Mount Sinai	Protocol Title:	Subcutaneous Injection of Botulinum Toxin A for At-Level Back Pain in Patients with Spinal Cord Injury
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	Date Revised:	12/29/2015
	~~Study Number:~~	~~HS: 14-01107 GCO: 14-2212(0001)~~

MSSM Protocol Template HRP-503a

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
2. *For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document.* ***Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
3. *If you reference page numbers, attach those pages to this protocol.*
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Brief Summary of Research (250-400 words):

At-level SCI pain localized to the back is a common secondary condition of acute and chronic spinal cord injury (SCI), which impacts both activity participation and quality of life.(1, 2) Back pain, which may include both at and below-level SCI (neuropathic) pain and ~~nociceptive subtypes, has been reported to occur in 18-84% of persons with SCI.~~ (2-12) Pharmacologic and non-pharmacologic interventions currently used to treat these types of pain are limited by marginal efficacy and often intolerable side effects;(13-16) as such, there is an urgent need for a safe and effective treatment.

Intramuscularly administered botulinum toxin type A (BoNT) is a widely accepted treatment for muscle over-activity that has been shown to be safe, effective, and well tolerated (17-20). Recently, subcutaneous administered BoNT has shown preliminary evidence of efficacy in the treatment of non-SCI neuropathic pain and at-level SCI pain. (21-25)

We aim to investigate the potential effects of BoNT on persons with SCI with at-level SCI pain localized to the back. We hypothesize the following: In persons with SCI who have at-level SCI pain localized to the back, a one-time sub-cutaneous administration of BoNT at the site of pain will significantly decrease the average daily intensity of the pain for at least 12 weeks post treatment.

In order to test the hypothesis, we propose a randomized double-blinded placebo

controlled cross- over study in which persons with SCI who report the presence of at-level SCI pain of at least moderate intensity for at least 4 weeks (with or without musculoskeletal back pain that has been clearly differentiated by the subject from the at level SCI pain) will receive either subcutaneous BoNT or placebo through subcutaneous injections (maximum of 80) during one visit within the dermatomes where the pain is located. We predict that patients with one-time subcutaneous administration of BoNT at the site of pain will significantly decrease the average daily intensity of the pain for at least 12 weeks post treatment.

Subjects will be evaluated at baseline and post-injection at 2 weeks, 4 weeks, 8 weeks, and 12 weeks. Subjects will be crossed over after 12 weeks. Subjects that had initially received subcutaneous BoNT will receive subcutaneous placebo and vice versa. Subjects can elect to have the repeat injection at the time of crossover or opt to postpone the injection each 4-week period, for up to 12 weeks if pain control is deemed adequate. Following the cross-over injection, subjects will be evaluated at 2 weeks, 4 weeks then every 4 weeks for 12 weeks to determine the magnitude and duration of pain relief. Depending on when the cross-over injection is administered, crossover follow-up could range from 12 to 24 weeks.

1) Objectives:

Research Question: Will subcutaneous injections of botulinum toxin A provide pain relief in spinal cord injury patients with back pain near the level of injury in the spine?

We hypothesize that in persons who have at level SCI pain localized to the back, a one-time subcutaneous administration of BoNT at the site of pain will significantly decrease the average daily intensity of the pain for at least 12 weeks post treatment.

This study will investigate whether BoNT is safe and effective for the control of at-level SCI pain. If BoNT is effective, this approach has significant advantages over the majority of existing treatment strategies in that systemic side effects are rare, has no abuse potential, and is minimally invasive.

2) Background

Back pain is a common secondary condition of acute and chronic spinal cord injury (SCI) which impacts activity, participation and quality of life.(1, 2) Back pain, which includes both neuropathic and nociceptive subtypes, has been reported to occur in 18-84% of persons with SCI. (2-12) Historically, it has been difficult to classify pain in patients with SCI and multiple classifications have been proposed . Recently, experts in the field

published a consensus classification, the International Spinal Cord Injury Pain (ISCIP) Classification system. Despite the ISCIP classification system, back pain in SCI located at the neurological level of injury can be difficult to classify in some patients. This may be because back pain in SCI can present with both neuropathic and nociceptive features. (26)

At-level SCI (neuropathic) pain as defined within the ISCIP is a subtype of neuropathic pain that occurs within three dermatome levels at or below the neurological level of injury (NLI). It is believed to arise as a result of damage to the spinal cord or its nerve roots. (27) The presentation of neuropathic pain may include both evoked (allodynia and hyperalgesia) and non-evoked (spontaneous) pain. In SCI, the character of neuropathic pain is often described as “tightness”, “pressure” or “burning” in people with thoracic level injuries, and as “numbness”, “tingling”, “heat” or “cold” in those with cervical injuries. (1, 28) At-level (neuropathic) SCI pain is common, with a prevalence of about 40% at all years post injury.(1) Despite current use of a wide variety of pharmacological treatments including anticonvulsants, tricyclic antidepressants, topical sodium channel blockers, gabapentinoids, serotonin-norepinephrine reuptake inhibitors, selective-serotonin reuptake inhibitors and opioid medication, it remains difficult to control. Most of the medications have limited efficacy, similar to placebo, or marginally better; therefore, there is a need for new treatments.(13-16, 29)

Botulinum toxin A is a neurotoxin protein produced by the bacterium *Clostridium botulinum*. It is a neuropeptide that acts at the pre-synaptic SNARE complex at the neuronal endplate, specifically cleaving the SNAP-25 protein, preventing vesicular docking at neuronal endplates, thus inhibiting the release of acetylcholine at the neuromuscular junction. (47) On average, the onset of action of the toxin occurs 6 hours after administration, with the clinical effects evident within 2 to 3 days. (48) The peak clinical effect occurs about 2 weeks after administration, followed by approximately 10 weeks of stable results. (48) It is commonly used in the treatment of myofascial diseases and neuromuscular hyperactivity diseases. Recently, animal model and clinical studies have shown that this mechanism of action can also be applied to neuropathic and nociceptive pain.(21-25, 47, 49-63)

The exact mechanism of action of BoNT in pain is not fully understood. It has been shown that at the level of the peripheral nerves BoNT inhibits synaptic release of neuropeptides related to pain transmission. Glutamate, substance P, and calcitonin gene-related peptide are neuropeptides related to pain.(64-67) In rodent studies, administration of botulinum toxin is associated with the decreased secretion of glutamate,

substance P and calcitonin gene-related peptide (CGRP), as well as the increased appearance of cleaved SNARE proteins.(64-67) In normal physiology, neuropeptides are stored within vesicles at the nerve terminal. The SNARE protein complex allows docking of the vesicle to the nerve ending, followed by the release of the neuropeptides into the neuromuscular junction (NMJ). BoNT inhibits the secretion of the neuropeptides by cleaving the SNARE complex, thus preventing the docking and release of neuropeptides. (47) Neuropeptide release is not the only action within the cell that relies on intracellular vesicular docking. Ion receptor channels, like the transient receptor potential cation channel subfamily V member 1 (TRPV1), also rely on the vesicular docking to express itself.(68) The TRPV1 is a calcium-permeable, ionic receptor that is considered an integrator of heat perception and nociception (e.g. capsaicin) and has been shown to heighten the excitability of nociceptors. It is dependent on the SNARE protein for its expression on the cell membrane. In vitro studies with amphibian oocytes have demonstrated that the presence of BoNT reduces expression of TRPV1 on the cell surface.(68, 69) Together, these studies highlight the probable mechanism of BoNT at the peripheral nervous system and its basis for pain control at a cellular level.

BoNT has been shown to act at the level of the central nervous system. When injected directly into the intrathecal space, BoNT decreases the pain in the peripheral limbs of rodents (54). An interesting concept is the transportation of the toxin from the peripheral limb to the central nervous system. This was demonstrated by Bach-Rojecky et al. after they had injected BoNT into one (ipsalateral) limb of rodents with painful diabetic neuropathy. (54, 55) They found that a pain-like behavioral response in both the ipsalateral and the contralateral side was reduced compared to control groups, suggesting that BoNT had an effect in the central nervous system despite it administration in the periphery. (54) Other studies have shown that BoNT can be transported both anterograde and retrograde along the nerve axon.(70, 71) These studies together demonstrate that peripherally administered BoNT can act at the central and peripheral nervous system to control the transmission of pain.

In addition to the pre-clinical research that is performed on animal models, there have been a number of published clinical studies and case reports using subcutaneous administration of BoNT in the treatment of neuropathic pain. Randomized, double-blinded, placebo-controlled studies have shown efficacy in neuropathic pain control in subjects with post-herpetic neuralgia, (22, 72) post-traumatic/post- operative neuropathy(53, 58) and painful diabetic neuropathy.(24) In addition, there are multiple prospective studies showing possible efficacy of subcutaneous BoNT in the treatment of

trigeminal neuralgia, (21, 23, 47) and case reports reporting the benefit of BoNT in the treatment of complex regional pain syndrome (CRPS)-related neuropathic pain, (57, 73) post-thoracotomy neuropathic pain(58) and at-level SCI neuropathic pain. (25) In one case report, Jabbari et al. describes two patients with cervical spinal cord lesions (tumor and cord ischemia) who developed at-level (neuropathic) SCI pain and failed oral medications. After the administration of subcutaneous BoNT injections, there was clinically significant pain relief that continued to persist beyond 3 months.(25)

BoNT has been shown to have a favorable safety and tolerability profile across a broad spectrum of therapeutic uses. (48, 74) Compared to gabapentin, a commonly prescribed medication for neuropathic pain, adverse events with BoNT are less frequent and less severe. (74) Adverse events reported to be associated with BoNT administration are generally related to the mechanism of action of the toxin, most commonly dose-dependent focal weakness. Other local side effects include short-duration injection-associated pain, edema, erythema, ecchymosis, headache and short-term hyperesthesia. (74) These side effects are usually temporary. Systemic side effects include nausea, fatigue, malaise, rash and flu-like symptoms. There has been a case report suggesting a possible anaphylaxis reaction to the toxin; (75) however, in clinical trials, there has not been any reported anaphylaxis or any serious systemic adverse effects related to BoNT. (74, 76) Long term studies on the safety of BoNT have found the appearance of primary and secondary resistance over a 10-year period (resistance defined as <25% improvement after 2- 3 consecutive treatments). (74) There was no other identified long term side effect. If we combine the reported data of clinical studies (21-25, 53) using subcutaneous BoNT injections (6 studies, total of 73 subjects receiving BoNT), the incidence of AE is under 5% (3AE out of 73 subjects), the most common being local swelling at the injection site. There were no permanent side effects reported. It is also noted in the literature that the subcutaneous injection may cause mild-moderate pain during the actual procedure itself.(22, 23)

Sub-cutaneous administration of botulinum toxin A (BoNT) has been reported in the literature to decrease neuropathic pain in patients with a variety of conditions, including post-herpetic neuralgia, post- traumatic/post-operative neuropathy and diabetic neuropathy. Recent animal studies have demonstrated that BoNT has a significant effect on both the peripheral and the central nervous system.

Of note, a few studies have demonstrated that intramuscular botulinum toxin administration has demonstrated pain relief in low back pain, and myofascial pain syndrome. (51, 59, 61-63)

3) Setting of the Human Research

This study will be a randomized double-blinded placebo controlled cross-over study in which 32 human subjects with at-level SCI (neuropathic) back pain will receive either subcutaneous normal saline (placebo) or botulinum toxin injections. The subjects will have the procedure performed in an outpatient clinic setting at Mount Sinai Hospital with follow up (office visit, telephone or internet email follow-up) at 2 weeks, 4 weeks, 8 weeks, and 12 weeks post-injection. Subjects will then be crossed-over. Those who had received placebo will receive BoNT and vice versa. They will be followed every 4 weeks after the cross-over agent (office visit, telephone or internet email follow-up) to determine the magnitude and duration of pain relief.

4) Resources Available to Conduct the Human Research

The proposed study aims to recruit 32 individuals with traumatic SCI. More than 110 patients with SCI are admitted to Mount Sinai's inpatient rehabilitation program each year, and many more return for outpatient medical and therapy services. Given past experience, we expect it will be feasible to recruit the desired number of subjects in a reasonable timeframe.

Study procedures will be conducted by attending physicians and residents with support from one research assistant who is acting under the supervision of project investigators. All research staff have prior experience working with individuals with SCI at Mount Sinai Medical Center. All study staff have also completed all required PPHS education training modules related to Human Subjects Research Protections, Data Security, and HIPAA for Research. All investigators and research staff have been involved in the conduct of research studies with this participant pool, and are knowledgeable about the Mount Sinai study site and societal and cultural considerations relevant to those eligible for the study. Regular communications will occur between the investigators and all research team members to ensure that details of the protocol are communicated to all and that all staff are familiar with their study-related duties and functions.

5) Study Design

a) Recruitment Methods

Potential subjects will be recruited from a number of sources:

1. The outpatient SCI clinical practices at Mount Sinai Hospital and its affiliated Faculty Practice Associates. Most outpatients with SCI are seen by the investigator on this

project, Dr. Bryce and co-investigator, Dr. Escalon. Dr. Ragnarsson and Dr. Shetreat-Klein also see SCI outpatients, and will invite their patients.

2. Advertisements will be distributed to all those on the Mount Sinai SCI program mailing list via newsletter and email blast. There are currently 900 individuals with SCI on the mailing list; for less than half of those an email address is available. An announcement will be placed inside the newsletter. The same announcement will be sent out to individuals for whom an email address is available, with or without other news announcements, depending on the volume of information to be communicated at that time. Advertisements will be posted in the outpatient SCI clinical practices at Mount Sinai Hospital and its affiliated Faculty Practice Associates. The advertisement is submitted with this application.

b) Inclusion and Exclusion Criteria

Inclusion Criteria

1. Between the ages of 18 and 80 years old
2. Diagnosed with traumatic spinal cord injury
3. Target pain is considered by the physician as at-level SCI in nature to a high degree of certainty (4 or 5 using a Likert confidence scale ranging from 0-5 where 0 is "purely a guess" and 5 is "absolutely certain")
4. Able to give written informed consent
5. Target pain that has been continuously present for at least one month
6. Target pain is of at least moderate average intensity over the past week, e.g., greater than or equal to 4/10 on a numeric rating scale, the cutoff point for moderate pain in an SCI population(77)
7. Target pain is localized within the dermatome which identifies the NLI or within 3 levels below the NLI
8. Subject has been on a stable dose of analgesic mediation (or not on analgesic medication) for at least 3 weeks and is agreeable to remaining on current regimen for the duration of the study (previous prescribed breakthrough analgesics will be allowed)

Exclusion Criteria

1. Pregnancy

2. History of intolerance, hypersensitivity or known allergy to botulinum toxin or its preservatives

3. History of intolerance, hypersensitivity or known allergy to EMLA cream (lignocaine/prilocaine eutectic mixture) which is used as an analgesic during BoNT injection

4. Recent history of administration of botulinum toxin (within previous 6 months)

5. Contraindications to botulinum toxin (myasthenia gravis or other disease of the neuromuscular junction)

6. Coagulation disorder

7. Current infection

8. Insufficient command of English to complete self-report instruments.

c) Number of Subjects

We conducted power analyses for the primary outcome of change on the Numeric Pain Rating Scale (NPRS) from baseline to the 4 week time point for proportions of participants expected to exceed the minimal clinical important difference (MCID). The analysis for a cross-over design was based on assumptions that the MCID value of a decrease in pain rating is 2/10 or more points (78) on NPRS, that 30% of participants in the placebo group would have a positive response to treatment (79), and that 40% more participants (70%) would respond in the treatment group.(24) Assuming two-sided alpha of 0.05, a sample size of 28 will provide 86% power that a difference will be fund. Assuming a 15% drop out rate, a sample size of 32 enrolled participants is necessary for the study to be sufficiently powered to detect a treatment effect.

d) Study Timelines

In this study, there will be 2 procedure performed. The first procedure will be named P1 and consists of subcutaneous injection of either placebo or BoNT. The second procedure will be the cross-over procedure named P2. For the cross-over procedure, the subjects who had initially received BoNT will receive placebo and the subjects who had initially received placebo will receive BoNT.

Randomized Double-Blinded Placebo Controlled

Recruited subjects will be consented, enrolled and evaluated immediately prior to P1 (or during a visit prior to the visit for procedure P1). After the initial pre-treatment

evaluation, subjects will randomly receive either placebo or BoNT subcutaneously (P1). A telephone follow-up (or e-mail follow up) will be performed at 2 weeks and 8 weeks post-P1. An onsite follow up will be performed 4 weeks post P1 and 12 weeks post P1.

Cross-over Study

After the 3rd month on-site evaluation (12 weeks post P1), during the same visit, the subject will proceed to the cross-over study. At this time, the patient will have the option to receive a repeat subcutaneous injection of the cross-over agent. If they desire one, a subcutaneous injection of the cross-over agent will be performed at that same visit. If they wish to defer the repeat injection, they will be contacted and asked every 4 weeks (between 12 weeks and 24 weeks post P1 (no subject will receive P2 after week 24) if they would like to have the subcutaneous injection of the cross-over agent. If they desire one, a repeat injection will be scheduled for the following week.

The rationale for a variable length of time after the initial BoNT/Placebo injection (P1) is to document the variability of individuals' pain response after BoNT. It has been reported in literature, of the subjects that respond to subcutaneous BoNT injections for pain, most will return to their base-line pain score in 12-24 weeks.*(24, 25, 51, 52)*

After P2, a telephone follow-up (or e-mail follow up) will be performed at 2 weeks and 2 8 weeks. An onsite follow up will be performed 4 weeks post P2 and 12 weeks post P2. Subjects will be continued to follow monthly until 24 weeks post P2 to determine duration of effectiveness.

The following outlines the sequence of study procedures for four groups of subjects, those asking for reinjection at 12 weeks (group 1), 16 weeks (group 2), 20 weeks (group 3) or 24 weeks (group 4), respectively

P1 = procedure 1
P2 = procedure 2
Office = onsite evaluation
Tel = telephone contact, evaluation or internet evaluation

	G1	G2	G3	G4	
weeks					months
-1	(eval)	(eval)	(eval)	(eval)	
0	P1	P1	P1	P1	0
1					
2	tel	tel	Tel	tel	
3					
4	office	office	Office	office	1
5					
6					
7					
8	tel	tel	Tel	tel	2
9					
10					
11	tel	tel	Tel	tel	
12	office: P2				3
13					
14	tel				
15		tel	Tel	tel	
16	office	office: P2			4
17					
18		tel			
19			Tel	tel	
20	tel	office	office: P2		5

21					
22			Tel		
23				tel	
24	tel	tel	Office	office: P2	6
25					
26				tel	
27					
28	tel	tel	Tel	office	7
29					
30					
31					
32	tel	tel	Tel	tel	8
33					
34					
35					
36	tel	tel	Tel	tel	9
37					
38					
39					
40		tel	Tel	tel	10
41					
42					
43					
44			Tel	tel	11
45					
46					
47					
48				tel	12

The anticipated enrollment end date is December 2018. The study data collection will be completed within 6 months following the last participant enrollment.

e) Study Endpoints

A number of outcome measures will be used, as listed below:

1. *Pain intensity – past week.* Average pain intensity over the past week will be the primary outcome measure for determining treatment effect. Subjects will be asked to rate their average pain over the past week on a 0-10 numeric pain rating scale (NPRS) with end points 0="no pain" and 10="pain as bad as you can imagine." Average pain over the past week is part of the International Spinal Cord Injury Pain Basic Data Set (ISCIPDS) (80) whose validity and utility in persons with SCI has been demonstrated (81); it also is among measures recommended for use in SCI clinical trials. (82) The lowest and highest pain intensity over the past week will also be recorded to provide additional descriptive information about the pain the participants are experiencing.
2. *Douleur Neuropathique 4 Questions (DN4)* – This is an originally French instrument designed to discriminate between neuropathic and non-neuropathic pain. No psychometric testing in the English version of the instrument has been performed for SCI. In French and Swedish versions, it has shown good inter-rater reliability and validity. (82) It consists of 10 items, each scored on a binary scale. This test will be used to distinguish between at level (neuropathic) pain and nociceptive pain in SCI subjects.
3. *Spinal Cord Injury Pain Instrument (SCIPI Version 1.1)*. The SCIPI is an interview based screening instrument consisting of 7 items designed to differentiate neuropathic from non- neuropathic pain in individuals with SCI.
4. *International Basic Pain Dataset.* The International Basic Pain Dataset is an assessment tool which includes several components including: location of pain, temporal qualities of the pain, type of pain, pain interference measures of activity, sleep, and mood. It has been shown to be valid in an interview/self-report format.(81) This will be collected for up to 3 pains localized to the back which can be differentiated as unique pains. These pains may or may not be neuropathic.
5. *7-Point Guy/Farrar Patient Global Impression of Change (PGIC)* – This scale measures the global treatment effect from very much improved to very much worse. Subjects will be asked to rate the treatment's effect at each re-evaluation. In this investigation, the PGIC rating will take the form of, "Taking into account your pain level and how it affects your life, are you feeling better, the same or worse than when you started treatment?" If the individual states that there is no change, then the rating is complete. If he or she is worse or better, the individual is asked to quantify the

magnitude of the change as 1-very much better; 2-better; 3-somewhat better; or 5-somewhat worse; 6-worse; 7-very much worse. The PGIC will be a secondary outcome measure of treatment effect. The PGIC one of the recommended scales for measuring the global treatment effect and can be used to complement the one-dimensional pain intensity scales. (82)

6. *Adverse Effects (AE)* – Subjects will be monitored for adverse effects. As mentioned in the literature review, the most common side effects are focal weakness, local edema, short-term hyperesthesia, fatigue, malaise, and flu-like symptoms. There are no expected serious side effects.

7. *Pain Medication Usage/Other treatments* – Subjects will be asked to report the use or lack of use or changes in dose or use of other pain medications and other treatments they are receiving.

8. *Static and Dynamic Mechanical Allodynia testing.* Mechanical allodynia is a characteristic of evoked pain in subjects with neuropathic pain. Static allodynia to mechanical stimuli will be defined as a sensation of pain evoked by the pressure of the end of a wooden stick. The end of a wooden stick will touch the affected region with enough pressure to indent the skin, for 10 seconds. Afterwards, the subject will be asked to rate the perceived pain on an 11-point NRS. Dynamic allodynia will be tested by stroking the affected region gently with a cotton swab, 4 times at a rate of 3-5cm per second over an area of 5cm. If there is an evoked clear sensation of pain, the subject is asked to rate the intensity of dynamic allodynia using the 11-point NRS. The region of static and dynamic allodynia, if present, will be marked and recorded.

9. *Punctate Hyperalgesia.* Punctate hyperalgesia will be defined as the altered sensation produced with a safety pin when applied to the marked identified painful region as compared to a reference region (an area of normal sensation above the level of injury). The reference region will be tapped twice with a safety pin for about half a second with a 5 second interval between taps. The subject will rate his or her pain with the 11-point NRS. Then, the test will be repeated on the affected region and the subject will be asked to rate their pain again. The test is considered positive if there is an increase of at least 2 points on the 11-point NRS for pain.

10. *Wind-up pain/Temporal Summation.* Mechanical wind-up pain will be defined as the perceived increase in pain intensity when a painful stimulus is delivery repeatedly. To test for mechanical wind-up pain, the reference region (an area of normal sensation above the level of injury) will be tapped with the safety pin at a rate

of approximately 2-3 taps per second (2Hz) for 30 seconds. The subject will rate his or her pain on the 11-point NRS. Then, the test will be repeated on the affected region. The subject will be asked to rate the pain caused by the safety pin at the end of the test using the 11-point NRS for pain. The test is considered positive if there is an increase of at least 2 points on the 11-point NRS for pain.

11. *Patient Generated Index (PGI).* Activity is highly individual-specific, and it is not thought that any of the standard validated functional instruments, such as the Functional Independence Measure (FIM), would be sensitive in detecting changes in activity due to decreasing pain. We will adapt the Patient-Generated Index (83, 84) to develop an individualized measure of activity that is sensitive to short-term changes in activity levels due to a change in pain severity. In the PGI, subjects are asked to: (1) list five activities that are affected by their pain (a listing of activities nominated by many SCI subjects with pain may be used to stimulate their memory); (2) rate how they function in each chosen area, on a scale from 0 to 100, where 0 represents the worst they can imagine, and 100 means "exactly as they would like to be"; and (3) quantify the relative importance of these five areas by distributing 50 points over them, thus assigning importance weights. The PGI score is calculated as the sum (across the five areas) of the products of importance and rating of pain effect. A decrease in pain resulting in improvement in activity level would result in a higher PGI score. As in other studies utilizing "customized" functional or quality of life measures (85, 86) the PGI was found to be more sensitive to low back pain interventions than were other standard measures. (84) To accomplish a high level of sensitivity, the subject-identified activities in the present study must be ones that (1) are completed at least weekly (actually or preferentially), (2) at baseline, are rated at 75 or less on the 0-100 scale (to offer room for gain), and (3) are not limited by the SCI itself, but are stated to be limited by the pain. We will ask subjects to complete the PGI first at the initial assessment visit (Visit 1). At all later follow up, subjects will perform only steps (2) and (3) above, guaranteeing that the activities considered are the same throughout the study. Statistical analysis will consider the effect, if any, of changes in importance weights over time (step 3). If these are significant, either the baseline weights will be used throughout, or an average of the weights for the same activity will be used at all time points. The PGI will serve as a secondary outcome measure of treatment effect.

12. Back pain impact. For many patients, the (almost) continuous presence of pain in the back from the moment of getting up in the morning is what in its cumulative

effect limits their activity level. Thus, even if the maximum pain severity remains unchanged with BoNT injection, pain over a shorter time may be a worthwhile outcome. To assess this, participants will be asked to report on the day of evaluation (1) on average, for the past week, what time did you get up; (2) on average, for the past week, about what time, if at all, did your pain become so problematic or significant that you stopped the activity you were doing, or at least modified it (going slower, etc.) or took a rest; (3) on average, for the past week, how often did the pain become so significant that you stopped what you were doing and took a rest? (4) If you did take a rest, how long of a rest do you have to take before you are able to resume the activity you were doing?

f) Procedures Involved in the Human Research

Study Design

This is a randomized double-blind placebo controlled cross-over study.

Study Procedure

Recruited subjects will be consented, enrolled and evaluated. During the pre-procedure evaluation, subject history and a physical exam will provide information about the pain, including localization, pain characteristics, and current analgesics medication use. The subjects' existing medical therapy (including analgesics) will be continued during the study period (but changes, e.g. decrease in analgesic intake, will be noted).

During the physical exam, the painful region will be identified with palpation. The borders of the painful region will be marked with a marker. Using a plastic circle cutout with a 1cm radius, injection sites will be measured out and clearly marked. Photographs of the marked painful region with the identified injection sites will be taken, printed out and kept on file. For the cross-over injection procedure, the images will be used to replicate the injection pattern. Subjects can elect to have the procedure performed on the same day as their evaluation or return at a later date to have the procedure performed.

Subjects will receive subcutaneous injections into the marked painful region. The injection will consist of either placebo or BoNT. The syringes will be prepared by a third party prior to the injection and the administrator of the procedure will be blinded to syringe content. This physician will be performing the injections under sterile conditions. Local anesthesia, EMLA (lignocaine/prilocaine eutectic mixture) cream, up to 4 grams, will be applied topically for local anesthesia. After 50 minutes, the cream will be cleaned off. Overlying skin will be sterilized with either betadine or alcohol solution.

1. *Placebo:* Placebo consists of 0.9% normal saline. Each injection will be 0.2mL, administered with a 25 gauge needle subcutaneously into the affected area. The marked area will have subcutaneous injections (maximum of 80) each separated from the surrounding ones by a radius of 1 cm.

2. *Botulinum Toxin:* Each vial of botulin toxin (100U, BOTOX, Allergan) will be reconstituted with 4ml non-preserved saline solution (0.9%) as recommended by the manufacturer (concentration of 5 units BoNT/0.2ml). Each injection will be 0.2mL (BOTOX, 5 units), administered through a 25 gauge needle. The marked area will have subcutaneous injections, each separated by a radius of 1 cm, from the other injections into the marked area, (maximum of 80 injections, 400 Units).

The procedure described above, adapted from recent studies using subcutaneous injections of BoNT, is estimated to last about 45 to 60 minutes. (22-24). Patients will be monitored for 5 minutes post-procedure for immediate adverse effects. There are no expected serious adverse effects.

The procedure above will be repeated for the cross-over portion of the study.

Procedures to Lessen the Probability or Magnitude of Risk

Risks are expected to be low because no reported significant adverse events have been reported in the literature. The procedure will be performed under sterile condition and patient will be monitored 5 minutes post procedure for any adverse effects. Patients will be educated on known adverse events of BoNT and will be provided a contact number should there be any questions. For serious adverse events they will be referred to the nearest emergency room.

g) Specimen Banking

Not Applicable

h) Data Management and Confidentiality

All research data will be kept in password-protected files on the Mount Sinai network or in hard copy form in locked files in the offices of research staff. All research data will be labeled with a study ID number rather than subject name. Subject contact information and a list matching subject names with IDs (linking file)* will be kept separate from research data. Data will be stored until the conclusion of the project (including composition of manuscripts) and as long as necessary to ensure compliance with regulatory requirements. Data will be accessible to Mount Sinai investigators only.

* The linking file will be stored electronically on a Mount Sinai server. As with all other electronic files containing data or participant information, the file will be secured by two levels of password protection, one at the level of the workstation from which the server will be accessed and another at the level of the file itself.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

Part I: Elements of a Data and Safety Monitoring Plan

1. ***MSSM Principal Monitor:***

Principle Investigator:

Last Name: Bryce

First Name: Thomas

Academic Title: MD

Department: Rehabilitation Medicine

[redacted]

Phone: 212-241-6321

Fax: 212-369-6389

E-mail: Thomas.bryce@mountsinai.org

2. Patient monitoring will be conducted by the principal investigator. The principal investigator has prior experience working with individuals with SCI at Mount Sinai Medical Center, as well as experience with botulinum toxin in intramuscular injections.
3. Adverse events, subject compliance with the protocol and drop outs will be monitored for safety.

4. Significant adverse events are not expected to occur. Thus, accumulated adverse events will be reviewed quarterly.

5. There is no expected interruption or alteration of the study design.

6. There are no expected dose selection procedures to be performed to minimize toxicity.

7. There is no specialized grading system that will be used to evaluate adverse events.

8. Physicians will complete case forms, and turn them over to the research assistant. The assistants will review them for completeness, legibility and clarity, and return them to the

physician as necessary. The research assistant will enter the data in an Excel file; all entries will be compared by an investigator against the case report form (CRF), and errors corrected. The PI will monitor the presence of all CRFs to be completed over time for each subject.

9. In addition to the PPHS, the FDA, sponsor and IRB will be notified should there be a temporary or permanent suspension of the study.

j) Withdrawal of Subjects

Participants may withdraw voluntarily from the study at any time. No negative effects are expected to be experienced by participants who choose to withdraw from the study. Participants may be withdrawn from the study by the investigators without their consent if it is determined that their eligibility or appropriateness for inclusion changes after enrollment. Once a participant withdraws (or is withdrawn) from study participation, all study procedures for that participant will cease. The participant will continued to be followed for adverse events.

6) Risks to Subjects

BoNT has been shown to have a favorable safety and tolerability profile across a broad spectrum of therapeutic uses. (48, 74) Compared to gabapentin, adverse events in BoNT are less frequent and less severe. (74) Adverse events reported to be associated with BoNT administration are generally related to the mechanism of action of the toxin, most commonly dose-dependent focal weakness. Other local side effects include injection-associated pain, edema, erythema, ecchymosis, headache and short-term hyperesthesia. (74) These side effects are usually temporary. Systemic side effects include nausea, fatigue, malaise, rash and flu-like symptoms. There has been a case report suggesting a possible anaphylaxis reaction to the toxin; (75) however, in clinical trials, there has not been any reported anaphylaxis or any serious systemic adverse effects related to BoNT. (74, 76) Long term studies in the safety of BoNT have found the appearance of primary and secondary resistance over a 10-year period (resistance defined as <25% improvement after 2-3 consecutive treatments). (74) There was no other identified long term side effect. If we combine the reported data of clinical studies (21-25, 53) using subcutaneous BoNT injections (6 studies, total of 73 subjects receiving BoNT), the incidence of AE is 5% (3AE out of 73 subjects), the most common being local swelling at the injection site. There were no permanent side effects reported. It is also noted in the literature that the subcutaneous injection may cause mild-moderate pain during the actual procedure itself.(22, 23)

7) Provisions for Research Related Injury

The physicians performing the procedure are trained and experienced clinicians and can take action if they observe any signs of harm. In case of adverse events, subjects will be referred to their own physician, to the Mount Sinai Emergency Room, or to a psychological counselor in their own community, as deemed appropriate.

8) Potential Benefits to Subjects

Participants in this study may or may not experience direct benefits. The direct benefit would be temporary (12+ weeks) relief of at-level back pain.

9) Provisions to Protect the Privacy Interests of Subjects

Communications with participants will take place at a place and time of their choosing. Conversations with and physical examinations of participants will take place in private locations (i.e. exam room with closed door) to avoid participants being seen or overheard by others not involved with the study. Participants will be asked if they are comfortable with the setting of the examination before it begins. Research team members will have received training in appropriate interactions with research participants and will approach all participants in a respectful manner.

10) Economic Impact on Subjects

No medical costs will be incurred as part of participation in this study. Participants will be expected to travel to Mount Sinai Hospital either three or four times. There are no plans for reimbursement at this time.

11) Payment to Subjects

There will be no payments to the subject at this time.

12) Consent Process

Interested subjects will be pre-screened to confirm that they meet the inclusion and exclusion criteria. The inclusion and exclusion criteria will be read to the subject in full without interruption. The subject will be instructed not to give any information. If the subject does not meet the inclusion and exclusion criteria, he or she will withdraw from the screening process without the interviewer knowing which of the criteria they did not meet.

Consent will be obtained prior to the initial assessment, in a suitable meeting room at

Mount Sinai (most likely a private office or conference room in the Rehabilitation Medicine Dept.), or in a private room in the outpatient clinic area. Either one of the investigators or a consent delegate will explain the study and obtain consent. Potential participants may ask questions about the study at any time, and will be given as much time as they feel they need to decide about participation.

Subjects will be asked to state in their own words the following: purpose of the study; methods; risks and benefits; voluntary nature of participation and alternatives. If their response indicates a lack of understanding, explanations will be repeated, and potential participants will again be asked to describe the study in their own words. Subjects who after a second explanation fail to grasp the nature, method and risks of the study will not be allowed to participate.

If a potential participant decides to enroll in the study, s/he and the research team member will complete the consent form, a copy of which will be provided to the subject for his/her records. Consent procedures will take place in accordance with Standard Operating Procedure HRP- 090 Informed Consent Process for Research.

Children, cognitively-impaired adults, and non-English speakers are excluded from participation in this study.

13) Process to Document Consent in Writing

The standard PPHS consent template will be used to document informed consent.

In cases where a signature is being sought from the participant, but s/he is unable to physically sign the consent form due to upper extremity impairment, consent will be documented on the signature page of the consent form, to which a section has been added to document the circumstances of the situation, the method used by the subject to demonstrate understanding and consent to participation, and the signature of an impartial witness to the consent process. The content of this section was designed to address the policy described in section 3.3 of PPHS SOP-091.

14) Vulnerable Populations

Include	*Exclude*	*Vulnerable Population Type*
	X	*Adults unable to consent*
	X	*Individuals who are not yet adults (e.g. infants, children, teenagers)*

	X	*Wards of the State (e.g. foster children)*
	X	*Pregnant women*
	X	*Prisoners*

15) Multi-Site Human Research (Coordinating Center)

Not applicable

16) Community-Based Participatory Research

Not Applicable

17) Sharing of Results with Subjects

Findings of the study will shared with study participants and others with SCI via the SCI rehabilitation program's newsletter, and other similar venues.

18) External IRB Review History

Not applicable

19) Control of Drugs, Biologics, or Devices

BOTOX (onabotulinumtoxinA, *Allergan*) will be provided for research subjects at no charge to them or their insurance providers. The study drug/agent will be shipped by the manufacturer to:

Thomas Bryce, MD
Rehabilitation Medicine Associates
[redacted]

Placebo consists of 0.9% normal saline. It will be supplied by *Allergan*. Both placebo and BOTOX will be stored in a locked refrigerator (2-8 degrees Celsius) at a Mount Sinai

Hospital. The principal investigator will be the only person with access to the key. The labels for the study drug will include the following: "Store at", "Keep Out of Reach of Children", "For Clinical Trial Use Only", "Caution: New Drug: Limited by Federal (USA) Law to Investigational Use Only". In addition, a black box warning will read: POTENTIAL FOR HUMAN BIRTH DEFECTS.

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