A Placebo-Controlled, Double-Blind, Randomized, Cross Over Pilot Study Of The Efficacy And Tolerability Of Incobotulinum Toxin A (Xeomin®) As A Treatment For Focal Task-Specific Dystonia Of The Musician's Hand
PI: David Simpson, MD
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Mount Sinai	Protocol Title:	A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED, CROSS OVER PILOT STUDY OF THE EFFICACY AND TOLERABILITY OF INCOBOTULINUM TOXIN A (XEOMIN) AS A TREATMENT FOR FOCAL TASK-SPECIFIC DYSTONIA OF THE MUSICIAN'S HAND
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	Date Revised:	10/22/2019
	Study Number:	HS: 13-00822 GCO: 13-1679

Header:

- **Protocol Title**
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  Principal Investigators

  David Simpson, M.D.

- **Date Revised**
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  GCO#13-1679/HSM#13-00822

Brief Summary of Research (250-400 words):

The investigational drug being studied in this protocol is Incobotulinumtoxin A (Xeomin®). Botulinum toxin (BoNT) prevents the release of the acetylcholine from peripheral nerves, inhibiting muscle contractions. BoNT is effective in relaxing overactive muscles. In musician's dystonia, the ability to reduce abnormally overactive muscles in the hand can be critical for the musical professional to continue his or her career. With the use of EMG/electrical stimulation and/or ultrasound guidance, the injector can precisely localize the individual muscles that are affected in this condition with great accuracy. Prior studies have shown that BoNT injections produce beneficial effects in forearm muscles, and less effect in shoulder or proximal arm muscles.

Possible risks in treating patients with BoNT include excessive weakness of the injected muscles. The drug may also affect non-targeted muscles. However these risks will be minimized during the screening period by carefully targeting the affected muscles and by administering low doses of BoNT. Small booster doses may be given at follow up visit (2, 4, 14 and 16-weeks after the primary injection date) if the initial injection was insufficient to produce sufficient efficacy in relief of the focal dystonia and did not produce excess weakness of the targeted muscle.

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1) Objectives:

The research question of this exploratory crossover pilot trial is: compared to placebo, does BoNT significantly improve the motor performance and subjective disability of patients suffering from focal task specific dystonia of the musician's hand? Focal task-specific dystonia of the musician's hand is a disorder that frequently impairs or ends the careers of highly skilled performing artists. Dr. Frucht has personally evaluated more than 170 of these patients over the last decade; clinically and anecdotally, BoNT is often used to treat these musicians, but few studies exist that quantify their motor and subjective improvement or the prevalence of adverse effects. This trial will be performed using BoNT versus placebo in 20 patients with musician's hand dystonia, to refine quantitative measures of performance using Musical Instrument Digital Interface (MIDI) technology and high speed video analysis, demonstrate efficacy and tolerability of BoNT injections, and provide power calculations for a future multi-center double blind clinical trial.

2) Background

Musician's dystonia (MD) is characterized by sustained muscle contractions and the loss of voluntary muscle control; this leads to incoordination and an inability to properly play one's musical instrument. The condition is almost exclusively triggered by the act of playing music, and is therefore considered to be a type of focal task-specific dystonia. (1,2,12,13) The dystonia can involve muscles of the hand, limb, or embouchure.(1,4) MD typically affects highly trained musicians and is often disabling; it affects up to 1% of professional musicians. (3)

The pathophysiology of musician's dystonia is not well understood. A commonly accepted theory suggests deregulation of normal mechanisms of brain plasticity. Changes in brain plasticity have been demonstrated in string players where the sensory-motor cortical receptive fields of the fingers enlarge with repetitive tasks.(5) As these new cortical projections are created, they not only have the potential to augment fine motor control of individual fingers, but may also be susceptible to disorganization which may lead to dystonia. (6,7) Genetic predisposition is also thought to be a factor in the development of MD. In one study, up to 10% of patients with MD were found to have at least one family

member with dystonia. (3) This familial relationship was noted to be much higher in another study after a thorough history and clinical exam was conducted amongst musicians with dystonia as well as their family members. (8) No specific candidate gene has been identified to date.

Risk factors that are thought to be contributory to the development of MD have been observed in a German study of 591 patients with MD. These included prolonged hours of practice, movements that required a high level of spatial and temporal precision as well as a predefined temporo-spatial constraints, chronic pain, anxiety and perfectionism. In addition, males appeared to be slightly more affected than females. (7)

Treatment of musician's dystonia is often challenging as the pathophysiology of the condition is not well understood, and there are often high expectations for a curative measure by the patient. Available treatment options include both pharmacologic and non-pharmacologic treatments. Non-pharmacologic treatment consists of rehabilitation techniques that practice tactile discrimination with the hope that sensory retraining could alleviate the motor symptoms of MD. Ergonomic changes to the musical instrument have also been tried to help alleviate motor symptoms. Pharmacologic treatment consists of oral medications such as trihexyphenidyl, baclofen, phenytoin and primodone, and injections with botulinum toxin. (9) Unfortunately, with the exception of botulinum toxin injections, most treatment options have shown suboptimal results.

BoNT injections have shown mixed results in treating focal dystonia, including focal task specific dystonia.(11) The toxin can chemically denervate the overactive muscle by blocking the transmission of nerve impulses that innervate the dystonic muscle. With EMG/electrical stimulation guidance, the muscles contributing to the movement disorder can be targeted with fine precision. More recently ultrasound has been employed effectively in muscle targeting. BoNT therapy works best for forearm muscles and does not show great effect in treating embouchure's dystonia or dystonia affecting shoulder or proximal arm muscles. (2,9) In one study that treated 84 patients with MD with injections of botulinum toxin, 58% of musicians experienced improvement of symptoms and 36% experienced long term benefit in their performance ability. (10)

Musician's dystonia is a highly disabling disorder and can be a devastating condition to the professional musician. Although there is no cure that is currently available, treatment with BoNT can offer great symptomatic relief which may enable the musician to continue their ability to perform.

3) Setting of the Human Research

The research will be conducted at the Faculty Practices of Dr. Simpson and Shin at Mount Sinai Medical Center located at 1468 Madison Ave, New York, NY 10029. The Faculty Practice and office of Dr. Frucht is located at The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders.NYU Langone Medical center. 240 East 38TH ST, 20th Floor, New York, NY, USA 10016**.** The offices of Drs. Simpson and Shin are located on the 2nd Floor of the Annenberg Building in the Neurophysiology Department, Section 218.

4) Resources Available to Conduct the Human Research

Drs. Frucht and. Simpson are experts in the treatment of focal dystonia. They have many patients that fit the inclusion criteria of musician's dystonia. Many of the patients will be referred from Dr. Frucht's practice at NYU Langone Medical Center due in part to his connections with musicians from the Julliard School and other music schools, organizations, and support groups. A total enrollment of 20 patients is anticipated over the course of the study.

The study team meets monthly to discuss the research projects which are enrolling and the various stages of recruitment and to troubleshoot any issues which arise. Additionally the study team will be educated about the protocol, the investigational product, and their trial-related duties and functions, through these study team meetings. More frequent meetings will be added should a delay in enrollment occur or if there are major issues concerning the flow of subjects through the visits of the study.

Drs. Simpson's, Shin's and Frucht's qualifications are included in this application which includes their biosketches. Their required research education and conflict of interest statements are available for review

5) Study Design

a) Recruitment Methods

Patients will be recruited from the Faculty Practices of Drs. Frucht and Simpson. A majority of patient recruitment is anticipated through Dr. Frucht's practice. Furthermore, flyers will be posted throughout Mount Sinai Medical Hospital and NYU Hospital to increase the potential of recruitment of musicians diagnosed with dystonia and forwarded to musical training institutions, musical organizations and advocacy groups for patients with dystonia. IRB approval will be sought when the flyers are designed and the study team deems the need for this approach to increase study enrollment.

b) Inclusion and Exclusion Criteria

Any adult patient is eligible for inclusion, provided they meet the following inclusion and exclusion criteria:

INCLUSION CRITERIA:

- Patients with focal task-specific dystonia of one or both hands, selectively triggered by performance on a musical instrument.
- Patients must have been evaluated by Dr. Frucht at the Movement Disorders Division of NYU Langone Hospital as part of their clinical care.
- Patients whose performance on an instrument is directly linked to their occupation.
- Patients must be between the ages of 18 and 80.
- Impairment in musical performance must be visible and demonstrable.

EXCLUSION CRITERIA:

- Patients whose dystonia is not severe enough to interfere with musical performance in the opinion of a skilled examiner.
- Patients with unstable medical conditions or psychiatric conditions.

c) Patients with a medical condition that precludes them from receiving BoNT injections. Number of Subjects

This will be a placebo-controlled, double-blind, randomized, cross-over pilot study to assess the efficacy and tolerability of BoNT injections to treat musician's dystonia. The study will enroll a total of 2 patients that will be divided into two groups:

1) Group 1: Naïve to BoNT treatment (10 patients).
2) Group 2: Prior treatment with BoNT (10 patients).

The study anticipates screening 26 patients to enroll 21 who are eligible for randomization.

d) Study Timelines

There will be 7 or 10 visits depending on which week would be your optimal dosing over the 24-28 week study period. Patients will be seen at weeks 1, 2, 4, 12, 14, 16, and 24, (see attached flow sheet – appendix 1). If patient needs booster dosage at week 2 or 4, patient will be asked to return to have another visit at 4 week after optimal dosing. There will be a total of 7-10 research visits over a 24-28 week period. All visits are expected to last approximately 2-3 hours. The study started in January 2014 and anticipates ending in June 2020 . During the study, we may split Visits so that the patient can be seen easily by Dr. Frucht and not create a hardship for the participant. If the study visit is split, it will mean that Dr. Frucht's assessment will occur prior to the assessment and treatment at Dr. Simpson's location on two consecutive days.

e) Study Endpoints

Primary Outcome Measures:

The principal outcome measure will be improvement in musical performance, measured by self-rated questionnaire, quantitative MIDI analysis and blinded high speed video analysis.

Secondary Outcomes Measures:

Patient reported outcomes will be measured by questionnaires that address adverse events; and modified hospital anxiety depression scale (mHADS), and perceived stress scale to capture impact of anxiety, depression and stress.

Motor strength will be tested using the Medical Research Council (MRC) muscle scale and a dynamometer to document any weakness the treatment may produce as compared to the baseline visit.

f) Procedures Involved in the Human Research

Every patient's dystonic movement disorder will be videotaped at each time point. The patient will bring in their instrument if possible; a keyboard will be provided for pianists. The patient will be encouraged to wear similar clothing/jewelry/nail polish etc. so each video recording will be identical at each time point.

The study will last a total of 24-28 weeks with the schedule as follows:

Visit 1- (Day 0) - Screening and baseline:

- Consent Form Process – completed prior to any research procedures
- Comprehensive Neurologic History and Physical Examination (MRC scales and dynamometry)
- Blood tests
- Patient's subjective rating scale of symptoms at baseline, HADS and perceived stress (questionnaires)
- Video of targeted hand(s) by Dr. Frucht at NYU Langone medical center
- Selection of Muscles to inject – by Dr. Frucht at NYU Langone medical center.
- Identification of the muscles and Injection of muscles

Visit 2 and Visit 3 will contain the following evaluations:

- Brief neurological exam to evaluate for weakness of the targeted muscles and surrounded non-targeted muscles (dynamometry, and MRC)
- Patient's subjective rating scale of symptoms, HADS and perceived stress (questionnaires)
- Assess for side effects
- Video of targeted hand(s) by Dr. Frucht at NYU Langone medical center.
- Administer booster to patients who feel symptoms have not improved

Visit 4

- Brief neurological exam to evaluate for weakness of the targeted muscles and surrounded non-targeted muscles (dynamometry, MRC)
- Patient's subjective rating scale of symptoms, HADS and perceived stress (questionnaires)
- Assessment of side effects
- Video of targeted hand(s) Injection of muscles by Dr. Frucht at NYU Langone medical center.

Visit 4a or 4b. This is optional visit at Week 6, 8 are depending on optimal dosing at weeks 2 and 4.

This visit will assess the improvement in musical performance. It will be 4 weeks after optimal booster injection.

- Brief neurological exam to evaluate for weakness of the targeted muscles and surrounded non-targeted muscles (dynamometry, and MRC)
- Patient's subjective rating scale of symptoms and perceived stress (questionnaires)
- Assess for side effects
- Video of targeted hand(s) by Dr. Frucht at NYU Langone medical center.

Visit 5; Week 12 (week 14 or 16 depending on previous dosing schedule) will contain the following evaluations:

- Brief neurological exam to evaluate for weakness of the targeted muscles and surrounded non-targeted muscles (dynamometry, and MRC)
- Patient's subjective rating scale of symptoms, HADS and perceived stress (questionnaires)
- Assess for side effects
- Video of targeted hand(s) (Groups 1 & 2 will be crossed over and will receive their 2nd injection cycle) by Dr. Frucht at NYU Langone medical center.
- Treatment may be deferred for up to 2-4 weeks in any individuals who have persistent weakness from the first treatment cycle

Visit 6 and visit 7; Week 14 or 16 or 18 depending on previous dosing schedule will contain the following evaluations:

- Brief neurological exam to evaluate for weakness of the targeted muscles and surrounded non-targeted muscles (dynamometry, and MRC)
- Patient's subjective rating scale of symptoms, HADS and perceived stress (questionnaires)
- Assess for side effects
- Video of targeted hand(s) by Dr. Frucht at NYU Langone medical center
- Administer booster to patients who feel symptoms have not improved

Visit 7a or 7b is optional visit which will be 4 week after optimal dosing injection.

- Brief neurological exam to evaluate for weakness of the targeted muscles and surrounded non-targeted muscles (dynamometry, and MRC)
- Patient's subjective rating scale of symptoms, HADS and perceived stress (questionnaires)
- Assess for side effects
- Video of targeted hand(s) by Dr. Frucht at NYU Langone medical center

Visit 8 Final follow-up evaluation, this visit will be 12 weeks after optimal dosing injection which will be week 24 or 26 or 28

- Brief neurological exam to evaluate for weakness of the targeted muscles and surrounded non-targeted muscles (dynamometry, and MRC)
- Blood Tests
- Patient's subjective rating scale of symptoms, HADS and perceived stress (questionnaires)
- Final assessment for side effects
- Video tape targeted hand(s). This will occur at Dr. Frucht's office at NYU Langone Medical Center. Participants will be referred for clinical care.

Rating at the completion of the study:

1. Patient rater (self): Will provide a subjective self-assessment score of symptom improvement in questionnaire form at every visit. They will also be asked to rate their recorded video performances that will be presented to them in a random order.

2. Musician rater: A professional musician (of similar genre) will review the recorded performances in random order and will be asked to rate performance and presence of dystonia.

3. Neurologist rater: Will review the recorded performances in random order and asked to rate dystonia and performance.

Participants will be asked to abstain from getting pregnant during the study treatment period. Women who are of child bearing potential will have a pregnancy test prior to each visit which has an injection. Participants (men and women) will be asked to maintain birth control throughout the study period and their choice of birth control will be notated in the source documents.

Should a subject become pregnant during the study treatment period, study treatments will be discontinued and the pregnancy will be reported as an unexpected AE to the IRB. Pregnancies and their follow-up will be monitored by the study team and reported to the sponsor and the IRB. The pregnancy follow-up will include the outcome of the pregnancy.

g) Specimen Banking

Blood specimens are being banked for the possible future analysis of antibody development. This will be done should there be an adverse event or lack of response to treatment during the study or to provide safety data for publication

h) Data Management and Confidentiality

Source documents will be created during each study visit for each participant and stored in a locked cabinet in Dr. Simpson's research locked office on Annenberg 2nd Floor. Only study staff will have access to these paper records, and only as required to perform their roles. The participant demographics form and the informed consent document, which contain

identifying data will be kept separately from the other documents. All other documents will be identified by the participant's study identification (ID) number only. De-identified data will be entered into a password protected database that is housed on a secure, encrypted, Mount Sinai network drive. 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. Frucht's research area. The de-identified videos will be downloaded on the password protected database that is on the secure, encrypted NYU Langone network drive. Only the study team will have access to these videos. At the time of the analysis, a blinded neurologist and a blinded musician will be shown these tapes, on the encrypted network within the locked office of the study team. Data will be shared through an approved platform called www.box.com provided by the Sinai IT division for the purpose of sharing the data from this study. The videotapes will be kept indefinitely for scientific presentations and educational forums.

The statistical analysis will be performed by the investigators with the help of a biostatistician at Mount Sinai research institute, Dr. Emilia Bagiella. A total of 20 subjects will be enrolled to this two-treatment (BoNT vs. placebo) crossover study. The probability is 80% that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between the treatments is 0.935 units. This is based upon the assumption that the within-patient standard of the response variable is 1. Although the signal to noise ratio is not optimal due to the small subject size, we believe that this study will be able to detect a significant difference between the study drug and placebo. This is based on reviews of video of robust improvement in treated patients. Keeping the sample size small also allows us to finish recruitment within two years, and to complete all phases of the study by 24 months in order to supple information for planning for a larger definitive study. We hope that the dropout rate will be less than 3%.

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

Drs. Frucht and Simpson will be responsible for monitoring the data to ensure the safety of all of the participants in the study

MSSM Co-Principal Monitor:

Last Name: Frucht
First Name: Steven
Academic Title: Professor
Phone: 212-263-4838

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Drs. Frucht and Simpson have extensive experience in the area of movement disorders. Dr. Simpson is an expert in the use of toxin's in the treatment of dystonia and Dr. Frucht in highly knowledgeable about the musicians who have been diagnosed with dystonia as it relates to playing his or her musical instrument. Their extensive knowledge will ensure patient safety throughout the study.

1) 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.

2) Accumulated safety and data information will be reviewed by the monitors (Simpson and Frucht) during study team meetings.
3) The study does not require any stopping rules for interrupting the study or altering the study design. The treatments used for the study are lower doses than standard of care.
4) Incobotulinumtoxin A is being used on average doses between 10U and 30 Units per subject, but at no time will any subject receive over 100 Units. Each study visit, the assessing physician will select the muscles and the amounts of medication to be injected. The selection sheet will be provided to the unblinded co-investigator to preparing the syringes either with placebo or study drug.
5) 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.

6) All data will be reviewed by Drs. Simpson and Frucht for completeness and accuracy

Should a temporary or permanent suspension of the study occur, in addition to the PPHS, we would need to inform the funding agency. The study has received an IND exemption from the FDA.

j) Withdrawal of Subjects

Participants may withdraw from the study at any time, with an early withdrawal follow up visit to examine and ensure patient safety. Withdrawal or discontinuation due to an AE should be distinguished from withdrawal/discontinuation due to an insufficient response to the study drug/treatment.

6) Risks to Subjects

Risks from BoNT injections:

a) Potential risks of BoNT includes over relaxation of the targeted muscles. Furthermore, non-targeted muscles may be affected. Participants may experience pain and discomfort while receiving the injections.

b) Risks for people with breathing or swallowing problems:

Treatment of BoNT to subjects with breathing or swallowing problems may pose some degree of risk, although this is quite small, particularly with the very low doses of BoNT (100 units or less) employed in this study of focal musician's dystonia. 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.

c) Risks from blood sampling

d) The risk of the loss of privacy.

e) 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. The participant and his/her insurance company will be responsible for the medical costs.

8) Potential Benefits to Subjects

While there are no direct benefits to the participants, injections of BoNT may weaken over-active muscles and improve the function of the hand(s). Participants may then be able to play their desired instruments, possibly at the professional level.

Examination of the effects of BoNT will broaden the knowledge in the treatment of musician's dystonia and other neurological illnesses for the scientific community.

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 in the study will be conducted with the sensitivity of maintaining the participants privacy.

10) Economic Impact on Subjects

Participants of the study will not be responsible for any costs.

11) Payment to Subjects

Participants will receive a payment of $75 for each visit including reimbursement for transportation from NYU Langone medical center to Mount Sinai Hospital by check which may take up to 4-6 weeks for processing.

12) Consent Process

The study team will use the SOP-090 for conducting the consent form process for all potential study participants; said consent will apply for all subject visits. Prior to any study activities, participants will be provided a copy of the consent form, and undergo a consent process, be screened, and will discuss the details of the

study. The exam rooms are located at the private practices of Dr. Simpson at Mount Sinai Medical Center, located at 1468 Madison Ave, New York, NY 10029. The office of Dr. Frucht is located at The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders. NYU Langone Medical Center, 240 East 38th St., 20th Floor, New York, NY, 10016.

The offices of Drs. Shin and. Simpson are located on the 2nd Floor of the Annenberg Building in the Neurophysiology Department, Section 218.

The study will not enroll cognitively impaired adults. The study team will provide a non-English language consent form for approval should a patient be eligible for the study that does not speak English to the IRB prior to enrolling the subject. A translator will also be present during the consent form process for non-English speaking subjects. The

study team is committed to including patients who are musicians suffering from task-specific dystonia of the hand.

13) Process to Document Consent in Writing

The study will use the SOP-091 and the consent will be documented in writing using the standard PPHS consent template.

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)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

Subjects will be offered generalized information about the study after the completion of the data analysis. Until the study is complete the participants will not be provided their research information.

18) External 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.

All study drug will be maintained by the study unblinded co-investigator in a locked cabinet, in a locked room which only the study team has access. During the treatment visits, the blinded investigator will assess the patient and provide detailed specifications on the injection form the muscles to be targeted and the amounts of drug/placebo to be prepared in syringes for injection. The unblinded co-investigator will prepare the study drug/placebo according to the detailed information. A log will be maintained by the study team of the study drug vials and the lot used for each subject. Upon completion of the study, used and unused study drug will be given to Pharmacy for destruction.

References:

1. Jankovic J., Ashoori A. Movement Disorders in Musicians. Movement Disorders 2008; 23:1957-1965.
2. Pullman S., Hristova A. Musician's Dystonia. Neurology 2005;64:186-187.
3. Altenmu¨ller E. Focal dystonia: advances in brain imaging and understanding of fine motor control in musicians. Hand Clin 2003;19:523–538.
4. Frucht SJ, Fahn S, Greene PE, et al. The natural history of embouchure dystonia. Mov Disord 2001;16:899–906.
5. Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. Science 1995;270(5234):305–307.
6. Munte,T.F., E. Altenm¨uller&L. J¨ancke. 2002. The musician's brain as a model of neuroplasticity. *Nat. Rev. Neurosci.* 3**:** 473–478.
7. Altenmuller E., Baur V., Hofmann A., et al. Musician's cramp as manifestation of maladaptive brain plasticity: arguments from instrumental differences. Annals of the New York Academy of Sciences 2012; 1252:259-265.
8. Schmidt A, Jabusch HC, Altenmuller E, et al. Dominantly transmitted focal dystonia in families with musician's cramp. Neurology 2006;67:691–693.

9. Altenmuller E., Jabusch HC. Focal Dystonia in Musicians: Phenomenology, Pathophysiology, Triggering Factors, and Treatment. Medical Problems of Performing Artists 2010; 25: 3-9.
10. Schuele S, Jabusch H-C, Lederman RJ, Altenmüller E. Botulinum toxin injections in the treatment of musician's dystonia. Neurology 2004; 64: 341–343.
11. Pullman SL, Greene P, Fahn S, Pedersen SF. Approach to the treatment of limb disorders with botulinum toxin A. Experience with 187 patients. Arch Neurol 1996;53:617–624.
12. Peterson DA, Berque P, et al. Rating scales for musician's dystonia: The state of the art. Neurology 2013; 81(6):589-98.
13. Chang FC, Frucht SJ. Motor and Sensory Dysfunction in Musician's Dystonia. Curr Neuropharmacol 2013; 11(1):41-7.