Botox for the Treatment of Recurrent Chronic Exertional Compartment Syndrome

NCT05006417

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ONABOTULINUMTOXINA (BOTOX) EFFECT ON PAIN AND FUNCTION IN RECURRENT CHRONIC EXERTIONAL COMPARTMENT SYNDROME: A PILOT STUDY

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Principal Investigator: Michael Suer, MD

PROTOCOL VERSION and AMENDMENTS

Protocol Version	Date	Change Initiated (Initials)	Brief description of protocol modification/actions requested, if any
Template V1	8/26/2020	MJS	Original
V2	9/21/2020	MJS	Corrected error in hypothesis statement, added Courtney Morgan, clarified definition of R-CECS to include pressure testing, clarified recruitment
V3	5/2/2021	MJS	Reviewed and updated for IRB comments
V4	8/3/2021	MJS	Reviewed and updated for IRB comments

STATEMENT OF COMPLIANCE

(1) The research will be carried out in accordance with Good Clinical Practice (GCP) as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) ICH E6
All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: ____Michael Suer, MD_____
Print/Type Name

Signed: _____

Funding Sponsor: University of Wisconsin Division of Rehabilitation Medicine

Study Product: OnabotulinumtoxinA (Botox)

Participating sites: University of Wisconsin Hospitals and Clinics

List of Abbreviations

AE	Adverse event
CECS	Chronic Exertional Compartment Syndrome
IMP	Intramuscular Pressure
PT	Physical Therapy
R-CECS	Recurrent Chronic Exertional Compartment Syndrome
SAE	Serious Adverse Event
US	Ultrasound
UP	Unanticipated Problem
UWRI	University of Wisconsin Running Index

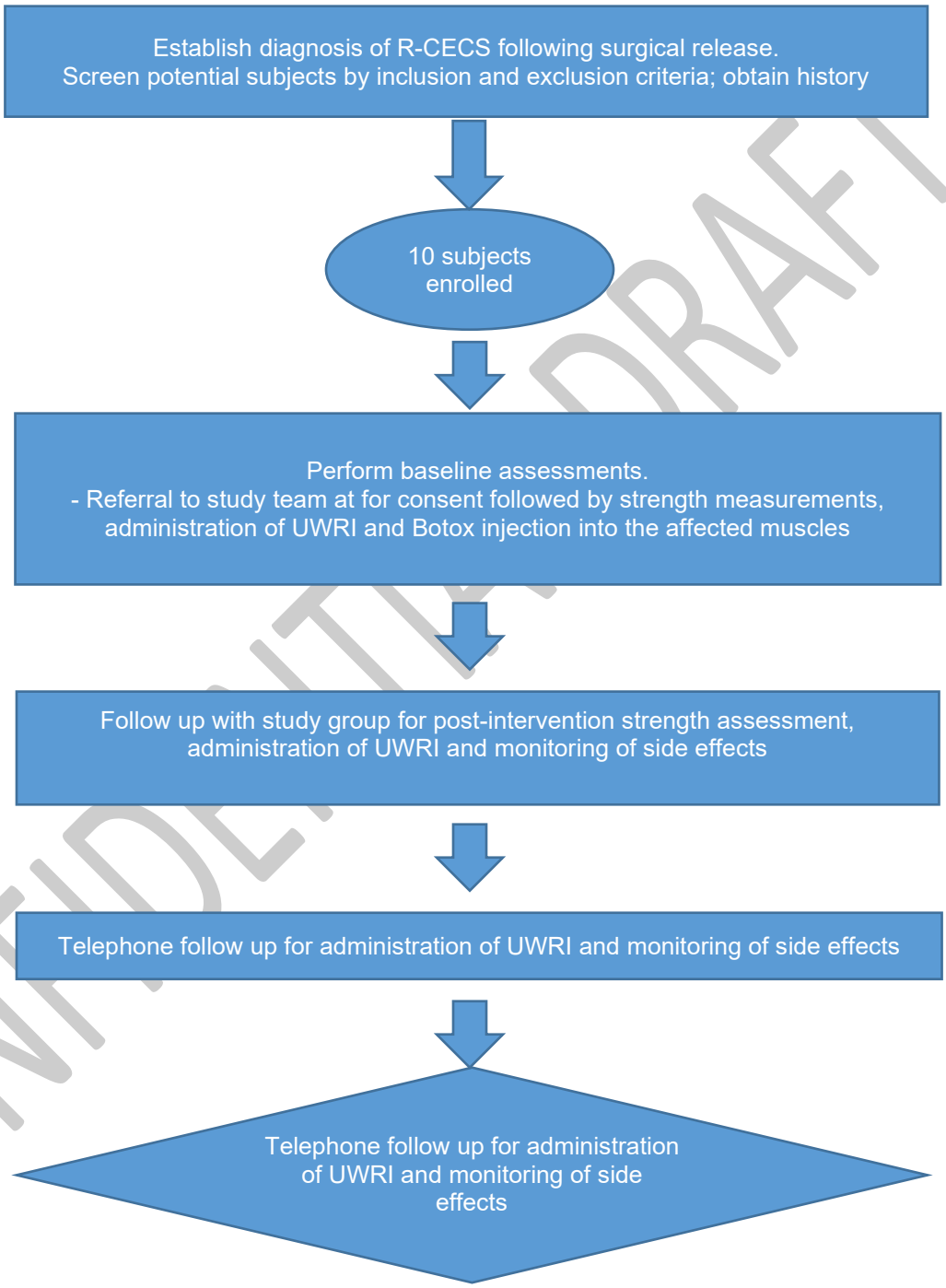
Study Summary

ONABOTULINUMTOXINA (BOTOX) EFFECT ON PAIN AND FUNCTION IN RECURRENT CHRONIC EXERTIONAL COMPARTMENT SYNDROME: A PILOT STUDY

Title	OnabotulinumtoxinA (Botox) effect on pain and function in recurrent chronic exertional compartment syndrome: a pilot study
Short Title and Precis	Botox for the treatment of recurrent chronic exertional compartment syndrome
Methodology	Open label pilot study
Study Duration	2 years
Study Center(s)	University of Wisconsin Hospitals and Clinics
Objectives	Determine effect of Botox on pain and function using the University of Wisconsin Running Index
Number of Subjects	10 subjects consisting of 20 legs
Diagnosis	Recurrent chronic exertional compartment syndrome (R-CECS)
Main Inclusion Criteria	Patients greater than 18 years of age with diagnosis of R-CECS
Main Exclusion Criteria	Diagnosis other than CECS
Study Product, Dose, Route, Regimen	Botox (reconstituted at 100 units/mL) to be injected under standard palpatory technique into the affected lower leg compartment. Dosage will be based upon the affected muscles
FDA status of product	FDA approved
Duration of administration	6 month follow up time after injection of medication. Typical duration of action of Botox is 10-12 weeks
Reference therapy	No direct comparison
Statistical Methodology	Using a one-way ANOVA and assuming independence of leg scores for each patient, we will have 80% power to detect an overall significant F-test (assuming a 2 (SD=1) point decrease in pain score from baseline to 6 months) with n=6 patients (e.g. 12 legs). Accounting for potential drop-out (15%) and, additionally, adjusting for non-parametric analyses, n=10 patients (e.g 20 legs) will be sufficient to provide preliminary effect sizes at each time point which will help inform power analyses for studies planned beyond this pilot study.

Schematic of Study Design

Flow diagram or study calendar (e.g., randomized controlled trial)



Contents

1. Key Roles

Following is a list of all personnel in key roles:

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2. Background and Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice, applicable government regulations, and Institutional research policies and procedures.

2.1 Background and Rationale

Chronic exertional compartment syndrome (CECS) is an overuse injury first described by Mavor[i] in 1956 that typically affects young endurance athletes, classically distance runners. CECS occurs primarily in the

lower leg, predominantly in the anterior compartment, although it has been reported elsewhere in the body[ii,iii,iv,v,vi].

The pathophysiology of CECS is not completely understood[vii,viii,ix]. Similar to acute compartment syndrome, it is thought to result from increased pressure within the restrictions of the fascial planes of a muscle compartment. Exercise increases blood flow to active muscles causing them to expand. If constricted by surrounding noncompliant fascia, such swelling increases pressure within the muscle compartment. Ultimately, pressure within the compartment reduces blood flow leading to muscle ischemia and pain when metabolic demands cannot be met. Several studies[x] have demonstrated decreased blood flow and oxygenation in the legs of symptomatic patients with CECS.

Cessation of inciting activities resolves symptoms in most cases of CECS. Without this cessation, the prognosis for CECS is poor if treated non-operatively. Should symptoms continue, patients are referred for possible muscle compartment release, currently the most widely accepted treatment approach despite a significant number of treatment failures[x,xi,xii]. To date, no alternative non-operative approach has successfully treated refractory symptoms[ii,viii,xiii,xiv].

Recently, it has been hypothesized that botulinum toxin could reduce intramuscular pressure in CECS[xv]. Isner-Horoboti et al[xv], performed abobotulinum toxin A injections into the anterior and anterior/lateral compartments in 16 individuals with a mean follow up of 4.4 months (range 3-6 months). Fifteen (95%) patients were asymptomatic after intervention with fourteen (88%) exhibiting normalized postexercise compartment pressures. Using manual muscle testing, they determined that 11 patients displayed decreased strength though did not produce noticeable subjective weakness. A later case report by Baria and Sellon[xvi] presented the first long-term follow up (14 months) of a CECS case treated with botulinum toxin injections (Botox) in which the patient reported continued pain relief and had resumed her active lifestyle without adverse effects. Finally, Hutto et al[xvii] demonstrated 11 months of pain relief following botulinumtoxin injection in a military recruit for CECS.

The proposed investigation will aim to build upon the results of existing studies. The novelty of our approach involves a differing dosage of the toxin (Botox) into a more targeted muscle group. Further, while previous studies have used manual muscle testing to test strength, many studies have found this method unreliable. As such, we will be using the Kiio force sensor at multiple time points to determine weakness quantitatively. We will be utilizing the reliable and validated University of Wisconsin Running Index to evaluate return to sport. Finally, and most importantly, we will be treating a group of patients (R-CECS) for whom no current treatment is available. To date, there are no published articles on using Botox to treat R-CECS although, in clinic, the PI has treated an individual with great success utilizing this approach.

2.2 Hypothesis

Hypothesis: Injection of Botox into the affected muscle group will alleviate pain associated with R-CECS.

2.3 Study Agent

OnabotulinumtoxinA (Botox) does not have FDA approval for the proposed use. It does have FDA approval for spasticity in both upper and lower extremities, cervical dystonia, bladder dysfunction, chronic migraine, primary axillary hyperhidrosis, blepharospasm, and strabismus.

Maximum dosage is not well defined; dosage is dependent upon treatment effect and indication. The maximum cumulative dose should generally not exceed 400 units in a 3-month interval when treating one or more indications.

Description:
Formerly known as botulinum toxin type A; IM toxin that reduces local muscle activity. Approved and off-label uses include cervical dystonia, blepharospasm, strabismus, upper limb spasticity, lower limb spasticity, facial wrinkles, migraine prophylaxis, cerebral palsy, low back pain, excessive sweating, overactive bladder, and urinary incontinence associated with neurologic conditions. Distant spread of botulinum toxic effects from the site of injection has resulted in symptoms suggestive of systemic

botulism (including respiratory compromise and death) after the use of botulinum toxins types A and B. Botulinum toxins types differ and different types are not exchangeable or substitutable for one another.

Mechanism of Action
OnabotulinumtoxinA blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering nerve terminals, and inhibiting the release of acetylcholine. Inhibition occurs as the neurotoxin cleaves a protein (SNAP-25) integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. After intramuscular injection of a therapeutic dose, onabotulinumtoxinA produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. Additionally, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. Evidence exists that suggests that reinnervation of the muscle may occur thereby slowly reversing muscle denervation produced by the neurotoxin.

A reduction in sialorrhea may also occur by blocking the liberation of acetylcholine in autonomic nerve terminals in the parotid and submandibular glands. There is no evidence of axonal sprouting and consecutive innervation in autonomic nerve fibers in sialorrhea studies.

For treatment of neurogenic bladder, after injection into the detrusor muscle the efferent pathways of detrusor activity are affected via inhibition of acetylcholine release; inhibition of afferent neurotransmitters and sensory pathways is also thought to occur. Therapy increases maximal bladder capacity, reduces maximum detrusor pressure, reduces incontinence episodes, and may reduce the need for anticholinergics in patients with neurogenic overactive bladder.

2.4 Summary of Relevant Preclinical Data

2.5 Summary of Clinical Data

Recently, it has been hypothesized that botulinum toxin could reduce intramuscular pressure in CECS[xviii]. Isner-Horoboti et al[xv], performed abobotulinum toxin A injections into the anterior and anterior/lateral compartments in 16 individuals with a mean follow up of 4.4 months (range 3-6 months). Fifteen (95%) patients were asymptomatic after intervention with fourteen (88%) exhibiting normalized postexercise compartment pressures. Using manual muscle testing, they determined that 11 patients displayed decreased strength though did not produce noticeable subjective weakness. A later case report by Baria and Sellon[xix] presented the first long-term follow up (14 months) of a CECS case treated with botulinum toxin injections (Botox) in which the patient reported continued pain relief and had resumed her active lifestyle without adverse effects.

To date, there exists no published papers utilizing botulinumtoxin to treat R-CECS. However, in clinical practice, the PI has treated individuals with success utilizing this approach.

2.6 Dose Rationale

Dosing considerations were made in looking at previous studies[xv,xviii] as well as medical expertise of the investigators. A previous study[xviii] have injected 40 units (20 proximal and 20 distal) into the each the TA, extensor digitorum longus, and extensor hallucis longus. Our protocol changes this dosing to the following:
- 50 units total (25 proximal and 25 distal) into the TA for anterior symptoms
- 50 units in to the peroneal longus for the lateral compartment
- 50 units into each the medial and lateral gastrocnemius for superficial posterior symptoms
- 50 units into the tibialis posterior for deep posterior symptoms

We chose a dosage on the low end recommended by the previous studies for hypertonicity in the respective muscles in conjunction with the investigator's clinical expertise. To ensure placement of the medication into the proper muscle, we will be using standardized palpatory techniques as is common in Botox injections for spasticity. A single injection will be performed in this study as previous studies have shown prolonged pain relief despite a known

duration of action of the medication to be 2-6 months to help determine the duration of relief in this diagnosis. Given this duration of action, most side effects associated with muscle weakness are temporary and resolve over time.

2.7 Potential Risk and Benefits to Subjects

2.7.1 Known Potential Risks

Immediate risks
- Pain during injection
- Infection of injection site
- Bleeding following injection
- Swelling at injection site

Long-range risks
- TA weakness resulting in foot drop
- Lateral compartment weakness resulting in eversion weakness
- Plantarflexion weakness resulting in weakness with plantarflexion
- Distant spread resulting in botulism-like symptoms including muscle weakness all over body, vision problems, difficulty speaking or swallowing, trouble breathing, loss of bladder control, respiratory compromise, death (see black box warning of Botox labelling)

Reproductive
- Injections will not be performed in individuals who are or who have a reasonable possibility of being pregnant.
- Should potential subjects be of unknown pregnancy status and wish to enroll in the study, a urine pregnancy test can be performed prior to enrollment.

Rationale
- Despite the above risks, Botox has established as a safe procedure with minimal likelihood of serious side effects when done under sterile technique. The immediate risks are temporary and/or easily treated ameliorated with prompt treatment.

Value
- R-CECS remains a difficult-to-treat entity as established treatments are limited and outcomes are less than ideal

Please see package insert in appendix

2.7.2 Protection Against Risks

Immediate risks
- Pain during injection
    - Barring other risks, this will be temporary and will be involved in the pre-injection consent. The needle to perform the injection will be of the smallest gage that can be reasonably considered to successfully perform the injection including visualization under US. The discomfort that can be experienced with some injections of Botox cannot be mitigated.
- Infection of injection site
    - Sterile technique will be maintained with an assistant in the room to both assist with the injection and to monitor for sterile technique. Injection will be performed at a clinic that regularly performs injections under US guidance and has extensive experience in maintaining sterile technique.
- Bleeding following injection
    - Subject on blood-thinning medication will not be included in the study. The guage of the needle will be relatively small and poses a minimal risk for prolonged bleeding. Should this occur, proper protocol of

manual pressure and possible pressure bandage will be applied and the patient monitored for cessation of bleeding prior to departure from the clinic

- Swelling at injection site
    - Subject will be counseled on proper wound care and have investigating physician contact information and rehabilitation on call physician information prior to injection should further guidance be warranted after the injection.
- Ultrasound
    - Should abnormal findings be noted on scanning for appropriate injection location, patients will be instructed to follow up with referring provider for further work-up.

Long-range risks

- Lower extremity, foot, ankle weakness
    - Should this weakness occur, the subject will have some functional dorsiflexion from these spared muscles as well as sparing the soleus for plantarflexion. If this effect does occur, the injection physician will follow up with the subject sooner than the planned 2 month follow up and can consider further treatment such as ankle foot orthosis to aid in safe ambulation at the cost of the research funding source.
- Distant spread resulting in botulism-like symptoms including muscle weakness all over body, vision problems, difficulty speaking or swallowing, trouble breathing, loss of bladder control
    - Subject will have proper physician contact information to monitor for side effects. The risk will be explicitly discussed during written consent prior to the injection as it is a black box warning mandated by the FDA for the treating medication.
    - Should these effects occur, subject with speak with either the investigating physician or rehabilitation physician on call. Effects will be triaged and appropriate referrals made up to and including evaluation in the emergency department.

Withdrawal

- Patients who wish to withdrawal from the study may do so by verbal or written request to the investigator. Or they may indicate withdrawal by failure to follow up with study protocol.

2.7.3 Potential Benefits to the Subjects

Given uncertainty in patient treatment benefits, current subjects may or may not experience benefit from the study though future patients may benefit from study findings.

2.7.4 Risk Minimization:

To avoid risks associated with injection, sterile technique will be maintained by the treating physician and assistant during the injection. The assistant will also aid the treating physician in monitoring the sterile field for violations of sterile technique. Subjects will also be given follow-up instructions and instructions for contacting appropriate physician (investigating or on call rehabilitation physician) should adverse effects occur.

3 Study Objectives and Purpose

- Primary Objective: To assess the efficacy of OnabotulinumtoxinA (Botox) on decreasing pain associated with R-CECS.
- Secondary Objective: To assess the safety and tolerability of Botox injections of Botox for patients with R-CECS
- Secondary Objective: To assess the ability to return to sport following injection of Botox in subjects with R-CECS

4 Study Design and Endpoints

4.1 General Design

- Design: Pilot study without randomization or blinding
- Please see page 6 for schematic design of trial including duration of subject participation
- Summary: Subjects will be enrolled in study at initial clinic visit by study staff at which time diagnosis of R-CECS will be established based on elevated pressure measurements in patients who have had surgical release of the affected compartments. Pressure testing will be performed outside of the clinical study and will be required to establish the diagnosis of R-CECS.

  Initial clinic visit with study staff will consist of baseline measurements of ankle plantarflexion, dorsiflexion, inversion, and eversion strength using Kiio Force Sensor. The clinic visit with study staff will establish time point 0 and will consist of written consent for participation, Botox injection, and baseline UWRI. Two months following this visit, the patient will have follow up with study staff. Study staff will again measure ankle strength (ankle inversion, eversion, plantarflexion, and dorsiflexion) using the Kiio Force Sensor utilizing the same strength assessment protocol. Study staff will monitor for side effects and administer the UWRI. Telephone follow up assessment of the UWRI will be made by study staff at 4 and 6 months. For patient incentive, money will be distributed in person consisting of: $100 at time of injection, $50 at 2 month follow up, and $50 following the 6 month follow up. The final payment will be mailed to the subject to an address they provide at the time of follow up.

4.1.1 Primary Study Endpoints

1. Decrease in pain by 2 points on 0-10 numeric rating scale with activity, measured in each leg

4.1.2 Secondary Study Endpoints

The following parameters will be measured or evaluated in each leg for independent analysis of each limb

1. Change in ankle dorsiflexion strength
2. Change in ankle plantarflexion strength
3. Change in ankle inversion strength
4. Change in ankle eversion strength
5. Change in ability to perform activities of daily living
6. Subject frustration with injury
7. Subject perception of recovery from injury
8. Pain in the 24 hours following running
9. Change in running duration including weekly and longest run
10. Change in running speed
11. Subject confidence in increasing the duration and intensity of running

4.1.3 Primary Safety Endpoints

1. Lower extremity weakness
2. Bruising, bleeding, pain, redness, or swelling where the injection was given

5 Study Subjects – Enrollment and Withdrawal

- Accrual Goal: Goal of 10 patients (e.g. 20 legs) within 18 months to complete 6-month follow up of all patients in 2 years. Goal is based upon study being a pilot study. Previous studies[1] have performed 18 legs (9 patients) and did serve as a baseline for our study. After discussions with 2 surgeons at the University of Wisconsin with clinical expertise in performing fasciotomy and fasciectomy, it has been determined that they will anticipate seeing over 15 of these patients in the next year the majority of whom are otherwise healthy and would meet inclusion and exclusion criteria to be eligible for the study. Providing some of these individuals will not wish to participate in the study or otherwise be excluded, 18 months provides a realistic goal accrual period.

- Screening will be performed at initial diagnosis prior to enrollment and prior to first injection. At the time of injection, investigator will review contraindications with participant including local infection, known hypersensitivity to botulinum toxin, neuromuscular disorder, dysphagia, breathing difficulties, and pregnancy.

5.1 Subject Population

Subjects will be greater than or equal to 18 years of age at the time of enrollment with no upper limit of age provided the subject meets inclusion criteria. There will be no limitations on enrollment based on race or ethnicity of the subject. Female subjects of childbearing potential will be screened for pregnancy prior to enrollment with urine pregnancy test.

5.2 Inclusion Criteria

Inclusion Criteria	
1	Willing to provide written informed consent
2	Willing to comply with all study procedures and be available for the duration of the study
3	Male or female, at least 18 years of age
4	Documented diagnosis of R-CECS determined with elevated compartmental pressure testing following lower extremity fascia release (fasciotomy or fasciectomy)
5	Females of childbearing potential must have a negative urine pregnancy test prior to enrollment and agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to randomization, for the duration of study participation, and for 7 days following completion of therapy. • A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: ○ Has not undergone a hysterectomy or bilateral oophorectomy; or • Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

5.3 Exclusion Criteria

Exclusion Criteria
1. History of hypersensitivity or allergy to any of the study drugs or drugs of similar chemical classes
2. Known neuromuscular disease
3. Known pulmonary disease including but not limited to asthma, pneumonia, or upper respiratory tract infection
4. Dysphagia
5. Known cardiac disease including but not limited to congestive heart failure, arrhythmia, or history of myocardial infarction
6. Enrolled in another clinical trial or has used of any investigational drugs, biologics, or devices within 30 days prior to enrollment
7. Currently or have taken in the past medications that affect neuromuscular function, aminoglycosides, muscle relaxants, or other botulinum neurotoxin agents. Currently taking any blood-thinning medications including, but not limited to Plavix, Coumadin, Eliquis, Xarelto
8. Women who are pregnant or breast-feeding
9. Vulnerable populations
10. Not suitable for study participation due to other reasons at the discretion of the investigator

5.4 Subject Screening for Recruitment

5.4.1 Subject Identification

Potential subjects will be identified at the time of diagnosis by the investigators. Using their clinical discretion, discussion of the study will be offered alongside current standard treatments. Should the participating be interested in participation, the written consent form will be provided and clinic appointments scheduled with study staff for enrollment. Participant name and contact information will be provided to study staff by the diagnosing investigator for further contact with the study team.

Prior to enrollment, primary investigator will discuss via telephone call the timeline, interventions, goals, potential side effects, and incentive of the study. Subjects will also be screened for inclusion and exclusion criteria prior to enrollment. If more discussion is desired by potential subjects, co-investigators can contact potential subjects by telephone prior to scheduled enrollment. Eventual enrollment in the study will be elective provided the subject meets inclusion criteria.

5.4.2 Recruitment and Retention Strategies

Investigators have practice specialties of sports medicine, vascular surgery, and pain medicine that lend themselves to identifying potential subjects in clinic. As this is a pilot study, there will be no differentiation amongst sexes, races, or ethnicities and simply the first ten individuals enrolled and undergoing treatment will be the group studied.

Retention strategies include incentives provided at the time of injection, 2-month follow up, and 6-month follow up. Incentive will consist of $100 at the time of injection, and $50 at each the 2-month and 6-month follow up for a total of $200. Second retention measure is telephone follow up for the 4 and 6-month follow ups in lieu of clinic visit

5.5 Vulnerable Populations

Vulnerable populations will not be included in this study.

5.5.1 Subject Capacity

Subjects must have the capacity to provide informed consent as determined by the PI and study team.

5.5.2 Subject/Representative Comprehension

Prior to providing written consent, investigator will ask that subjects recall and restate what they have been told during the informed consent process to ensure comprehension. Further, teams will follow state laws and institutional policies to determine who will serve as legal authorized representative (LAR) and that research teams will include these LARs to the extent possible in the consent process.

5.6 Informed Consent

Study staff will be responsible for ensuring that valid written consent is obtained and documented for all subjects.

5.6.1 Process of Consent

- Written informed consent will be obtained by the physician performing the Botox injection prior to injection being performed.
- Consent to perform the injection will be performed on the standard UW Health Botulinum Toxin Injection Consent Form (301647-DT) available on UConnect. Consent for participation in the study will also be signed prior to enrollment.
- Informed consent will be obtained in person by competent individuals making witness signature unnecessary.

- Investigator will review the consent form with the subject and obtain written consent prior to performing Botox injection at the time of the first clinic visit (time 0). For individuals that are non-English speakers, a translator will be present to review consent in the same manner as with subjects who speak English.

5.6.2 Consent Form (see templates for UW-Madison)

Please see supporting documents

5.6.3 HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA documentation will be integrated into the consent form (Appendix 2). Attached as part of our application is a signed subject authorization form that includes:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

5.6.4 Revoking Consent

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

5.6.5 Costs to the Subject

There will be no cost to subjects for the clinic visits or procedures that are done for research purposes only and are not part of subject's regular care. These services will be paid for via Division of PM&R research grant.

Subjects will have to pay for basic expenses like any childcare, food, parking, or transportation related to study activities. Study will also not provide compartment pressure measurements.

If treatment for side effects is needed while in the study, the subject or subject's insurance will be financially responsible for this treatment.

5.6.6 Payment for Participation

For completion of all the study visits, subjects will receive a total of $200 for completing in this study.

- We will give $100 for receiving the Botox injection, obtaining baseline strength measurements, and filling out the UWRI questionnaire.
- We will then provide $50 after having strength measurements repeated at 2 months and following up with physician for monitoring of side effects and completion of UWRI.
- Final $50 will be mailed to the participant after the 6-month telephone call for completing the study.
- If subject chooses to leave or we take subject off the study for any reason, they will be allowed to keep the money already given them.

Enrollment of individuals with a potential status relationship, including family members of the research team, will be declared in an application to the IRB (Initial Review Application, Change of Protocol) and justification for the

inclusion of these subjects provided. The IRB will then assess on a case-by-case basis whether the inclusion is warranted by the protocol, the recruitment and consent process are free from undue influence, and the confidentiality of these subjects will be protected adequately.

5.7 Early Withdrawal of Subjects

5.7.1 Premature termination of study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Division of PM&R and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

5.7.2 When and How to Withdraw Subjects

As the study involves a one-time injection, subjects will be withdrawn of their own volition or by failure to adhere to protocol requirements.

5.7.3 Data Collection and Follow-up for Withdrawn Subjects

Intervention is a one-time injection. Therefore, patients who opt out of the study will not be able to opt out of treatment once injection is performed.

6 Study Agent

6.1 Description and Formulation

Botox will be prepared by the central pharmacy per standardized protocol as directed by Allergan:
Prior to injection, reconstitute each vacuum-dried vial of BOTOX with only sterile, preservative-free 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent (1 mL) in the appropriate size syringe, and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTOX should be stored in a refrigerator (2° to 8°C).

NOTE: State is the study agent is IND/IDE exempt. If not, state reference number and identify the holder.

6.2 Packaging

- Study drug will be supplied by the central pharmacy within 24 hours of scheduled injection per their usual protocol.
- Drug will be packaged in a clear plastic bag with the patient's identifying information clearly visible on the outside and placed in the refrigerator set between 2^{o} and 8^{o} C.

- Individual syringes will also be labeled with subject's identifying information

6.3 Preparation, Administration and Storage of Study Drug

Botox will be prepared by and delivered by the UW Pharmaceutical Research Center (PRC) per standardized protocol as directed by Allergan:

> Prior to injection, reconstitute each vacuum-dried vial of BOTOX with only sterile, preservative-free 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent (1 mL) in the appropriate size syringe, and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTOX should be stored in a refrigerator (2° to 8°C).

Contact agent at the UW Pharmaceutical Research Center is Susan Johnston, who can be reached at (608) 263-8863.

6.4 Route of Administration

- Dose will be determined based upon patient location of symptoms as follows:
  - - 50 units total (25 proximal and 25 distal) into the TA for anterior symptoms
  - - 50 units in to the peroneal longus for the lateral compartment
  - - 50 units into each the medial and lateral gastrocnemius for superficial posterior symptoms
  - - 50 units into the tibialis posterior for deep posterior symptoms
- Treatment duration: Established duration of action on muscular weakness of other uses of Botox is between 2 and 4 months. Given this novel treatment, duration of action in our study is unknown.
- Expected side effects include:
  - Weakness in the muscle injected
  - Injection site pain
  - Injection site bleeding

6.5 Starting Dose and Dose Escalation Schedule

None

6.6 Dose Adjustments/Modifications/Delays

Following injection, dosage cannot be changed and study will maintain the aforementioned dose for the duration of this study. Based on studies for other indications, Botox has been shown to take effect in approximately 2 weeks and last between 2 and 4 months.

6.7 Prior and Concomitant Therapy/ Standard of Care

Patient will not undergo concomitant medical therapy including, but not limited to physical therapy or surgical fasciotomy. If the patient has undergone previous physical therapy for the same diagnosis, this data will be collected but will not alter ability to participate in the study. Allowed in the study are over-the-counter pain medications including NSAIDs and Tylenol as needed.

6.8 Randomization and Blinding of Study Drug

The subjects and drug will not be blinded in this study and subjects will not be randomized into differing treatment arms.

6.9 Receiving, Storage, Dispensing and Return or Disposal of Study Agent

Table 2: Study Agent information at a glance:

Name	Source	Storage	Dispensing	Disposal
Botox	UW Pharmacy	Stored in Pain Clinic refrigerator until time of injection	One-time injection will be performed by treating physician	Excess medication will be disposed of in appropriate medical waste containers

6.9.1 Receipt of Drug Supplies

After reconstitution, study team will collect the medication from the the UW Pharmaceutical Research Center and deliver the medication to the UW Clinic at The American Center. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files.

6.9.2 Storage

Drug will be stored in a cooled container during transport and stored at the UW Clinic at The American Center refrigerator set between 2° and 8° C until the time of injection.

6.9.3 Dispensing

Drug will be ordered by the lead investigator prior to the scheduled clinic visit one. The drug will be prepared, assigned to the appropriate patient, and delivered to the UW Clinic at The American Center by the UW Pharmacy within 24 hours of the appointment. Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

6.9.4 Return or Disposal

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study drug. Drug destroyed on site will be documented in the study files.

7 Study Procedures

Procedure: Botox injection

Under ultrasound guidance, the affected muscle group will be identified. After placing ultrasound transducer gel over the area, a 10-mHz linear ultrasound probe will then be utilized to localize the specific, respective muscles within the compartment being analyzed in both short and long axis. After cleansing the skin with chlorhexidine solution and utilizing semi-sterile technique, the muscle will be injected proximally and distally with the respective amount Botox mixed to 100 unit: 1 mL. Ultrasound-guidance will be utilized to guide the needle placements into the mid-depth of the respective muscle utilizing long-axis view with injections being performed with in-plane technique. The area will be scanned to ensure avoidance of neurovascular structures. Following injection, the sites will be monitored for cessation of bleeding and any immediate side effects prior to discharge from the clinic.

Identification of muscles by landmark[xx]:

- Gastrocnemius medial head
    - Located within the most prominent portion of the muscle belly located 1/4 the distance from the popliteal crease to the achilles insertion. Subject with plantarflex their foot against slight resistance allowing palpation of the muscle belly which becomes tendon about ½ way down the lower leg. Muscle belly will be identified on ultrasound with depth appropriate to delineate the soleus from the gastrocnemius.

- Gastrocnemius lateral head
    - Located within the most prominent portion of the muscle belly located 1/3 the distance from the fibular head to the achilles insertion. Subject with plantarflex their foot against slight resistance allowing palpation of the muscle belly which becomes tendon about ½ way down the lower leg. Muscle belly will be identified on ultrasound with depth appropriate to delineate the soleus from the gastrocnemius.
- Fibularis longus / Lateral compartment
    - Located ¼ of the distance from the fibular head to the to the tip of the lateral malleolus. Subject can laterally flex their foot against slight resistance to accentuate the muscle belly which becomes tendon ½ way down the lower leg.
- Tibialis anterior
    - Located 1/3 the way between the fibular head and the tip of the medial malleolus directly lateral to the anterior border of the tibia. Subject can dorsiflex their ankle against slight resistance to accentuate the muscle belly.
- Tibialis posterior
    - Medial approach is midway between heel and popliteal crease, which will avoid nerves and vessels. Injection depth is just posterior to the tibia after passing through the gastrocnemius and soleus.

7.1 LABS

There are no labs that are anticipated to be drawn in this study.

7.2 Established Standard of Care:

Table 3. Study Calendar

Process	Screening	Baseline (initial clinic visit; time 0)	Follow-up 1 (2 months, in clinic)	Follow-up 2 (4 months, telephone)	Final Visit (6 months, telephone)
IMP Measurement	SOC	X			
UWRI		X	X	X	X
Kiio Force Measurement		X	X		
Botox injection into TA		X			

Indicate if study or standard of care by using “X” for study and “SOC” for standard of care.

7.3 Study Visits

7.4.1 Screening/Baseline:

Screening and consent will be discussed with PI at clinic visit in which IMP measurement (CECS diagnosis) is taken prior to enrollment in the study. If patient is not from local community, study will be discussed over telephone prior to enrollment. Once consent is obtained, baseline force measurements and UWRI (at study clinic visit 1) will both be scheduled within 1 month of IMP measurement.

7.4.2 Follow up:

Table 4. Acceptable Window for Study Visits (including weekends)

Visit	Window	Activities

Study visit 1 (establishes time 0 of study)	Within 1 months of IMP measurement	• Written consent reviewed and collected • UWRI baseline • Kiio Force measurement • Botox injection
Follow-up 1 (Clinic)	2 months +/- 5 days	• UWRI • Kiio Force measurement of • Evaluation for side effects
Follow-up 2 (Telephone)	4 months +/- 1 week	• UWRI • Evaluation for side effects
Follow-up 3 (Telephone)	6 months +/- 1 week	• UWRI • Evaluation for side effects

7.4.3 Unscheduled:

Possible AEs: Following investigators learning of potential AEs, subject will be contacted over telephone to discuss case. If deemed warranted by the investigator's clinical impression, subject will be scheduled for evaluation in clinic at earliest available appointment. Subject will be evaluated by investigator and symptoms addressed as clinically appropriate. If symptoms deemed a side effect of the medication, these will be documented in the patient's chart for inclusion in the medication effects.

7.4.4 Final Study Visit

Study will conclude for each subject after the 6-month telephone follow-up encounter as each subject will only undergo a single injection for the study and will not be evaluated again under this protocol. Given the medication duration of action, adverse effects should not occur following this encounter. However, participants will be permitted to contact the study investigators should possible AEs occur, at which point the protocol mentioned above in 7.4.3 will be followed.

8 Study Analysis

8.1 Sample Size Determination

Using a one-way ANOVA and assuming independence of leg scores for each patient, we will have 80% power to detect an overall significant F-test (assuming a 2 (SD=1) point decrease in pain score from baseline to 6 months) with n=6 patients (e.g. 12 legs). Accounting for potential drop-out (15%) and, additionally, adjusting for non-parametric analyses, **n=10 patients (e.g 20 legs) will be sufficient** to provide preliminary effect sizes at each time point which will help inform power analyses for studies planned beyond this pilot study.

8.2 Statistical Methods

Basic descriptive statistics, means (SD) and medians (IQR) for continuous variables and frequencies (percentages) for categorical variables will be used to summarize patient outcomes. For the primary outcome, change in pain (from baseline on 0-10 numeric rating scale) will be assessed at each time point (2,4,6 months) using Friedman's ANOVA. Friedman's ANOVA is the non-parametric analog to one-way repeated measures ANOVA and is often

used for ordinal outcomes. If necessary and feasible, GEE models will be constructed to further assess changes in pain while accounting for intra-subject correlation. Secondary endpoints utilizing the UWRI will also be assessed in this manner. Change in strength outcomes at baseline and 2 months will be assessed using Wilcoxon signed rank tests or, if necessary, linear mixed effects models for repeated measures, to account for intra-subject correlation (left and right legs).

8.3 Subject Population(s) for Analysis

The subject population for analyses will include all patients who receive the Botox injection. We intend to minimize loss to follow-up; however, if patients drop out of the study, we will attempt to use statistical methods that allow for missing outcomes (e.g. GEE/Linear models for repeated data) so that all available data can be used for analysis.

8.4 Planned Interim Analysis:

No interim analyses are planned for this study.

9 Data Collection, Handling and Record Keeping

9.1 Data Confidentiality

- Subject encounters include questionnaires will be submitted to the electronic record on RedCap according to the subject's respective medical record number. Following conclusion of the study, the investigators will utilize the database to review the medication effect and perform data analysis.
- Except for publication, data will not be shared with other researchers and identifiable information will not be released to third parties.

9.1.1 Confidentiality of Subject Records

By signing the protocol, the Investigator agrees that IRB representative may consult and/or copy study documents in order to verify CRF data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying CRF information, the subject will be identified by unique code only and full names and similar identifying information (such as medical record number or social security number) will be masked.

The Clinical Site Investigators will ensure that the identity of subjects will be protected. All study records will be maintained in a secure fashion with access limited to essential study personnel only. All study documents submitted to the Coordinating Center will have identifiers removed other than dates of birth and service and subjects will be identified with a study-specific identification number only. The Clinical Site Investigators will maintain, in a secure location, an enrollment log that includes subject identifying information and links subjects to their study-specific identification number.

9.2 Data Capture

9.2.1 Source Documents

1. Physical therapy clinic notes
2. Procedure note
3. Copies of transcription certified after verification as being accurate and complete from clinic visits with investigators
4. Completed UWRI questionnaires from both clinic and telephone encounters that had been entered into RedCap

9.2.2 Data Collection Tools

Study will utilize RedCap for data collection and management.

9.3 Data Management

Investigator, Michael Suer, will serve as the DCC for the study. The DCC agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operation procedures (SOPs) to ensure that trial is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (International Conference on Harmonization E6), and all applicable federal, state, provincial, and local laws, rules, and regulations relating to the conduct of the clinical trial in an ongoing and auditable manner."

9.4 Records Retention

Data will be retained for 4 years following the conclusion of the study.

10 Assessment of Safety

10.1 Specifications of Safety Parameters

Lower extremity weakness will be both quantitative and qualitative data.
Bruising, bleeding, pain, redness, or swelling where the injection was given will be qualitative data

10.1.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

10.1.2 Definition of Serious Adverse Events (SAE)

Serious adverse event or serious suspected adverse reaction. An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.1.3 Definition of Unanticipated Problems (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

10.2 Classification of an Adverse Event

10.2.1 Severity of Event

All AEs will be assessed by the clinician using a protocol defined grading system. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

10.2.2 Relationship to Study Agent

In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.2.3 Expectedness

Principle investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

10.3 Time period and frequency for event assessment and follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.
Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

10.4 Reporting procedures

Reporting will be performed by Michael Suer according to HSIRB standard protocols:
Immediate Report to the IRB

An AE/SAE meeting the above definition of an unanticipated problem must be reported to the IRB immediately if **both of the following conditions are met**:

- The event occurred at a site under the purview of the UW Health Sciences (HS) IRB or Minimal Risk (MR) IRB
- The event is immediately life threatening or severely debilitating to other current subjects

The IRBs expect that these reports will be rare. SAEs that meet these conditions must be reported to the IRB Chair or IRB Director via telephone (preferred) or email as soon as possible, but no later than 1 business day after the research team becomes aware of the event. The research team will then discuss with the IRB Chair or IRB Director what action needs to be taken related to the occurrence (e.g., suspension of study enrollment, change in treatment regimen) to prevent further harm from occurring. This initial report to the IRB Chair or IRB Director must be followed with the submission of a reportable event in ARROW within 2 business days after the local research team becomes aware of the event.

10.4.1 Adverse Event Reporting

Any other AE/SAEs that meet the definition of an unanticipated problem as described above must be reported to the HS or MR IRB within 14 business days.

10.4.2 Serious adverse event reporting

The study clinician will complete a SAE Form within the following timelines:
All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See **Section 1, Key Roles** for contact information. Other SAEs regardless of relationship, will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

10.4.3 Unanticipated problem reporting

The site investigator will be responsible for creating and completing a UP report form. Incidents that meet the OHRP criteria for UPs will be reported promptly on the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 14 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 14 business days of the IR 's receipt of the report of the problemfrom the investigator.

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

10.5 Study Halting Rules

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Division of PM&R and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

10.6 Safety Oversight

The Principal Investigator will serve as the DMC. REDCap will provide the DMC and the study biostatistician the ability to efficiently collect the needed data and provide safety oversight of the protocol.

11 Study Monitoring, Auditing, and Inspecting

11.1 Medical Monitoring

The Principal Investigator will serve as the medical monitor for the study. In the design of the study, the investigators will have regular follow up with the research participants to allow close monitoring for AE/SAEs. Should AE/SAEs occur outside of clinical hours, participants will be provided at time of consent with appropriate instructions for contacting clinician for triage.

11.1.1 Study Monitoring Plan

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the principal investigator
- Monitoring will be provided during all clinic visits by qualified study staff including initial assessment and 2-month follow up. He will also be responsible for monitoring participants immediately following intervention prior to a safe discharge from the clinic. The remainder of monitoring will be targeted data verification of endpoint and safety.
- PI will be provided copies of monitoring reports within 7 days of visit.
- Independent audits will not be conducted
- Investigators will perform internal quality management of study conduct, data collection, documentation and completion.

11.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

The site PI/staff will be responsible for continuous vigilance to identify and report deviations to the protocol. These will be reported within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to Program Official and DCC. Protocol deviations will be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

11.3 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB (or their representatives), the sponsor, government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, applicable local and state laws, and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment ___ for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

Funding will be provided by an internal Department of Orthopedics and Rehabilitation Research Fund.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All UW investigators will follow the UW conflict of interest policy.

13.3 Subject Stipends or Payments

For patient incentive, money will be distributed in person consisting of: $100 at time of injection, $50 at 2-month follow up, and $50 following the 6-month follow up. The final money amount will be mailed to the subject to an address they provide at the time of follow up.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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