TITLE: Comparison of Botulinum Toxin Versus Placebo Injections to Temporalis and Masseter Muscles in the Management of Myofascial Pain Disorder: A Randomized Clinical Trial

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Statement of Compliance

[The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and 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, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

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Institution Name

_____	_____	_____
Principal Investigator's Name	**Principal Investigator's Signature**	**Date**

List of Abbreviations

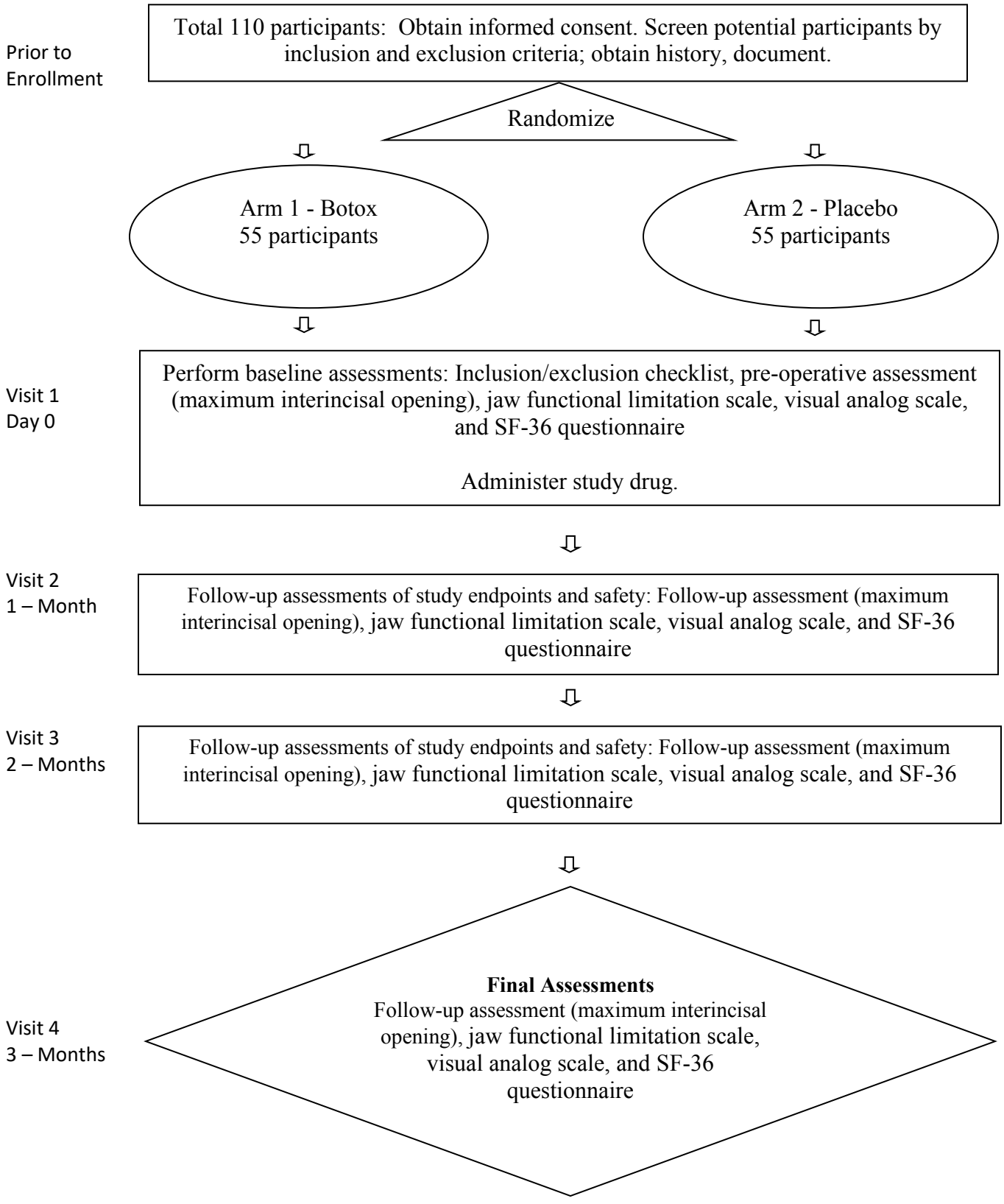
AE	Adverse Event
BTA	Botulinum Toxin-A
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
MPD	Myofascial Pain Disorder
PHI	Protected Health Information
PI	Principal Investigator
RDC	Research Diagnostic Criteria
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMD	Temporomandibular Disorders
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	Comparison of Botulinum Toxin Versus Placebo Injections to Temporalis and Masseter Muscles in the Management of Myofascial Pain Disorder: A Randomized Clinical Trial
Short Title:	Botox Injections for MPD
Principal Investigator:	Gwendolyn Reeve, DMD
Study Description:	Double-blind placebo controlled clinical trial with participants receiving either a solution of placebo injected into the masseters and temporalis muscles or a solution of botulinum toxin A for treatment of myofascial pain
Sample Size:	N = 110
Enrollment:	This study will enroll 110 subjects and screen up to 175
Study Population:	Eligible participants will be male and female adults ages 18 – 65 identified as having a myofascial pain diagnosis according to the research diagnostic criteria
Enrollment Period:	18 months
Study Design:	The study design will be a double-blind placebo controlled clinical trial. The participants will receive either a solution of placebo (total 4cc unpreserved 0.9% sodium chloride) injected into the masseters and temporalis muscles or a solution of botulinum toxin A (a total of 100 units reconstituted with 4cc unpreserved 0.9% sodium chloride). The patients will be stratified into gender groups. The participants will be monitored for 3 months. The primary outcome measure will be pain measured on a visual analog scale prior to treatment and at one, two, three months post-treatment. Secondary outcome measures performed at the same intervals will be quality of life (short form 36), maximum interincisal opening, and functional status via the jaw functional limitation scale
Description of Sites/ Facilities Enrolling	
Participants:	**Weill Cornell Medicine** Division of Oral and Maxillofacial Surgery Clinic 525 East 68th Street, F-2132 New York, NY 10065 **University of Illinois, College of Dentistry** Oral and Maxillofacial Surgery Clinic 801 S. Paulina Street, Room 110 Chicago, IL 60612
Study Duration:	December 31, 2022
Participant Duration:	Subjects will participate in one injection visit plus 3 follow-up visits at 1-month, 2-months, and 3-months post-injection for a total of 4 months
Study Agent/Device Name	
Intervention Description:	The participants will receive either a solution of placebo (total 4cc unpreserved 0.9% sodium chloride) injected into the masseters and temporalis muscles or a solution of botulinum toxin A (total of 100 units reconstituted with 4cc unpreserved 0.9% sodium chloride)

Primary Objective:	The primary objective will be to compare the pain measured on a visual analog scale prior to treatment and at one, two and three months post-treatment in both the Botox and placebo groups.
Secondary Objectives:	The secondary objectives will be to compare the quality of life (SF-36), maximum interincisal opening, and functional status via the jaw functional limitation scale in both the Botox and placebo groups.
Exploratory Objectives:	None
Endpoints:	The primary endpoint is improvement of pain on a visual analog scale (VAS) between pre-op, 1, 2, and 3 months post-op. The secondary endpoints are function (MIO/jaw limitation scale) and quality of life (SF36)

1.1 Schema


Prior to Enrollment
Total 110 participants: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
Arm 1 - Botox
55 participants
Arm 2 - Placebo
55 participants
Visit 1
Day 0
Perform baseline assessments: Inclusion/exclusion checklist, pre-operative assessment (maximum interincisal opening), jaw functional limitation scale, visual analog scale, and SF-36 questionnaire
Administer study drug.
Visit 2
1 – Month
Follow-up assessments of study endpoints and safety: Follow-up assessment (maximum interincisal opening), jaw functional limitation scale, visual analog scale, and SF-36 questionnaire
Visit 3
2 – Months
Follow-up assessments of study endpoints and safety: Follow-up assessment (maximum interincisal opening), jaw functional limitation scale, visual analog scale, and SF-36 questionnaire
Visit 4
3 – Months
Final Assessments
Follow-up assessment (maximum interincisal opening), jaw functional limitation scale, visual analog scale, and SF-36 questionnaire

1.2 Study Objectives

1.2.1 Primary Objectives

The primary objective will be to compare the pain measured on a visual analog scale prior to treatment and at one, two and three months post-treatment in both the Botox and placebo groups.

1.2.2 Secondary Objectives

The secondary objectives will be to compare the quality of life (SF-36), maximum interincisal opening, and functional status via the jaw functional limitation scale in both the Botox and placebo groups.

2. Background

2.1 Disease

Myofascial pain is classically used to describe pain experienced in the masticatory muscles and its associated structures (1). It afflicts nearly 10% of Americans (2). There have been many described treatments such as the use of oral appliances, non-steroidal anti-inflammatory medications, physiotherapy, behavioral therapy and counseling, acupuncture, and botulinum toxin injections (2). However, no single treatment has been found to be significantly superior to the others (2).

2.2 Investigational Agent

Botulinum Toxin-A (BTA) inhibits the release of acetylcholine at the neuromuscular junction, thus preventing further muscle contraction, resulting in paralysis of the affected muscles (3). It is reasonable to expect that those with pain associated with the muscles of mastication will have relief with BTA injection. There will be substantial clinical significance if BTA injections are found to reduce myofascial pain, as this has classically been difficult to treat.

2.3 Rationale

Myofascial pain is classically used to describe pain experienced in the masticatory muscles and its associated structures (1). It afflicts nearly 10% of Americans (2). There have been many described treatments such as the use of oral appliances, non-steroidal anti-inflammatory medications, physiotherapy, behavioral therapy and counseling, acupuncture, and botulinum toxin injections (2). However, no single treatment has been found to be significantly superior to another (2).

Botulinum Toxin-A (BTA) inhibits the release of acetylcholine at the neuromuscular junction, thus preventing further muscle contraction, resulting in paralysis of the affected muscles (3). It is reasonable to expect that those with pain associated with the muscles of mastication will have relief with BTA injection. The clinical significance would be substantial if BTA injections are found to reduce myofascial pain as this has classically been difficult to treat. Prior investigations have been conducted to demonstrate the clinical effectiveness of Botulinum Toxin-A (BTA) for reduction in pain associated with myofascial pain disorder (4). However, no double-blinded randomized controlled

clinical trials have been conducted. The existing evidence is suggestive of a reduction in pain from BTA injections, however there has not been a robust demonstration of this in the literature.

A study conducted by Freund et. al. in 1999 studied 15 subjects who were treated with BTA. 150 units of BTA were injected into the masseter and temporalis muscles bilaterally. Subjects were assessed at 2 week intervals for a total of 8 weeks. There was a statistically significant reduction in the visual analogue scale of pain for these patients with a 45% reduction in reported pain level after 8 weeks (1).

Another study by Guarda-Nardini et al. in 2012 examined 30 patients who were randomized to either receive BTA injections or fascial manipulation techniques (5). A 32% reduction in pain level was found for patients who underwent BTA injections. The existing literature demonstrates a benefit from BTA in pain reduction. This should be examined more closely with a double blinded randomized controlled clinical trial. BTA has been previously FDA approved to treat muscle spasticity of the upper limb as well as chronic migraines but it is considered an off-label use for treatment of myofascial pain disorder in the masticatory region.

Gwendolyn Reeve, DMD is a full-time faculty member of the division of oral and maxillofacial surgery at Weill-Cornell Medicine. She practices the full scope of oral and maxillofacial surgery but has developed a special interest in minimally-invasive temporomandibular disorder treatment efforts including arthroscopic joint surgery and intra-muscular botulinum injections into the masticatory region for myofascial pain disorder. She currently has other research efforts in the area of temporomandibular joint disorder. She is collaborating with a scientist, Dr. Mildred Embree, at Columbia University to grow stem cells from the cartilage, synovial tissues, and synovial fluids removed during the arthroscopic and open temporomandibular joint surgery Standard of care treatment for myofascial pain disorder at Weill Cornell/NYP involves the use of muscle relaxants, NSAIDS, warm compresses, night guards, and physical therapy. Botulinum injections into the masticatory muscles is a commonly performed adjudicative procedure for treatment of myofascial pain disorder at Weill-Cornell/NYP.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

Risks of BTA include side effects such as:

- problems swallowing, speaking, chewing, or breathing due to weakening of associated muscles
- spread of toxin effects causing muscle weakness
- allergic reactions
- discomfort at the injection site
- headaches
- bruising at injection site
- syncope due to anxiety or needle related pain
- muscle atrophy
- facial palsy
- localized numbness
- skin infections

2.4.2 Known Potential Benefits

Possible direct benefits of participating in the study are a decrease in pain level, increase in range of motion of the jaw (mouth opening), or improved jaw function. Possible indirect benefits of participating in the study are improvement of quality of life by decrease in pain and improved jaw function. Participants may have increased ability to eat and speak without pain or limitation in function. Information collected in the study may help benefit others who suffer from myofascial pain disorder. We hope to learn more about the efficacy of BTA in treatment of this disorder.

2.4.3 Assessment of Potential Risks and Benefits

Subjects will be informed of all potential risks and benefits of BTA prior to consent and enrollment on the study so that they can determine whether or not they would like to participate in the study.

2.5 Correlative Studies Background

Not Applicable

3. Study Design

3.1 Overall Design

The proposed study is a randomized clinical trial comparing BTA to placebo injections into the masseter and temporalis muscles in management of myofascial pain disorder. The hypothesis is that injections of BTA reduces the intensity of myofascial pain more than placebo. Currently, in the literature, there is no evidence for the best non-surgical treatment modality for treatment of myofascial pain disorder of the muscles of mastication. Many different approaches have been described such as oral appliances, medications (NSAIDS and muscle relaxants), physiotherapy, acupuncture, trigger point injections, and botulinum injections. To date, the literature concerning trigger point injections and botulinum injections for treatment of myofascial pain disorders of the muscles of mastication is limited. Currently, injection of BTA is not FDA approved for myofascial pain disorder of the masseters and temporalis muscles.

Eligible participants in the clinical trial will be male and female adults ages 18 – 65 identified as having a myofascial pain diagnosis according to the research diagnostic criteria. All subjects will have myofascial pain disorder. Healthy controls will not be involved in the study.
The study design will be a double-blind placebo controlled clinical trial. The participants will receive either a solution of placebo (total 4cc unpreserved 0.9% sodium chloride) injected into the masseters and temporalis muscles or a solution of botulinum toxin A (total of 100 units reconstituted with 4cc unpreserved 0.9% sodium chloride). Both treatment groups are considered investigative. The patients will be stratified into gender groups. The participants will be monitored for three months.

The primary outcome measure will be pain measured on a visual analog scale prior to treatment and at one, two and three months post-treatment. Secondary outcome measures performed at the same intervals will be quality of life (short form 36), maximum interincisal opening, and functional status via the jaw functional limitation scale. The only study procedures are the injection of botulinum toxin or placebo and the use of visual analog scale, measurement of maximum incisal opening and the use of visual analog scale and questionnaires.

On the first visit, participants will be asked to fill out questionnaires. The questionnaires completed on the first visit include health history and history of present symptoms. Participants will then rate their pain on a visual analog scale. The visual analog scale is a 10cm line in which participants are asked to place a hash mark somewhere along that line to represent the amount of pain they feel. The other questionnaires completed on your first visit will be the short form 36 quality of life scale and the jaw functional limitation scale. The participant will then undergo an injection of either botulinum toxin or saline into the masseter and temporalis muscles. The participants are then reevaluated at one, two, and three months post-treatment. They will be asked to fill out the same questionnaires about quality of life and jaw function. They will again rate their pain on the same visual scale. Maximum incisor opening will be measured at these visits.

3.2 Scientific Rationale for Study Design

Botulinum Toxin-A (BTA) inhibits the release of acetylcholine at the neuromuscular junction, thus preventing further muscle contraction, resulting in paralysis of the affected muscles (3). It is reasonable to expect that those with pain associated with the muscles of mastication will have relief with BTA injection. The clinical significance would be substantial if BTA injections are found to reduce myofascial pain as this has classically been difficult to treat. Prior investigations have been conducted to demonstrate the clinical effectiveness of Botulinum Toxin-A (BTA) for reduction in pain associated with myofascial pain disorder (4). However, no double-blinded randomized controlled clinical trials have been conducted. The existing evidence is suggestive of a reduction in pain from BTA injections, however there has not been a robust demonstration of this in the literature.

3.3 Justification for Dose

Not Applicable

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed the initial treatment visit and all three of the follow-up visits required for the study. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

4. Subject Selection

4.1 Study Population

Eligible participants in the clinical trial will be male and female adults ages 18 – 65 identified as having a myofascial pain diagnosis according to the research diagnostic criteria. All subjects will have myofascial pain disorder. Healthy controls will not be involved in the study.

4.2 Inclusion Criteria

1. 18 – 65 years of age
2. Able to give informed consent
3. Myofascial pain of masticatory muscles as defined according to the RDC/TMD criteria
4. Baseline pain measured by the subject ≥ 3.5/10 on visual analog scale

4.3 Exclusion Criteria

1. Baseline pain measured by the subject < 3.5/10 on visual analog scale
2. Central/neuropathic pain disorder affecting the masticatory muscles
3. Temporomandibular joint arthralgia that is more severe than the myofascial pain disorder affecting the masticatory muscles
4. Previous temporomandibular joint surgery
5. Systemic arthropathies
6. Fibromyalgia
7. Allergy to study medications
8. Traumatic injury of masticatory muscles or temporomandibular joint within last 12 months
9. Mandibular fracture within the last 12 months
10. Pregnancy or breastfeeding
11. Cervical radiculopathy or surgery
12. Prior Botox injection in the masticatory muscles
13. Initiation of additional treatment of MPD within the past 3 months

4.4 Lifestyle Considerations

Not Applicable

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

4.6 Strategies for Recruitment and Retention

Physicians (neurologists, otolarygnologists, dentists) who would normally refer patients to oral and maxillofacial surgery at Weill-Cornell for treatment of myofascial pain disorder of the masticatory region will be made aware of the study and are welcome to refer patients for evaluation to participate in the study.

During the normal course of consultation in the office based environment, if a potential patient qualifies for participation in the research study, Dr. Gwendolyn Reeve will introduce the study and will obtain informed consent.

Study information will also be posted to social media sites, such as Facebook, Twitter and Instagram. IRB approved study fliers will be posted throughout the hospital to help boost enrollment

Participants in this study will be compensated for participation. The will receive $25 on Clincards per study visit for 4 visits, for a total of $100.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Sub-sites will send subject enrollment log along with redacted consent forms to WCM study staff to confirm Subject Registration. Sub-sites will also be entering subject data into the REDCap database created for this study.

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events

	Pre-Study	Treatment Visit	1-Month Follow-Up	2-Month Follow-Up	3-Month Follow-Up
Informed Consent	X				
Demographics	X	X			
Medical history	X	X			
Interincisal measurements		X	X	X	X
Visual Analog Scale		X	X	X	X
Jaw Functional Limitation Scale		X	X	X	X
SF-36		X	X	X	X
Botox/Placebo Injection		X			
Adverse Event Assessment		X	X	X	X

6.1.1 Pre-Study Visit

- Informed consent
- Inclusion/exclusion checklist
- Pharmacy order form completed and sent to pharmacy for randomization and processing
    - Eligible subjects will be randomly assigned to Botox injections or placebo treatment groups in a 1:1 ratio using a randomization scheme developed by the Dr. Paul Christos and the Division of Biostatistics and Epidemiology, Department of Healthcare Policy & Research

6.1.2 Treatment Visit

- Pre-operative assessment
- Demographics
- Medical history
- Interincisal measurements
- Visual Analog Scale
- Jaw Functional Limitation Scale
- Short Form 36 Health Survey
- Botox/Placebo injections

6.1.3 Follow-up Phase

6.1.3.1 1-Month Visit

- Interincisal measurements
- Visual Analog Scale
- Jaw Functional Limitation Scale
- Short Form 36 Health Survey
- Adverse event assessments

6.1.3.2 2-Month Visit

- Interincisal measurements
- Visual Analog Scale
- Jaw Functional Limitation Scale
- Short Form 36 Health Survey
- Adverse event assessments

6.1.3.3 3-Month Visit

- Interincisal measurements
- Visual Analog Scale
- Jaw Functional Limitation Scale

- Short Form 36 Health Survey
- Adverse event assessments

7. Study Intervention

7.1 Study Intervention/Device Description

Botulinum Toxin A will be shipped directly to the Investigation Pharmacy from Allergan.

7.2 Availability

Botulinum Toxin A is an investigational agent supplied to investigators by Allergan.

7.3 Acquisition and Accountability

Half of the study materials will be shipped to the study site upon full execution of the agreement with Allergan and study approval by the IRB. Study material is shipped directly to the Investigational Pharmacy for storage and accountability.

The other half of the study materials will be shipped to the study site upon achieving 50% of the target enrollment and written confirmation that the study has been registered on www.clinicaltrials.gov.

7.4 Formulation, Appearance, Packaging, and Labeling

Not applicable

7.5 Product Storage and Stability

The product will be stored in the Investigational Pharmacy at WCM.

7.6 Preparation

Subjects will be receiving either a solution of placebo, a total of 4 cc unpreserved 0.9% sodium chloride, or a solution of botulinum toxin A, a total of 100 units reconstituted with 4 cc unpreserved 0.9% sodium chloride. Study drug will be prepared by the Investigational Pharmacy at WCM.

7.7 Dosing and Administration

Subjects will be receiving either a solution of placebo, a total of 4 cc unpreserved 0.9% sodium chloride, or a solution of botulinum toxin A, a total of 100 units reconstituted with 4 cc unpreserved 0.9% sodium chloride. Injections will take place in the Oral and Maxillofacial Surgery clinic on Baker 21 at WCM or at the University of Illinois at Chicago Oral Surgery clinic.

7.7.1 Dosing Delays/Dose Modifications

Not applicable

7.8 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on follow-up assessment form throughout the course of the study and saved in REDCap.

7.9 Duration of Therapy and Criteria for Removal from Study

Study Termination Guidelines: A subject's follow-up in the study will end after one of the follow applies:

- Subject's voluntary withdrawal
- Subject lost to follow-up
- Subject death
- Completion of all scheduled study follow-up appointments

7.10 Duration of Follow Up

Subjects will be followed for 3-months after receiving treatment or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.11 Measures to Minimize Bias: Randomization and Blinding

The investigator and co-investigators are blinded to the randomization schema and treatment. The randomization schema was developed by Dr. Paul Christos and Gulce Askin, MPH in the Division of Biostatistics and Epidemiology, Department of Healthcare Policy and Research. They have shared the schema with the Investigational Pharmacy who draws up the appropriate study drug for the subject and is picked up by the blinded study team. After all subjects are enrolled and have completed follow-up, the study team will be unblinded.

Once the study has been fully closed to enrollment and all data collection has been completed, all participants who received study treatment will be unblinded. The rationale for this is to provide participants with the appropriate information about their treatment while on study so they can make decisions about future treatment and management of their TMJ. Unblinding will occur via email or mail (if email address is not available to the study team). The unblinding text will be submitted to the IRB for review and approval before use.

7.12 Study Intervention/Follow-up Compliance

Not applicable

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

There is only one study intervention, injection of BTA or placebo, so there will be no discontinuation of the study intervention.

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

Not applicable

9.1 Laboratory Correlative Studies

Not applicable

9.2 Special Studies

Not applicable

10. Measurement of Effect

Efficacy of treatment of myofascial pain disorder with BTA injections will be determined at the completion of the study.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.
All subjects enrolled in this clinical trial will have their data entered into the appropriate data entry forms in REDCap by the study staff at Weill Cornell Medicine and the University of Illinois at Chicago.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

Neither the Investigator nor BMS will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IEC/IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB/IEC requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify

potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file, locked in the Principal Investigator's office. Paper and electronic records will be maintained for 2 years after the investigation is discontinued according to FDA guidelines. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

Based on the preliminary data and the sample size calculations estimating a difference in mean pre-post VAS change between groups of 1 point or greater (on a scale of 1-10), we plan to enroll a total of 110 subjects between the two study sites. Estimated 55 subjects will be enrolled at Weill-Cornell Medical Center/ New York Presbyterian Hospital and 55 subjects will be enrolled at the University of Illinois at Chicago. With 55 patients in the botulinum toxin A injection group and 55 patients in the placebo group (N=110), the study will have more than 90% power to detect a difference in mean in pre-post change between groups of 1.0 point or greater on VAS, using a two-sided t-test and assuming a standard deviation of 1.5 for the mean difference. This calculation allows for 10% attrition rate.

An intent-to-treat design will be followed and all subjects will have scheduled outcome evaluations until the end of the study, death of the subject, or subject refusal. Subjects will be withdrawn from their randomly assigned treatment for considerations of subject safety only. Descriptive statistics including mean, standard deviation, median, range, frequency, and percent will be calculated for the entire cohort as well as by the study arm (botulinum toxin A and unpreserved 0.9% sodium chloride) to assess the results of randomization and identify potential confounders.

The primary analyses of the data will be performed according to subjects' original treatment assignment (i.e., intention-to-treat analyses) and the inclusion of all data from all subjects randomized in the final analysis. To assess the primary endpoint of improvement of pain on a visual analog scale (VAS) between pre-op, 1, 2, and 3 months post-op, a repeated measure of analysis of variance will be performed with one between subject factor (botulinum toxin A versus placebo) and one within subject factor (time). This analysis will also be used for the secondary endpoints: function (MIO/jaw limitation scale) and quality of life (SF12). In the event of significant loss to follow-up, we will explore the use of a linear mixed model to assess the independent effect of the study group on VAS over the study visits. The paired t-test, or the signed-rank test as appropriate, will be used to assess change in pain, function, and QOL between pairs of relevant time points for both study arms.

To assess the difference in proportion of adverse events between the botulinum toxin A and placebo groups, either the chi-square or Fisher's exact test will be used, as appropriate. All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals (95% CI) will be calculated to assess the precision of the obtained estimates.

All analyses will be performed in SAS Version 9.4 (SAS Institute Inc., Cary, NC). Note: This section was drafted in conjunction with Dr. Paul Christos and Gulce Askin, MPH in the Division of Biostatistics and Epidemiology, Department of Healthcare Policy and Research. They will be aiding in protocol design and development, data management, study implementation, study monitoring, and data analysis and reporting.

12.2 Sample Size/Accrual Rate

We plan to enroll 110 subjects in 18 months. About 55 subjects will be enrolled at Weill Cornell Medicine and the remaining 55 will be enrolled at the University of Illinois at Chicago.

12.3 Stratification Factors

Not applicable

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

To assess the primary endpoint of improvement of pain on a visual analog scale (VAS) between pre-op, 1, 2, and 3 months post-op, a repeated measure of analysis of variance will be performed with one between subject factor (botulinum toxin A versus placebo) and one within subject factor (time). In the event of significant loss to follow-up, we will explore the use of a linear mixed model to assess the independent effect of the study group on VAS over the study visits.

12.4.2 Analysis of Secondary Endpoints

The same analysis as that of the primary endpoints will also be used for the secondary endpoints: function (MIO/jaw limitation scale) and quality of life (SF36).

12.5 Interim Analysis

No interim efficacy analysis will be performed in this study because a small sample size is unlikely to yield any useful information.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards,

contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

Expected risks of BTA include:

- Problems swallowing, speaking, chewing or breathing due to weakening of associated muscles
- Spread of toxin effects causing muscle weakness
- Allergic reactions
- Discomfort at the injection site
- Syncope due to anxiety or needle related pain
- Muscle atrophy
- Facial palsy
- Localized numbness
- Skin infections

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by

the research staff and kept in the subject's research chart. All AEs that occur at the sub-site will be sent to WCM for review and submission to the DSMB.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

All anticipated adverse events are listed in the informed consent form that each subject receives a copy of after signature.

All adverse events are reviewed by the DSMB and should the board determine that subjects need to be informed of the new potential risk, the study staff will make every effort to contact subjects and update them on the current risks of participation in the trial.

13.1.6 Events of Special Interest

Not applicable

13.1.7 Reporting of Pregnancy

Institution will provide written notice to Allergan within 24 hours of any occurrence of either pregnancy or lactation during the use of study materials.

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to Allergan

Institution will send Allergan copies of any and all serious adverse event reports filed with the

FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial, within 24 hours after its first knowledge of the SAE in accordance with the SAE report form provided by Allergan. The SAE report form shall include an assessment of the causal relationship between the Allergan materials and the SAE.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). 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.

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.

Study investigators 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.]

14. Data and Safety Monitoring Plan (DSMP)

This study will use the WCM DSMB to monitor the study and ensure the safety of clinical research subjects and protect the validity and integrity of research data. The study participants will be questioned and examined at one, two and three months post-treatment for the occurrence of any adverse events. Anticipated adverse events for this study include:

- Problems swallowing, speaking, chewing or breathing due to weakening of associated muscles
- Spread of toxin effects causing muscle weakness
- Allergic reactions
- Discomfort at the injection site
- Syncope due to anxiety or needle related pain
- Muscle atrophy
- Facial palsy
- Localized numbness
- Skin infections

A report to the DSMB will be generated in the event of any adverse event at both sites and will provide details such as severity, relationship to treatment, onset, duration, and outcome. Adverse events will also be graded based on severity, attribution and expectedness. The DSMB will meet to review these reports upon every submission, and should any trend develop that suggest significant adverse outcomes, the study will be discontinued. A trend will be determined by more than one adverse event of similar presentation. If any serious adverse event occurs (death, life-threatening adverse experience, those involving prolonged hospitalization or disability), the other study sites, IRBs, and DSMB will be notified as per current institutional reporting guidelines. Adverse events such as death, life-threatening, or those involving prolonged hospitalization or disability may cause the termination or dropout of a subject from the study.

References

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3. Soares A., et al. Botulinum toxin for myofascial pain syndrome in adults. Chochrane Database of Syst Rev. 2014 Jul 25;(7):CD007533
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