A Randomized Prospective Evaluation of Four Injectable Neuromodulators in the Glabella Area

Protocol Number IRB Number *849045*

Clinicaltrials.gov *NCT05167864*

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Study Summary

Title	A Randomized Prospective Evaluation of Four Injectable Neuromodulators in the Glabella Area: Randomized Controlled Trial
Short Title	Glabella 4 Toxin Study
IRB Number	*849045*
Protocol Number	*NCT05167864*
Methodology	Randomized Control Trial
Study Duration	18 months
Study Center(s)	Single-center.
Objectives	To quantify the dynamic strain of four commonly available neuromodulators injected in the glabellar area over time as well as correlate patient satisfaction to the change in dynamic strain over time.
Number of Subjects	Approximately 140
Main Inclusion and Exclusion Criteria	Inclusion criteria: 1) Women ages 30-65 2) No neuromodulator treatment within 12 months 3) Have not undergone cosmetic procedures to the upper face above the malar region (cheekbone area). Exclusion: 1) Men 2) Patients who have previously been treated with a neuromodulator<12 months 3) Over 65 or under 30 years of age 4) Those with a prior known condition that affects facial animation (such as stroke, palsy), 5) Cannot be actively taking blood thinners, 6) Presence of eye ptosis 7) Autoimmune disease

Intervention	Randomization to one of four neuromodulator glabellar injections: 1) onabotulinumtoxinA 2) abobotulinumtoxinA 3) incobotulinumtoxinA 4) PrabotulinumtoxinA
Statistical Methodology	Descriptive statistics will be used to describe variables of interest. Fischer's exact test and Chi-square will be used to compare categorical variables, and linear regression will be used for continuous variables.
Data and Safety Monitoring Plan	PI will oversee the study, protocol, and data monitoring and storage.

Background and Study Rationale

1 Introduction

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including *[as applicable include the following regulations as they apply 45 CFR 46, 21 CFR Parts 50, 54, 56 All episodes of noncompliance will be documented.]*

The purpose of the study is to use 3D imaging to evaluate the effects of four FDA approved neuromodulators on facial lines, wrinkles and animation. Participation is available to women who have never had a cosmetic procedure above the malar region nor a treatment with a neuromodulator within 12 months. All subjects will undergo 3D imaging using the VECTRA M3 (Canfield Scientific, Inc, Fairfield, NJ) prior to treatment with a neuromodulator in order to determine their baseline dimensions. Imaging will be repeated post injection to determine change over time.

1.1 Background and Relevant Literature

With an annual rise and over 845% increase since the year 2000, botulinum toxin neuromodulation is the most commonly performed minimally invasive technique in cosmetic surgery [1]. In accordance, much research has been produced evaluating the characteristics and efficacy of the various toxin-strain modalities currently available for use [2-4].

One such method for evaluation involves 3D photogrammetry. This technology involves for high level feature enhancement and microscopic anatomical evaluation that was not previously possible [5]. 3D photogrammetry has been used for a range of studies in cosmetic and reconstructive medicine and surgery, including its use in evaluating minimally invasive injection efficacy [6-8].

In spite of the research, there are few FDA approved neuromodulators for the treatment of dynamic ryhtids, most of which have been available for a period of time and have been clinically described [8]. More recently, a newer neuromodulator, PrabotulinumtoxinA, has received FDA approval, although few studies have captured its onset and effect compared to currently available neuromodulators [9]. We aim to assess onset and quantify the efficacy of four neuromodulators to help determine appropriate treatment selection.

2 Study Objectives

The overall study object is to quantify the dynamic strain of four commonly available neuromodulators using 3D imaging as well as other potential physical measurements differences over time.

2.1 Primary Objective

To compare the efficacy of four commonly available neuromodulators using 3D imaging to quantify dynamic strain measurements

3 Investigational Plan

3.1 General Design

This study is a randomized controlled trial in which patients will be randomly assigned into one of four groups: those receiving onabotulinumtoxinA (Botox, Allergan, Irvine, California), abobotulinumtoxinA (Dysport, Ispen Biopharmacueticals Inc.Cambridge, MA), incobotulinumtoxinA (Xeomin, Raleigh, NC) or prabotulinumtoxinA (Jeuveau, Evolus, Newport Beach, California). Each patient will receive FDA approved dosages in which they are assigned in to treat rhytids within the glabella, as per FDA approved indications. All injections will be performed by a blinded single trained physician (Ivona Percec) according to a preset injection plan per FDA approved administration guidelines. Prior to injection patients will be imaged with 3-dimensional photogrammetry. All pre-procedure images will be evaluated for absolute strain performing two types of facial animation: 1) relaxed, and 2) frowning. Subjects will return Day 3, 30, 90, and 180, post intervention for re-imaging with the same expressions. Strain will be calculated using the same metrics.

3.2 Allocation to Interventional Group

Subjects will be randomized to either the prabotulinumtoxinA abobotulinumtoxinA, incobotulinumtoxinA or onabotulinumtoxinA groups. Subjects will be randomized in a one to one fashion using block randomization.

3.3 Study Measures

3D photogrammetry imaging of each subject at the pre-determined time points will be obtained using the VECTRA M3 (Canfield Scientific, Inc., Fairfield, NJ), This allows for dynamic measurements of facial strain. Each subject's face will be measured along lines of tension when the face is in the relaxed and then frowning. Each facial animation will be recorded as an image. Three-dimensional coordinates will be

calculated to generate each subject's topographic configuration, displacement, and surface strain of each detected point on the surface of the face relative to its original reference image.

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The primary endpoint is to quantify the change in dynamic strain of the glabella area after injection of four neuromodulators using 3D facial imaging measurements over time.

3.4.2 Secondary Study Endpoints

1) Quantify the change in the dynamic strain of the glabella area after injection between the four neuromodulators
2) Quantify the change of dynamic strain measurements of each facial animation over time.
3) Correlation of satisfaction as determined by the FACE-Q to the degree of dynamic strain overtime

4 Study Population and Duration of Participation

Adult subjects, ages 30-65, who are interested in rhytid treatment of the glabella with a neuromodulator under FDA approved use. Each participant will participate for 180 days.

4.1 Duration of Study Participation

The duration of study participation is a minimum of 180 days. Subjects will receive injections on day-1, and follow up imaging and analysis occurs on day 3, 30, 90 and 180 post intervention.

The overall study duration is estimated 12- 18 months. It may take approximately 6 months to enroll all subjects and complete initial imaging and procedures, 7 months for follow up imaging, and 4-5 months for data analysis. Each individual subject's participation time in the study will consist of the duration of the initial imaging session (approximately 20 minutes), procedure (15 minutes), follow up imaging (20 min).

4.2 Total Number of Subjects and Sites

140 patients will be enrolled from at a single location, the Hospital of the University of Pennsylvania.

4.3 Inclusion Criteria

- Female
- 30-65 years of age
- Interested in glabellar injections to reduce rhytids and facial strain
- Participants must sign the informed consent form

4.4 Exclusion Criteria

- Females under 30 or above 65 years of age
- Males

- Those who have received glabellar injections for rhytids <12 months
- Underwent cosmetic surgical procedure above the malar region
- Those with a condition that affects facial expression, such as prior stroke

4.5 Subject Recruitment

Patients will be recruited through the plastic surgery clinic, which is a high-volume practice for those who may be interested in cosmetic injections. Additionally, we plan to use of a flyer posted throughout the health system and campus. Injections to the glabellar region to reduce rhytids are a popular procedure and we do not anticipate significant difficulty in recruiting willing participants.

4.6 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Procedures

This section should list the procedures, observations, measures, etc. that will take place at each of the study visits. Every measure, procedure, observation, etc. that was listed in Section in Section 3.3 should be included in the study procedures section. A table can supplement this section. An example procedures table is included below in Appendix 15.1.

5.1 Screening

The screening visit involves patient evaluation of inclusion and exclusion criteria. This information is readily available on the intake visit and does not deviate from standard of care for a clinic visit, including age and past medical history. Once patients are deemed eligible, the process of informed consent will begin. Informed consent will take place.

5.2 Study Intervention or Observational Phase

Randomized Controlled Single Blinded Study

5.2.1 Visit 1 (sometimes referred to as the baseline visit)

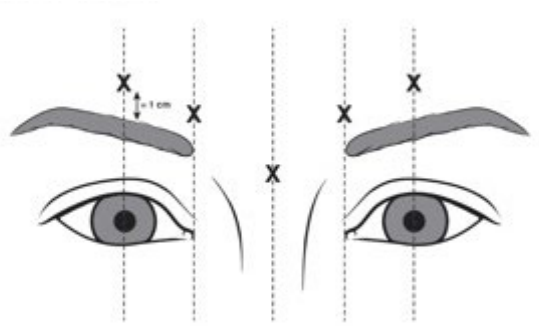
Visit 1 involves screening, consent, baseline imaging to measure dynamic strain, randomization, intervention. The subject will be photographed using 3D imaging with multiple facial animations. All pre-procedure images will be evaluated for absolute strain performing two types of facial animation: 1) relaxed, 2) frowning. Following the baseline images, subjects will complete a FACE-Q questionnaire and then randomized to one of the four neuromodulators onabotulinumtoxinA (Botox, Allergan, Irvine, California), abobotulinumtoxinA (Dysport, Ispen Biopharmacueticals Inc.Cambridge, MA), incobotulinumtoxinA (Xeomin, Raleigh, NC) or PrabotulinumtoxinA (Jeuveau, Evolus, Newport Beach, California) according to a preset injection plan per FDA approved administration guidelines. The injector will be blinded to the neuromodulator assigned to the subject via randomization at the time of injection in order to decrease any underlying bias during drug administration. The syringes will be documented and prepared by appropriately trained staff.

Intervention Preparation as described on the FDA approved medication guide

PrabotulinumtoxinA (Jeuveau)
Reconstitute 100 unit vials with 2.5 mL preservative-free 0.9% sodium chloride injection, USF. Load 0.5mL in a single syringe with a 30-gauge needle. Each of the five FDA approved injection points will receive 0.1 mL of the reconstituted solution (4 unit of toxin) intramuscularly for a total of 20 units in 0.5mL.

OnabotulinumtoxinA (Botox) and IncobotulinumtoxinA (Xeomin)
Reconstitute 50 unit vials with 1.25 mL preservative-free 0.9% sodium chloride injection, USF. Load 0.5mL in a single syringe with a 30-gauge needle. Each of the five FDA approved injection points will receive 0.1 mL of the reconstituted solution (4 unit of toxin) intramuscularly for a total of 20 units in 0.5mL

AbobotulinumtoxinA (Dysport)
Reconstitute 300 unit vials with 3.0 mL preservative-free 0.9% sodium chloride injection, USP. Load 0.5mL in a single syringe with a 30-gauge needle. Each of the five FDA approved glabella injection points will receive 0.1mL of the reconstituted solution (10 units of toxin) intramuscularly for a total of 50 units in 0.5mL.



Once reconstituted, unused toxin may be stored in the original container in a refrigerator at 2-8ºC or 36-46ºF. Do NOT freeze. All toxin must be discarded within 24 hours after reconstitution. All reconstituted vials should be single-use for one subject only.

5.2.2 Visit 2

Visit 2 which will occur 3-days post-injection, will consist of a repeat of the above measurements using 3D imaging with facial animations of 1) relaxed and 2) frowning. Subjects will also complete the FACE-Q via electronic REDCap survey and communicate any questions or concerns.

5.2.3 Visit 3

Visit 3 which will occur 30-days post-injection, will consist of a repeat of the above measurements using 3D imaging with facial animations of 1) relaxed and 2) frowning. Subjects will also complete the FACE-Q via electronic REDCap survey and communicate any questions or concerns.

5.2.4 Visit 4

Visit 4 which will occur 90-days post-injection, will consist of a repeat of the above measurements using 3D imaging with facial animations of 1) relaxed and 2) frowning. Subjects will also complete the FACE-Q via electronic REDCap survey and communicate any questions or concerns.

5.2.5 End of Study Visit 5

Visit 5 which will occur 180-days post-injection, will consist of a repeat of the above measurements using 3D imaging with facial animations of 1) relaxed and 2) frowning. Subjects will also complete the FACE-Q via electronic REDCap survey and communicate any questions or concerns.

TABLE 1 SCHEDULE OF STUDY PROCEDURES

	Baseline Visit 1	Intervention	Follow-up Visit 2 Day 3	Follow-up Visit 3 Day 30	Follow-up Visit 4 Day 90	Follow-up Visit 5 Day 180
Visit Window	**Day 1**	**Day 1**	**Day 3 ±1**	**Day 30 ± 5**	**Day 90 ±7**	**Day 180 ±10**
Eligibility	**X**					
Informed Consent	**X**					
Demographic	**X**					
Medical History	**X**					
Consultation	**X**					
Vectra Photography		**X**	**X**	**X**	**X**	**X**
FACE-Q		**X**	**X**	**X**	**X**	**X**
Adverse Events	**X**	**X**	**X**	**X**	**X**	**X**

5.3 Unscheduled Visits

Unscheduled visits will be handled on a case by case basis dependent upon the reasoning for the patients' visit. If subjects are displaying signs of immediate danger or instability, they will be referred to emergency department or directly admitted. However, unscheduled visits are rare for this type of procedure.

5.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator. Subjects may also be withdrawn following an adverse event that does not allow them to continue with the study. It will be documented

whether or not each subject completes the study. Subjects who withdraw early will have one final communication to collect final evaluations and assess for adverse events.

5.4.1 Data Collection and Follow-up for Withdrawn Subjects

Patients must document in a letter asking not to use the data collected and formalize the withdrawal. Otherwise, data up until withdrawal will be available for analysis.

5.5 Early Termination Visits

This may be due to the subjects' own choice or the investigator's decision. If the investigator makes the decision, subjects will be contacted and reasons for study termination will be thoroughly explained.

6 Statistical Plan

6.1 Sample Size and Power Determination

The sample size is based on a previously successful study with the same purpose [1], and an anticipated 15% drop-out/withdrawal rate. Significant decrease in the dynamic strain in OnabotulinumtoxinA and AbobotulinumtoxinA were determined at day 4, 14, and 90 post intervention compared to baseline. We are increasing the patient population to account for a potential increase drop out due to the number of follow-up visits.

1. Wilson AJ, Chang B, Taglienti AJ, et al. A Quantitative Analysis of OnabotulinumtoxinA, AbobotulinumtoxinA, and IncobotulinumtoxinA: A Randomized, Double-Blind, Prospective Clinical Trial of Comparative Dynamic Strain Reduction. Plast Reconstr Surg. 2016;137(5):1424–1433.

6.2 Statistical Methods

The primary analysis will be done using chi-squared testing and Fischer's exact test for categorical variables, where applicable, and the paired t-test for continuous variables. Analysis is preformed blinded at the end of the study. There is no interim analysis.

6.3 Control of Bias and Confounding

Block randomization will be employed to assign subjects into each study arm. 40 blocks consisting of 4 assignments per block will be used in sequence until study enrollment is complete. The injecting physician will be blinded to which neuromodulator is assigned at the time of injections prevent any underlying bias.

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as race).

6.3.2 Analysis of Primary Outcome of Interest

The primary analysis will be done using chi-squared testing and Fischer's exact test for categorical variables, where applicable, and the paired t-test for continuous variables.

7 Safety and Adverse Events

7.1 Definitions

7.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

For FDA regulated studies the FDA defines an adverse event as the following:

Adverse event means any untoward medical occurrence associated with the use if a drug in humans whether or not considered drug related.

7.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention

or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

7.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures should be characterized. The PI or medical monitor will determine how the relationship of the AE will be classified as:

- likely related – a well-known effect of the device or clearly not related to the subject or environmental factors
- probably related – is known or suspected effect of device or cannot be readily explained by subject or study procedures
- possibly related – is a possible effect of the device or can be explained by the subject or study procedures
- unlikely related – is not a suspected effect of the device or can readily be explained by the subject or environmental factors
- unrelated – is not a known effect of the device and can readily be readily and easily explained by the subject or environmental factors

7.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Investigators and the protocol sponsor (which may or may not be a Penn Investigator) must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible,

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally, all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies.

7.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

7.4.2 Investigator reporting: notifying the study sponsor

Investigators from all participating sites should report all unexpected and related adverse events, regardless of whether they are serious or not, and all unanticipated problems to the sponsor.

Any study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to the study sponsor by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form will be completed by the investigator and emailed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by sending via email to: [Evolus., Company Call Center: 1-877-EVOLUS1 (1-877-386-5871), Company Email: EvolusMI@druginfo.com]

Within the following 48 hours, the investigator will provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

7.4.3 Investigator reporting: notifying the Penn IRB

For single and multi-site studies each site PI will need to follow their local IRB reporting requirements in addition to the protocol outlined reporting.

7.4.4 Sponsor reporting: Notifying Participating Investigators

For clinical trials, in addition to reporting certain unanticipated problems and adverse events noted above to the FDA, it is the responsibility of the study sponsor to report those same adverse events or findings to participating investigators.

7.5 Medical Monitoring

It is the responsibility of the site Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. The lead PI will monitor all AEs reported.

7.6 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

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

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

7.7 Data Collection and Management

REDCap will be used to store and maintain the primary study records. The data entered into REDCap will be obtained from the study-relevant patient EMRs. Study personnel will be granted access to this project created in REDCap with each user obtaining individual access authenticated by a login system. Minimal patient identifiers will be collected and stored in the REDCap database. Patient name and date of birth will be collected in REDCap.

Source data will mainly be from the patient's EMR. When the study requires data not normally collected in the patient's EMR, the case report forms will also be the source document. Data from source documents (Appendix15.4, case report forms (case report forms definition- Appendix 15.5), will be entered into an electronic data capturing system. All source documents should be secure in private spaces with restricted access. After Visit 1 the FACE-Q will be sent electronically to the subject for each follow-up visit via a REDCap survey.

During procurement of data charts will be reviewed in private spaces to ensure the confidentiality of acquired data. Data will be stored for up to 7 years after completion of the last follow-up visit of the last patient randomized. Data may be collected for up to two years following the treatment.

7.8 Records Retention

The Principal Investigator at each site is responsible for storing regulatory documents, subject files and financial records for the period specified by law. The time period for maintaining research records is defined first by HIPAA regulations that require any HIPAA-regulated information, authorizations, waivers, etc. must be maintained for at least 6 years subsequent to the Institutional Review Board (IRB) acknowledgement of the termination of the research project and secondly by DHHS regulations (45 CFR 46.115) and FDA regulations (21 CFR 56.115) state that IRB records relating to research shall be retained for at least 3 years after completion of the research.

8 Study Monitoring, Auditing, and Inspecting

8.1 Study Monitoring Plan

This study will be closely monitored by the PI and the project manager. The PI will be participating and the data will be collected by the PI and one other study steam member from the patient's EMR. The study team member will enter the data into the REDCap and the project manager will monitor the entry to verify the compliance with respect to the protocol, data collection and source documents.

8.2 Auditing and Inspecting

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

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

9 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

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

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

9.1 Risks

All treatments used in this protocol will be used according to the FDA approved intended use. No unexpected risks should occur. Risks that may be experienced from any injection are swelling bruising, redness, itching, infection, or pain.

There is minimal risk to this study. This study is a prospective observational study of an FDA approved cosmetic drugs used as approved. The study protocol only adds 3D imaging required to make the observational measurements. The images will be identifying as they are of the face. All identifying images will be stored on a database or computer behind the firewall and a password.

Potential risks of the neuromodulators are:
- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- drooping eyebrows
- allergic reactions. Symptoms of an allergic reaction may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint.
- upper respiratory tract infection

Reproductive risks: If patient is of child-bearing potential, a urine pregnancy test may be administered prior to injection to confirm negative pregnancy status. The effects of this drug/device, there could be serious harm to unborn children or children who are breast-feeding. These effects could also harm the mother.

9.2 Benefits

Subjects participating in this trial may gain insight into the potential benefit of wrinkle reduction in the glabella area from participating in this study. The risks of this study are the same as those that would apply to any injection procedure, such as swelling and low-levels of pain. Additionally, a breach of confidentiality is a possibility although we have created measures to mitigate this risk. Although the benefits may not be readily apparent on an individual basis, the advancement of knowledge gained will serve the medical society and community

There is financial compensation for participation in this study. Subjects will be compensated $15 for each follow-up visit and questionnaire completed. The payment will be administered after completion of the fourth and final follow-up visit for a maximum total of $60. The subjects will receive the neuromodulators for no charge.

9.3 Risk Benefit Assessment

Subjects participating in this trial will unlikely experience an increase in risk as this is an observational study of FDA approved neuromodulators. No change in patient care will happen if the subject is consented. All subjects will be asked to return for four follow-up visits for observation and surveys.

9.4 Informed Consent Process / HIPAA Authorization

All subjects for this study will be provided a consent form describing this study providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The subject, or legally acceptable surrogate, must sign the consent form, and the investigator-designated research professional obtaining the consent. Subjects will be consented by the study Principal Investigator, or appropriate designee, in a room we have selected in which to perform consent, which is located outside of the clinic. Potential subjects will review the consent form in detail with the person designated to consent (either PI or CRC) and have the ability to take the consent home for further review.

10 Study Finances

10.1 Funding Source

Funding Sources pending

10.2 Conflict of Interest

None

10.3 Subject Stipends or Payments

There are no subject payments or stipends.

11 Publication Plan

Following data analysis and summary, data will may be presented to relevant conferences and submitted for publication. Once published, data is destroyed.

12 References

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13 Attachments