDA Acknowledge/Exempt IND Determination Letter
10. Telephone Consent
11. Satisfaction Survey
12. Advertisement