Comparison of Electrophysiologic And Ultrasound Guidance For Onabotulinum Toxin A Injections in Focal Upper Extremity Dystonia And Spasticity

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Protocol

Comparison of Electrophysiologic Guidance and Ultrasound Guidance for Botulinum Toxin Injections

Brief Summary of Research (250-400 words):

This is a study to investigate the use of two targeting techniques for botulinum toxin (BoNT) injection for the treatment of focal hand dystonia and upper limb spasticity: Electrophysiologic guidance, using electrical stimulation, and ultrasound. Subjects will be selected from the clinical programs of both Icahn School of Medicine at Mount Sinai and the National Institutes of Health who are already receiving onabotulinum toxin A injections clinically. The study will consist of four visits. Visit one consists of screening subjects who will then be consented and randomized to one of the two treatment techniques for their ona-BoNT injection: 1) Electrophysiologic guidance using electrical stimulation or 2) ultrasound. Visit 2 will occur at week 4 where the subjects will return for a follow up visit to have blinded evaluator measurements of efficacy and strength and capture safety data. Visit 3 will be at week 12 when subjects will cross over and have the alternate treatment technique during their ona-BoNT injection. Visit 4 will occur at week 16 as the final assessment where subjects will have measurements of efficacy and strength and capture safety data by the blinded evaluator.

1) Objectives:

Research Question:

Hypothesis: Neither Ultrasound or electrical stimulation will not show significant differences in the outcome measures.

1) Improvement in dystonia or spasticity severity on visual analogue scale.

Secondary objectives

1. Duration of the injection procedure
2. Weakness in targeted and adjacent muscles after the procedure
3. Number of needle sticks and needle re-direction within a muscle required for delivery with each technique
4. Side effects with each technique
5. Patient self-reported satisfaction with each procedure
6. Physician global impression of change
7. For dystonia, physician rated “Arm Dystonia Disability Scale”
8. For spasticity, physician rated Modified Ashworth scale
9. Patient discomfort assessed on a visual analog scale.

2) Background

Dystonia is characterized by muscle contractions causing abnormal movements or postures (Albanese, et al., 2013). Focal hand dystonia is a task-specific focal dystonia, occurring with one or several specific actions (Sheehy and Marsden, 1982). Assessment of dystonia depends largely on standardized clinical scales, like the Burke-Fahn-Marsden Dystonia Rating Scale (BFM DRS)(Burke et al., 1985).

Spasticity is an upper motor neuron syndrome associated with lesions of the corticospinal system (Lance, 1981). Causes including traumatic brain injury, spinal cord injury, cerebral palsy, multiple sclerosis or stroke result in an imbalance of excitatory and inhibitory synaptic influences and hyperexcitability of the stretch reflexes. It is typically classified as generalized, regional, multifocal and focal (Ward, 2008). The most widely used assessment method is the Ashworth scale, which quantifies the increased tone across each joint on a scale from 0 (normal) to 4 (fixed position) (Bohannon and Smith, 1987).

Botulinum neurotoxin (BoNT) injection therapy is the most effective established therapy for focal dystonia (Simpson et al., 2008). OnabotulinumtoxinA (Botox®, Allergan, Irvine, CA) has been approved by the FDA for treatment of upper extremity spasticity. Numerous controlled trials have shown improvement in muscle tone and functional outcomes using onabotulinumtoxinA in adults with upper extremity spasticity (Teasell et al., 2012).

BoNT injections are ordinarily performed using anatomical landmarks, and additional instrumented localization methods include EMG, electrical stimulation and US guidance. Anatomical localization is insufficient for ideal muscle localization (Schnitzler et al., 2012, Molloy et al., 2002). Studies suggest that electrical stimulation guidance improves muscle localization and targeting (Molloy et al., 2002) and effectiveness of BoNT injection (Ploumis et al., 2013). Ultrasound-guided localization is a more recent development (Alter, 2010), that is gaining wider acceptance. Standardized techniques and additional information sources are now available (Alter et al., 2013).

A limited number of recent studies have attempted a comparison of the currently available injection guidance techniques in spasticity patients (Picelli et al., 2013, Picelli et al., 2012). Within the limits of these studies, it was suggested that ultrasound guidance can improve outcomes of BoNT injections in limb spasticity.

In this study we propose a direct comparison of E-stim-based and US-based injection guidance techniques in patients with focal upper extremity dystonia and spasticity. Both localization techniques are considered standard of care and to date one has not been proved superior to the other. Employing one or the other of the guidance techniques does not, in itself, change the risk/benefit balance of the standard injection treatment, based on currently available data.

3) Setting of the Human Research

This is a study being conducted at two sites: The Icahn School of Medicine at Mount Sinai. New York, NY and the National Institutes of Health, Bethesda, MD. Both sites will recruit from patients who are currently receiving treatments with onabotulinumtoxin A within their clinical practices.

4) Resources Available to Conduct the Human Research

Both sites have many patients that are being treated for focal hand dystonia and upper limb spasticity with onabotulinumtoxin A. Each site will offer the study to their clinical patients by providing a copy of the consent form and answering questions about the study. Each site anticipates randomizing 15 participants for a total of 30 participants for the study. We aim to have an equal number of subjects with upper extremity spasticity and focal dystonia randomized to each sequence of e-stim and US and at each site.

The study teams will have an initial conference call meeting to launch the study once both sites have received IRB approval and all contractual obligations have been fulfilled. Then the sites will have monthly conferences to review the status of enrollment and the study procedures.

Both the Mount Sinai site under Dr. David Simpson, and the NIH site under the Dr. Mark Hallett (NIH/NINDS) have considerable experience with research clinical trials including those with BoNT.

NIH Biosketches will be provided to the IRB and the approved Human Subjects training for the entire study team.

5) Study Design

a) Recruitment Methods

At the Icahn School of Medicine site, patients will be introduced to the research project from the Movement Disorders Program and from Drs. Simpson's Shin's and Frucht's private practices, and by referral from other health care providers.

At the NIH site, patients will be introduced to the research project from the BoNT clinic, including the neurology and movement disorders practitioners at Suburban Hospital, Holy Cross Hospital, George Washington University Medical Center, Georgetown University Hospital, Johns Hopkins University Medical Center, The Parkinson Disease and Movement Disorders Center of Maryland, University of Maryland and others.

Subjects potentially interested will be provided information about the study, copy of the consent form will be provided which subjects can review and bring home for family or friends to review. They will have the opportunity to contact the investigators at the Icahn School of Medicine or the NIH for questions. We anticipate recruiting a total of 30 subjects with 15 subjects at each site within one year.

b) Inclusion and Exclusion Criteria

Inclusion criteria

- Confirmed diagnosis of focal upper extremity dystonia (FHD) or upper limb spasticity
- Stable onabotulinumtoxinA dose regimen with a stable response as judged by the physician and patient for at least 2 treatment sessions.
- Age 18 and above

Exclusion criteria

- Contraindications to botulinum toxin
- Pregnancy or nursing
- Cognitive impairment that prevents reliable outcome measures of self-report

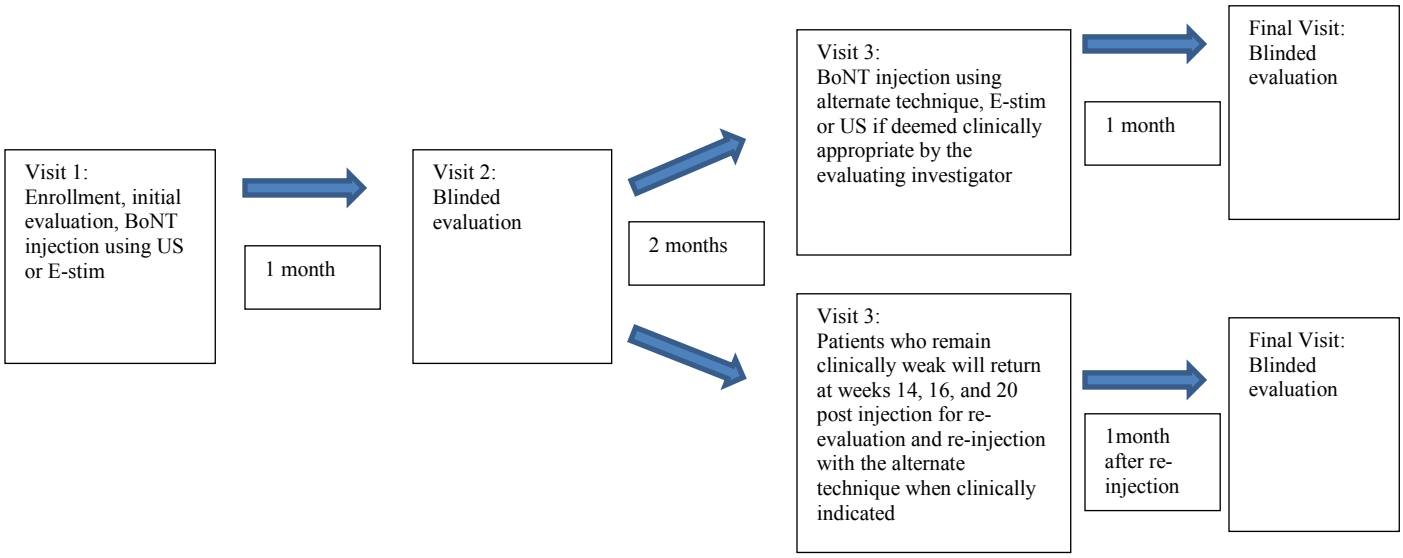
c) Number of Subjects

The study will enroll a total of 30 patients, with 15 patients at each site. Target number of patients to be treated and complete the study will be 18 subjects (to have sufficient statistical power.

d) Study Timelines

This is a randomized cross-over study, with two study sites. 4 outpatient visits of approximately 30-60 minutes each will take place over 16- 24 weeks. All NIH patients will also be enrolled in protocol 85-N-0195, and botulinum injections will be done under that protocol.

An outline of the procedures is depicted in the figure below:



The study anticipates enrollment of the first subject in February 2015. The study team anticipates an enrollment period of approximately 36 months with the last patient to be enrolled Dec. 2020 with the primary analysis completed by June 2021.

Study Endpoints

Outcome measures

Primary outcome measures

Improvement in dystonia or spasticity severity on a physician and patient self-reported visual analog scale.

Secondary outcome measures

(1) Duration of the injection procedure as follows:
   (a) E-Stim: time from needle In to needle Out
   (b) Ultrasound: Time from transducer contact on skin to needleout
   (c) Number of needle sticks/muscle and needle redirection with muscle for E-stim and US
(2) Weakness after the procedure in targeted and adjoining muscles
(3) Side effect incidence with each technique
(4) Patient self-reported satisfaction with each procedure
(5) Physician global impression of change
(6) For dystonia, physician rated "Arm Dystonia Disability Scale"
(7) For spasticity, physician rated Modified Ashworth Scale in targeted and adjoining muscles
(8) Patient discomfort assessed on a visual analog scale

e) Procedures Involved in the Human Research

Visit 1 - Screening

At the time of the first visit, the protocol, procedures, and the entire consent document will be discussed with the subjects. If the subjects agree to participate, they will sign the consent form and a copy provided before any screening procedures are initiated. Eligibility will be determined by history and physical examination.

The subjects' history is reviewed and eligibility established. After signing the consent document, the subjects undergo a standard neurologic evaluation focusing on the dystonia and /or spasticity manifestations. Before each treatment visit, women will be given a urine pregnancy test to confirm they are not pregnant.

Patients are randomized by a computerized system with each site provided the sequence of treatments prior to the patient treatment. Each patient will be scheduled to receive their stable, effective injections based upon prior stable regimen using either: a) Electrophysiologic guidance via electrical stimulation or b) US guidance. The same muscles, dose of onaBoNT-A formulation and dilution used previously during the patient's clinical session will be employed. This treatment is standard of care, with the purpose of measuring the two different targeting techniques. One injector and one blinded rater will be assigned for all of those taking part in the study. Both having comparable experience with the necessary procedures. Every effort will be made to reduce the patients discomfort during the process of measuring the two different muscle targeting techniques. Each injection site (as previously established) is approached using whichever above technique the patient has been randomized to. The number of attempts (sticks), and needle redirection or repositioning within the muscle to obtain the correct localization for each injection site will be recorded. Once the injector is satisfied with the placement based on the technique used, the injection proceeds as per standard of care. For e-stim technique, the time from initiation of the procedure ("needle in") to completion ("needle out") is documented. This will be measured from the time the needle is first inserted, until the time the injection is completed and needle removed. For US technique, the time from application of

the US probe to the skin to needle out is recorded. During this process of completing the injection the subject will be videotaped at visits 1 and 3. . The subjects will be asked to rate their level of discomfort with the procedure, on a visual analog scale, after the injection is complete.

Visit 2:

The subjects return to the clinic one month after injection, at the anticipated peak effect of ona-BoNT-A therapy. They will complete self-rating forms (Patient Global Impression of Change and Visual Analog scale for pain) and be evaluated by a blinded rater, who will not know what injection technique has been used (the patients will be instructed to withhold that information). The evaluation will include: visual analog benefit scale; visual analog weakness scale; review of side-effects; standardized clinical scale assessment (by clinician): Arm Dystonia Disability Scale for limb dystonia; Ashworth scale for spasticity; Global Assessment of Change/Clinical Global Impression of change; weakness assessed on the MRC scale; weakness of targeted and neighboring muscles as assessed with a mechanical force transducer (standard for both sites).

The blinded rater is the non-injecting neurologist who will be one of the co-investigators who did not participate in the subject's study visit and will remain the blinded rater consistently for the subject for the study. The blinded rater will provide an assessment of dystonia or spasticity without know the muscle targeting method used. The visual analog scales will be used by the blinded rater but the patient will complete a satisfaction scale of the procedure on a 10 point scale (see the attached appendix 1)

Visit 3:

An interval history will be obtained, and a targeted examination repeated. If on re-evaluation the patient's dystonia or spasticity has increased and retreatment is deemed to be clinically indicated then the patient will be re-injected. The muscle pattern and dose will remain the same as on visit one. Muscle localization will be with the second technique (crossover). As in Visit 1, the process of completing the injection of the subject will be videotaped. If on clinical evaluation the patient's severity of the patient's dystonia or spasticity does not require treatment re-injection will be deferred. The patient will return when clinically symptomatic (16-24 weeks), re-evaluated and re-injection will occur when clinically appropriate, as described above.

Visit 4:

This will be identical to visit 2, i.e. 4 weeks post re-injection. The study ends after visit 4.

End of Participation

Subjects will be referred back to their clinical care. If any new information pertaining to the patients' care is obtained during the study, it will be shared with the patients and their healthcare providers.

f) Specimen Banking

No samples are being stored. Data collected for research will be coded and stored on MSSM and NIH secured servers. Only the investigators will have access to the data and only the PI will have access to the code key. Any data that is shared between the sites will be done with a process that is encrypted and de-identified.

g) Data Management and Confidentiality

Data Collection

All data will be collected about each enrolled subject, e.g., Demographics, Standard clinical regimen, medical history, medications, randomly selected targeting method (ultrasound or e-stimulation), results of the blinded rater's review of muscle strength and response to post-treatment. A subject's response about discomfort during the study at each visit. The data will be documented on de-identified documents. This de-identified data will be shared by the two sites using an encrypted process with the NIH site inputting the data points into a statistical software for final analysis. The data to be stored indefinitely will be de-identified data. We will only need the link to patient files until the database is locked. We anticipate the link can be destroyed once the database is locked. This would be approximately 1 year after the last patient's last visit.

Analysis of data/ study outcomes

The investigators have scheduled an initial investigator's meeting (August 8, 2014) where training, data collection and verification process will be defined, protection, encryption, physical controls, and separation of identifiers and a system of data sharing). The intent is to de-identify all shared data, during storage, use, and transmission. Transmission would occur using an encrypted system. Quality control measures would be those which are customary by each research site and reviewed by the principal investigator of each site on a quarterly basis for of all collected data. Aggregate data will be reviewed quarterly by the team and discuss any unresolved outstanding issues to be addressed prior to the next quarterly review. Once all data is collected, the study team will review the completed data, address any items that need clarification. Data will be finalized and locked once all information is confirmed by each site and all outstanding queries have been resolved.

Repeated measures ANOVA will be used for the primary outcome. Patients who do not complete all 4 visits will be replaced, and all subjects will be included in the safety analysis. We will use $p<0.05$ as significance threshold. No interim analysis is planned.

Power analysis

Calculations are based on a α of 5% and a β of 80%, and the published SD for ona-BoNT-A therapy of 20%. There is an expected variation of 15% for the procedure. We hypothesize that US will demonstrate non-inferiority in comparison to E-stim based on previous experience performing the procedures. A total of 18 subjects (9 from each site) are needed to show the desired 15% variation. 15 subjects will be enrolled at each site to allow for screen failures and dropouts.

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

Adverse events will be reviewed at every visit. Patients will be asked specifically about pain or weakness. Patients will also have the option to contact the investigators between scheduled visits to report unanticipated events.

The procedures will be stopped if an individual reports any unexpected adverse event NCI grade 3 or higher.

Serious or unexpected adverse events and other unanticipated problems will be reported orally as soon as possible and in writing within 7 days if life-threatening and within 15 days otherwise. Expected or non-serious adverse events will be reported at the time of continuing review. Adverse events will be reviewed at every visit. Patients will be asked specifically about pain or weakness. Patients will also have the option to contact the investigators between scheduled visits to report unanticipated events.

The procedures will be stopped if an individual reports any unexpected adverse event NCI grade 3 or higher.

Serious or unexpected adverse events and other unanticipated problems will be reported orally as soon as possible and in writing within 7 days if life-threatening and within 15 days otherwise. Expected or non-serious adverse events will be reported at the time of continuing review.

Videos will be captured at Visits 1 and 3 of the injection process only. Every attempt will be made to videotape the study visits without showing a participant's face nor will names be used. The videos will be identified with the study subject number and stored in the locked cabinet and locked office in Dr. Simpson's research area. The de-identified videos will be downloaded on the password-protected database that is on the secure, encrypted Mount Sinai network drive within four weeks of study visit. Only the study team will have access to these videos. At the time of the analysis only the study team will exam these videos and confirm the capture of the data of timing, and muscles injected. These videos will be kept indefinitely for the purposes of research and education. The study subject will be asked to sign the Icahn School of Medicine Video consent form that will be discussed with the subject prior to any recording

Part I: Elements of a Data and Safety Monitoring Plan

i) Drs. Simpson and Lungu will share the responsibility for monitoring the data to ensure the safety of all the participants in the study.

MSSM Principal Monitor:– PI – Icahn School of Medicine

Last Name: Simpson
First Name: David
Academic Title: Professor
Department: Neurology

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MSSM Additional Monitor: PI- NIH Site

Last Name: Lungu
First Name: Codrin
Academic Title: Chief
Department: NIH, Parkinson Clinic

Mailing Address: NIH, 10 Center Drive, Bethesda, MD 20892-1428
Phone: 301-402-0976
Fax: 301-480-2286
E-mail: lunguci@ninds.nih.gov

1) Drs. Simpson and Lungu have special expertise in caring for patients with movement disorders and treating patients with onabotulinum toxin. This knowledge and experience will ensure patient safety throughout the study for each of the individual sites as well as collaborate when reviewing the study processes.

2) Adverse events (AE) will be monitored for safety. At each visit subjects will be asked non-leading questions such as "do you feel different in any way since the last visit?" All observed or volunteered AE's will be documented in the AE log.

3) Accumulated safety and data information will be reviewed by the monitors during the monthly study team calls.

4) The study does not require any stopping rules for interrupting the study or altering the study design. The treatments are standard of care.

5) Onabotulinumtoxin A is not under study. The subjects will receive their standard clinical treatment.

6) AEs will be classified as mild, moderate or severe based upon the following criteria: Mild = symptoms do not alter the subject's normal functioning, Moderate= symptoms produced some degree of impairment to function but are not dangerous, uncomfortable or embarrassing to the subject, Severe = symptoms are dangerous to the subject's well-being and causes significant impairment of function or incapacitation.

The relationship of the AE to the treatment will be classified as follows: Related: there is good reason(s) and sufficient evidence to assume that there is a causal relationship with the treatment and the AE. Not related: there is good reason(s) and sufficient evidence to exclude a causal relationship with the treatment.

All AEs will require the investigator to obtain adequate information to determine the outcome of the AE and to assess whether it meets criteria as a serious adverse event (SAE), which requires immediate notification to the funding agency and ethics review board. The investigator will obtain sufficient information to determine the causality of the AE (i.e. treatment or

other cause); and provide their opinion on causal association (i.e., whether they consider the AE related or not related to the study intervention). Subjects will receive follow up until the AE either resolves completely or stabilizes to a level acceptable to the investigator.

All SAEs will be reported within 24 hours of the investigator's knowledge of the event to the ethics review board and/or funding agency. An SAE is any AE during the time period of the study that: 1) results in death, 2) is life threatening and places the subject at immediate risk of death, 3) results in in-patient hospitalization, 4) results in significant disability/incapacity, where the disability is a substantial disruption of a person's ability to conduct normal daily life functions, 5) is an important medical event that may not result in death, be life threatening, or require inpatient hospitalization, but which based upon the appropriate medical judgment may require medical and/or surgical intervention to prevent one of the outcomes listed above.

7) All data will be reviewed by Drs. Simpson and Lungu for completeness and accuracy

8) Should a temporary or permanent suspension of the study occur, in addition to the PPHS, we would need to inform the funding agency and the NIH.

j) Withdrawal of Subjects

Participants may withdraw from the study at any time, with an early withdrawal, a follow-up visit to examine and ensure patient safety. Withdrawal or discontinuation due to an AE will be distinguished from withdrawal/discontinuation due to an insufficient response to the study treatment. It is rare that the study team will request a subject be withdrawn from the study because the treatment is standard of care, but if an adverse event does occur requiring the subject be withdrawn, a follow up visit to examine and ensure patient safety will be performed.

6) Risks to Subjects

The risks of BoNT injection will be reviewed with patients again at time of enrollment in this protocol. The possible side effects are:

- Over relaxation or muscle weakness of the targeted muscles. Furthermore, non-targeted muscles may be affected.
- Participants may experience pain and discomfort while receiving the injections.
- Infection at the injection site.
- A possibility the muscles will not be targeted similar to your previous treatments and you may not experience the same results as previous clinical treatments.

- Treatment of BoNT to subjects with breathing or swallowing problems poses substantial risks. Muscles in the neck that help in breathing and swallowing may be over relaxed. Subjects may experience severe breathing problems, and inability to swallow. Food and water may also enter the lungs. This potential risk is limited in this study because the muscles being injected are not in the neck but in the arm and hand.
- Allergic reaction, and/or skin or eye irritation
- Nausea
- Skin inflammation (dermatitis)
- The spread of BoNT may be life-threatening and may even lead to death, but this would be a rare occurrence due to the location of the study drug being injected.
- Bad effects have been seen in pregnant animals who were given Botox. Please tell your study doctors immediately if you get pregnant while on this study. If you become pregnant, you will be removed from the study.
- Risk of being videotaped is loss of confidentiality. To reduce this we will not include any personal information, such as your name, with the recording. We will discuss this with you prior to any recording and we will ask you to sign a separate video agreement for this.

There is no difference in procedures and associated risks due to participation in this protocol then treatment for clinical care.

There is some discomfort and local pain associated with insulated EMG injection needles or wire insertions as well as with the current delivered during electrical stimulation. Some patients have discomfort for 1-3 hours after hooked wire insertion, but most tolerate the procedure well. Patients are free to discontinue diagnostic testing or injection at any time.

There is no medical risk with ultrasound. There may be mild discomfort or skin irritation with the coupling gel used on the transducer.

There is a very small risk that the muscles will not be targeted equally due to using only one of the targeting methods to identify the muscle and subject could possibly not have results of previous clinical treatments.

There is a risk should a subject be pregnant or become pregnant during the study. These risks are unknown and could minor or major (death). Women of childbearing potential will have a pregnancy test prior to treatments and reminded to continue to use two forms of contraception. Men should not father a child while on this research study and will be requested to use condoms while participating in this study.

The patients have a potential risk for loss of privacy

There is always the possibility for unknown risks to occur

7) Provisions for Research Related Injury

Medical care will be available to participants in the occurrence of any adverse events. NIH will provide medical coverage for research-related injury in accordance with NIH policy. For those enrolled the Icahn School of Medicine site, the participant and his/her insurance company will be responsible for the medical costs

8) Potential Benefits to Subjects

Indirect benefits:

This study does not offer direct benefit to participants but is likely to yield generalizable knowledge about the best therapy paradigms using ona-BoNT. While there are no direct benefits to the participants, injections of BoNT may alleviate over-active muscles.

9) Provisions to Protect the Privacy Interests of Subjects

All study visits will occur in private exam rooms. Phone calls and any information concerning the participant's involvement of the study will be conducted with sensitivity of maintaining the participant's privacy.

10) Economic Impact on Subjects

Participants will not be responsible for any costs, and the drug for the treatment visit will be provided without cost to the participants.

11) Payment to Subjects

Participants will receive payments for each study visit for travel in the amount of $75 to be provided by check in approximately 4-6 weeks after each completed visit. If extra visits are required, these visits will receive compensation at $75/visit.

12) Consent Process

Consent procedures

The study teams will use the standard operating procedure for conducting the consent form process per the institutional guidelines. Prior to any study activities, participants will be provided a copy of the consent form, and undergo a consent process, which includes signing the consent and providing a copy to the subject prior to any screening activities. Once the consent process is completed, the screening process will be completed.

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing and at each study visit.

Consent documents

The consent document contains all required elements as required by regulations and will be provided to the respective institutions for ethical review. .

Children – N/A; Cognitively Impaired Adults - N/A

Non-English Speaking Subjects

For non-English speaking subjects at Mount Sinai – currently all subjects treated by Drs. Simpson, Frucht and Shin are English speaking Should a participate become eligible that does speak another language other than English, the IRB will be contacted and the appropriate translation of the consent will be requested from the IRB for approval. The subject will then be included and follow standard procedures for non-English speaking according to MSSMs consent SOP (i.e. include translator during each study visit). The NIH will follow standard procedures for their site when managing non-English speaking subjects. The NIH has a short form consent and the English consent form will be used as the script for the short form consent process.

Waiver or Alteration of the Consent Process – N/A

13) Process to Document Consent in Writing

The Icahn School of Medicine site will use the SOP-091 and the consent will be documented in writing using the standard PPHS consent template.

The NIH will use the standard consent process in writing as required to meet NIH guidelines.

14) Vulnerable Populations

Indicate specifically whether you will include or exclude each of the following 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)

There will not be a coordinating center, but the grant will be managed by Mount Sinai, the data will be coordinated by the NIH site. Drug will be shipped from the funding agency as a donation to both sites for the study.

16) Community-Based Participatory Research

Not/Applicable

17) Sharing of Results with Subjects

Any results which are part of the treatment are available to share with the patient and their clinician.

18) IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

N/A

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Appendix 1

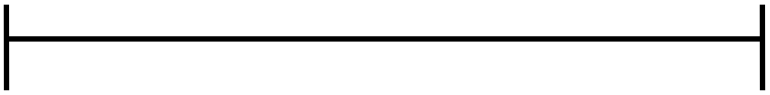
Visual analog scales: Benefit, Weakness, Discomfort

Visit 2 and 4

Benefit

Mark a vertical line that best demonstrates how beneficial you found the injections.

No improvement Normal use

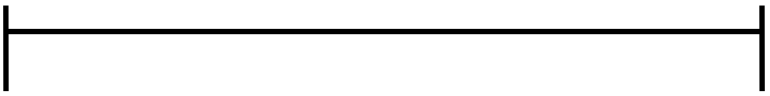


How long after the injection was any benefit *first* noted?
How long until maximal benefit was reached?
How long did the maximal benefit last?
How long did *any* benefit last?

Weakness

Mark a vertical line that best demonstrates how weak you have felt after the injections.

No weakness Unable to move



How long after the injection was weakness *first* noticed?
How long until maximal weakness was reached?
How long did the maximal weakness last?

How long did *any* weakness last?

Visit 1 and 3

Discomfort

Mark a vertical line where you feel best represents your pain or discomfort during the treatment.

No Pain Worst possible pain