Prospective Evaluation of Minimally Invasive Facial Cosmetic Procedures through Measured Volumetric Changes and Patient Reported Outcomes

Protocol Number: **IRB Number:**	*827003*
ClinicalTrials.gov Number	*NCT03460158.*

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Table of Contents

Contents

List of Abbreviations

Abbreviation	Description
AE	Adverse Event
CDC	Center for Disease Control
CRF	Case Report Forms
EDC	Electronic Data Capture
EMR	Electronic Medical Record
FACE-Q	Face Image Quality of Life Inventory
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HA	Hyaluronic Acid
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
PHI	Protect Health Information
PI	Principal Investigator
QoL	Quality of Life
SAE	Serious Adverse Event
UPHS	University of Pennsylvania Health System

Study Summary

Title	*Prospective evaluation of minimally invasive facial cosmetic procedures through measured volumetric changes and patient reported outcomes*
Short Title	*Galderma - Prospective*
IRB Number	*827003*
Protocol Number	*NCT 03460158*
Phase	*Post-market Study*
Methodology	*Prospective comparison of the dermal fillers for the treatment of age related aesthetic changes.*
Study Duration	*The active portion of the study will be the baseline visit and observational follow-up will occur approximately at baseline visit, 14 days, 28 days, and 90 days for a total of 90 day of patient participation.*
Study Center(s)	*University of Pennsylvania Health System (Penn Medicine)*
Objectives	*Primary:* • *Determine patient satisfaction with minimally invasive volume correction using patient reported outcomes and satisfaction with the validated survey FACE-Q* • *Determine the volumetric changes over 90 days* *Secondary:* • *Correlate degree of patient satisfaction with 3-dimensinal image analysis.*
Number of Subjects	*100 subjects*
Main Inclusion and Exclusion Criteria	*Inclusion Criteria* • *Female patients* • *Between the age of 40 - 65* *Exclusion Criteria* • *Male patients* • *Prior surgical facial rejuvenation procedures* • *Prior minimally invasive rejuvenation procedure ≤ 12 months* • *Known contraindications to devices or drugs used in this study* • *Facial paralysis* • *Congenital facial asymmetry* • *Pregnant women* • *Patient actively taking blood thinners*

Investigational Product (drug, biologic, device, etc.) **For Device include the planned use** **For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment**	*Restylane-L® used in the nasolabial folds and marionette lines up to a total of 4cc injections* *Restylane-L® Lyft used in the nasolabial folds and marionette lines up to a total of 2 cc injections* *Up to 1cc injections of Restylane® Silk may be placed in the lips and cutaneous vermillion (up to 2 cc total)* *Up to a total of 4cc injections of Restylane-L® Lyft may be placed in the malar region*
Duration of administration	*Injections to be placed during clinic visit.*
Reference therapy	*None*
Statistical Methodology	Standard descriptive statistics will be used to summarize baseline characteristics and study outcome measures at each visit, both overall, and within each arm. The validated FACE-Q will be used to determine patient satisfaction for each arm. Mean and standard deviation calculation with regression analysis will be performed for all survey variables. Analysis of variance will also be performed. The baseline and post treatment measurements from the Vectra 3D images will determine volumetric changes of the injections over time. The average volume change will be calculated. A correlation between patient satisfaction and volumetric changes will be calculated.

Prospective evaluation of minimally invasive facial cosmetic procedures through measured volumetric changes and patient reported outcomes

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, 312, 314 and 812 and Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH). Note: Only include ICH compliance if the study will actually comply with these requirements.] All episodes of noncompliance will be documented.*

1 Introduction

1.1 Background and Relevant Literature

Dermal fillers have been approved for the treatment of age related aesthetic changes, including facial volume loss, and attenuation of the static and dynamic rhytid. Despite widespread use of volumizing fillers there is little data quantifying the subjective benefit of these minimally invasive treatments from the patient perspective. Furthermore, there is little data comparing the subjective benefit with true objective volumetric results. Such data will provide much needed information for patient counselling and treatment optimization for patient perceived outcomes.

1.2 Name and Description of the Investigational Product

Three different dermal fillers will be utilized in this study. All products are FDA approved. Restylane-L® has FDA 510(k) approval for the indication for mid-to-deep dermal implantation for moderate to severe facial wrinkles and folds, such as nasolabial folds and marionette lines. Restylane-L® Lyft is FDA approved for the indication of implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds and marionette lines and malars (cheek/cheek bone area). Restylane Silk has FDA approval for the indication indicated for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21.

2 Study Objectives

The primary object of the study is to evaluate patient reported outcomes following minimally invasive rejuvenation using FDA approved dermal fillers.

2.1 Primary Objective

- To determine and compare patient reported outcomes and satisfaction with the validated survey FACE-Q over 90 days.
- To determine and compare the volumetric changes over 90 days

2.2 Secondary Objectives

- Determine facial volumetric changes after treatment and correlate to patient reported outcomes.

3 Investigational Plan

Screening will be completed during the clinic visit, and then the patient will be approached for informed consent process. Once the patient is consented, the baseline data will be collected. 3-D Vectra imaging will occur before and after the injections at the initial visit and then again at 14 days, 28 days and 90 days post injection with the FACE-Q survey.

3.1 General Design

This is a prospective study to evaluate the efficacy and to determine patient reported outcomes of dermal fillers. Screening will be performed during the patient's office visit. Approximately 100 patients will be enrolled. Patients will participate up to 90 days (Day 1, 14 days, 28 days, and 90 days).

Treatment – Restylane-L® or Restylane-L® Lyft, and Restylane Silk®

3.1.1 Screening Phase

Eligible subjects will be identified from all the principal investigators' clinical schedules, as well as recruiting local population including employees. Potential subjects will be screened by a member of the study team for eligibility using the electronic medical record (EMR) according to the inclusion/exclusion criteria. A member of the study team will give a written informed consent and will answer any questions the patients many have. Eligible patients may be contacted at home through a phone call by a member of the study team to introduce the study. A member of the study team will answer any questions the patient may have before and after the informed consent form is signed. The informed consent form will be documented in the subject's medical record or comparable source document.

3.1.2 Study Intervention Phase

Intervention will occur during the patient's previously scheduled office visit. The patient will be seen by the PI for the originally scheduled consultation. After the initial consultation, proper screening, and informed consent of the patient is completed the patient will answer one survey and undergo 3-D photography and standard digital photography. After injections the patient will have photographs and the survey administered again before the initial visit is complete.

3.1.3 *Follow Up Phase*

The follow-up phase of a patient is approximately 90 ± 7 days. Follow-up will begin after treatment is administered. Required visits occur at 14 ± 3 days, 28 ± 3 days and 90 ± 7 days. At each required follow-up visit one questionnaire will be administered, the FACE-Q in addition to the 3-D Vectra imaging.

3.1.4 Primary Study Endpoints

The primary endpoint will be to quantify patient satisfaction with minimally invasive volume correction.

- Determine patient reported outcomes and satisfaction with the validated survey FACE-Q
- Determine the volumetric changes at each time point up to 90 days

3.1.5 Secondary Study Endpoints

- Correlate degree of patient satisfaction with volumetric measurements from 3-D analysis after treatment over the 90 day period

4 Study Population and Duration of Participation

4.1 *Inclusion Criteria*

- *Female patients 40 – 65 years of age*

4.2 Exclusion Criteria

- *Male patients*
- *Prior surgical facial rejuvenation procedures*
  - *Facelift*
  - *Neck lift*
  - *Blepharoplasty*
  - *Facial fat grafting*
- *Prior minimally invasive rejuvenation procedure ≤ 12 months*
- *Known contraindications to devices or drugs used in this study*

- *Facial paralysis*
- *Congenital facial asymmetry*
- *Pregnant women*
- *Patient actively taking blood thinners*

4.3 Subject Recruitment

Eligible subjects will be identified from principal investigator's clinic schedule and recruited from local area including employees. Potential subjects will be screened by a member of the study team for eligibility, using the electronic medical record (EMR), according to the inclusion and exclusion criteria listed above. In clinic, the principal investigator will introduce the study to eligible patients. A member of the study team will give a written informed consent, and will answer any questions the patients may have. Eligible patients may be contacted at home through a phone call by a member of the study team to introduce the study to assess interest in participation. A member of the study team will answer any questions the patients may have before and after the informed consent is signed. The informed consent process will be documented in the subject's medical record or comparable source document.

4.4 Duration of Study Participation

Subject participation will begin during the office when the informed consent is signed. Once the patient is confirmed to be a study candidate by the participating physician, they can be enrolled. Patients will be asked to return for 3 follow-up visits over the next 90 ± 7 days.

4.5 Total Number of Subjects and Sites

Total accrual will be 100 patients. The aim will be to enroll all subjects at the University of Pennsylvania Health System (UPHS).

5 Study Intervention

The initial consultation by the principal investigator will determine the injection area and the volume of the injections. Injections of the fillers will be used according to the FDA approval indicated use. All three areas will be injected (nasolabial folds, marionette lines, and lips).

Restylane-L® used for the nasolabial folds and/or marionette lines up to a total of 4 cc (2 cc/side).
Restylane-L® Lyft used for severe nasolabial folds and or marionette lines up to a total of 2 cc (1 cc/side)
Restylane-L® Lyft used for malar deflation will receive up to a total of 4 cc of (2 cc/side)
Restylane® Silk in the lips and cutaneous vermillion used for perioral volume loss will receive up to 1cc per lip.

5.1 Description

Restylane-L® is indicated for mid-to-deep dermal implantation for moderate to severe facial wrinkles and folds, such as nasolabial folds. It is indicated for submucosal implantation for lip augmentation in patients over the age of 21. Restylane-L® consists of stabilized, hyaluronic acid (HA) generated by streptococcal bacteria and formulated to a concentration of 20 mg/ml, suspended in physiological buffer of pH7 with 0.3% lidocaine. Restylane-L® is a transparent viscous and sterile gel, supplied in disposable glass syringes contain 0.4 or 0.7 ml gel.

Restylane-L® Lyft is indicated for implantation into the deep dermis to superficial subcutis for the correction of severe facial folds and wrinkles, such as nasolabial folds and for subcutaneous to supraperiostal implantation for check augmentation correction of age-related midface contour deficiencies in patients >21 years of age. Restylane-L® Lyft is a sterile gel of stabilized hyaluronic acid generated by staphylococcus species of bacteria, suspended in phosphate buffer saline at pH 7 at a concentration of 20 mg/ml with 0.3% lidocaine.

Restylane® Silk is indicated for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients >21 years of age. Restylane® Silk is a gel of hyaluronic acid generated by streptococcus species of bacteria stabilized and suspended in phosphate buffered saline at pH 7 at a concentration of 20 mg/ml with 0.3%.

5.2 Intervention Regimen

5.2.1 Study Group

The patient will receive the injections of the fillers in all three areas the nasolabial folds, marionette lines, and lips as recommended by the PI during the initial consultation of the regularly scheduled appointment.

5.3 Receipt

Galaderma the manufacturer of Restylane-L®, Restylane-L® Lyft, and Restylane® Silk, will provide the fillers for the study. The products will be shipped directly to the PI and stored in a drug labeled refrigerator. The products will be inventoried when they arrive and designated as used per patient.

5.4 Storage

The products will be shipped directly to the PI and stored in a drug labeled refrigerator in the PI's office. Restylane-L®, Restylane-L® Lyft and Restylane® Silk must be used prior to expiration date printed on the package and stored at a temperature ≤ 77° F ≥ 36°F, protected from sunlight. Do NOT freeze.

5.5 Preparation and Packaging

Restylane-L®, Restylane-L® Lyft and Restylane® Silk come prepared in sterile disposable glass syringes with luer-lock fitting. Restylane products are co-packed with sterilized needles (needle gauge specified on package). Sterile syringes will be used for each vial assigned to each subject.

5.6 Administration and Accountability

Restylane® products come supplied with a patient record label as a part of the syringe label. Remove it by pulling the flap marked with three small arrows. This label is to be attached to patient records to ensure traceability of the product. The extra label will also be placed on the device accountability log.

5.7 Return or Destruction of Investigational Product

The unused products will be disposed in the fashion of biohazard material.

6 Study Procedures

TABLE 4 SCHEDULE OF STUDY PROCEDURES

	Baseline Visit	Intervention	Follow-up Visit 1 Day 14	Follow-up Visit 2 Day 28	Follow-up Visit 3 Day 90
Visit Window	**Day 1**	**Day 1**	**Day 14 ± 3**	**Day 28 ± 3**	**Day 90 ± 7**
Eligibility	**X**				
Informed Consent	**X**				
Demographic	**X**				
Medical History	**X**				
Consultation	**X**				
Vectra Photography		**X**	**X**	**X**	**X**
FACE-Q		**X**	**X**	**X**	**X**
Adverse Events	**X**	**X**	**X**	**X**	**X**

6.1 Study Intervention Phase

6.1.1 Screening/Baseline Visit (Day 1)

Electronic medical records from the most recent office visit will be used to initially screen according to the inclusion/exclusion criteria in Section 4.1 and 4.2. The current office visit will be used to confirm the patient's eligibility, if confirmed the patient will be approached to consent to participate in the study. When the patient is consented the screening/baseline documentation will take place. The screening and baseline data collection will include demographic information, medical history, and surgical history. The screening and baseline visit and intervention can occur in the same office visit.

- **Medical Record Review**
  Variables abstracted from the electronic medical record
  - Date of Birth
  - Height
  - Weight
  - Race
  - Gender
  - Any history of disease
  - Surgical facial rejuvenation history

- **Consultation**
  The patient will undergo the initial consultation with the PI. The consultation will be documented in the patient's EMR.

6.1.2 Intervention (Day 1)

- If patient is concerned of child bearing potential, a urine pregnancy test will be administered.
- FACE-Q survey will be administered prior to injections
- Photographs with the Vectra 3D camera will be administered prior to injections
- Injections
  - The patient will receive the fillers injectors as suggested in the consultation in all three areas of the face.
- Photographs with the Vectra 3D camera will be administered 30 minutes after injections

6.2 Follow Up Phase of the Study

6.2.1 Follow-up Visits

- **Visit 1 (Day 14 ± 3)**
  - Photographs with the Vectra 3D camera
  - FACE-Q will be administered

- **Visit 2 (Day 28 ± 3)**
  - Photographs with the Vectra 3D camera
  - FACE-Q will be administered

- **Visit 3 (Day 90 ± 7)**
  - Photographs with the Vectra 3D camera
  - FACE-Q will be administered

6.3 Unscheduled Visits

An unscheduled visit or extra visit will be defined as a visit scheduled outside of the protocol due to any concern of the patient's treatment related to the injections. If an unscheduled visit occurs, it is preferred to collect the information during the visit for example any adverse event. If an unscheduled visit is missed a follow-up phone interview is adequate if more information is required than is available in the patient's EMR.

6.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

6.4.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent to participate in the study may be asked for one final visit or phone interview to collect any study endpoints or adverse events at that time.

6.5 Early Termination Visits

If a subject decides to leave the study early or is asked by the investigator to cease participation in the study the subject's participation is complete.

7 Study Evaluations and Measurements

7.1 Efficacy Evaluations

To quantify the subjective benefit using the FACE-Q to determine the patient's satisfaction and comparing it with true objective volume changes measured with the Vectra 3D camera.

8 Statistical Plan

8.1 Primary Endpoint

The primary endpoint is to quantify patient satisfaction with minimally invasive volume correction and to measure the volume metric changes with fillers over time.

8.2 Secondary Endpoints

The secondary endpoints will correlate degree of patient satisfaction with the volumetric measurements from 3-dimensional image analysis.

8.3 Sample Size and Power Determination

The sample size was deemed appropriate to power the study based on previous literature in this area of research.

8.4 Statistical Methods

8.4.1 Baseline Data

Standard descriptive statistics will be used to summarize baseline characteristics and study outcome measures at each visit, both overall, and within each arm.

8.4.2 Efficacy Analysis

The validated FACE-Q will be used to determine patient satisfaction for each arm. The Mirror Software 3D software (Canfield Scientific Inc, Fairfield, New Jersey) will calculate the volumetric changes by comparing the treated area after filler injection to the baseline images. The baseline and post treatment measurements from the Vectra 3D images will determine volumetric changes of the injections over time. All volumetric measurements will be recorded in milliliters, and the average volume change will be calculated. A correlation between patient satisfaction and volumetric changes will be calculated.

Statistical tests will be performed as determined by the study team. Mean and standard deviation calculation with regression analysis will be performed for all survey variables. Analysis of variance will also be performed.

8.5 Subject Population(s) for Analysis

Per-protocol population: Any eligible patients randomized and adhered with their assigned treatment throughout the course of the trial.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 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.

9.1.2 Serious Adverse Event

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**.

9.2 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.

9.3 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

9.4 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.

9.4.1 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.

9.4.2 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:

[Galderma Laboratories, L.P., email: WELLS Sara <Sara.WELLS@galderma.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.

9.4.3 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.

9.4.4 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.

9.5 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.

9.6 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.

9.7 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.

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.

9.8 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.

10 Study Monitoring, Auditing, and Inspecting

10.1 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.

10.2 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.

11 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.

11.1 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.

All HA containing products have the risk of potential tissue loss if there is unrecognized intravascular injection of the fillers. All HA fillers are dissolvable and if you are strongly dissatisfied with the treatment filler or if there is evidence of tissue threat, HA can be removed with hyaluronidase (Vitrase)®. Restylane Silk carries an extra risk of hyperpigmentation to the risks from injection listed above. A risk related to all injectables used in this study is unevenness or lumps.

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.

11.2 Benefits

Subjects participating in this trial will not directly benefit participating in this study. If assigned to the treatment group, the patient will receive the treatment described in the initial consultation. If assigned to the control group, they may not receive the desired benefits of the requested consultation.

11.3 Risk Benefit Assessment

Subjects participating in this trial will unlikely experience an increase in risk as both groups receive injections. This study is designed to minimally change patient's care. Subjects participating in this trial are chosen due to the clinic consultation scheduled. No change in patient care will happen if the subject is consented. All subjects will be asked to return for three follow-up visits for observation and surveys.

11.4 Informed Consent Process / HIPAA Authorization

Eligible subjects will be identified from the practice of the PI. Potential subjects will be screened by a member of the study team for eligibility, using the electronic medical record (EMR), according to the inclusion and exclusion criteria listed above. In clinic, the participating investigator will introduce the study to eligible patients during the consultation visit. A member of the study team, identified to consent, will give a written informed consent and answer any questions the patients may have. Eligible patients may be contacted at home through a phone call by a member of the study team to introduce the study followed by presenting the consent form during the consultation visit. A member of the study team will answer any questions the patients may have before and after the informed consent is signed. It will be emphasized to the potential subject that three visits are required which are not considered standard of care. The informed consent process will be documented in the subject's medical record or comparable source document.

12 Study Finances

12.1 Funding Source

All product used in this study will be provided by the manufacturer, Galderma.

12.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

12.3 Subject Stipends or Payments

Subjects will not be compensated when they return to the clinic for the follow-up visits.

13 Publication Plan

The manuscript for this trial will contain the overall study results and be submitted to a peer-review journal. The final contents will be at the discretion of the PI. All results of the study performed under this protocol, or any of the information provided by the PI for the purposes of performing the study, will not be published or passed on to any third party without the consent of the PI. Any investigator involved with this study is obligated to provide the PI with complete test results and all data derived from the study.

14 References

Attachments

Investigator will attach sample Investigator Agreement and ICF prior to study activation

- Investigator Agreement (for any investigator, other than sponsor-investigator, who participates in the study)
- Sample Consent Form

15 Appendix

15.1 Reference for Safety Reporting Section- Common Definitions for Developing and Adverse Event Tracking and Serious Adverse Event Reporting Protocol

15.2 Expedited FDA Reporting Requirements

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/ IDE safety reports.

The following describes the IDE safety reporting requirements by timeline for reporting and associated type of event:

- **Within 10 working days**
  Any study event that is all:
  - associated with the use of the study drug, and
  - unexpected,
    regardless of the seriousness of the event.

- **Within 5 working days**
  - Protocol deviation to protect the life of the subject in emergency
  - Withdrawal of IRB approval
  - Lack of informed consent

Additional reporting requirements
Sponsors are also required to identify in IND/IDE safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Applicable events can be reported to the FDA using Form FDA3500A or in narrative format. The report must be sent to the correct division. Specific information that must be included in the reports can be found in 21 CFR 312.32 or in 21 CFR 812.150.

15.3 DSMB Reference: The following section of guidance language draws from: the FDA Guidance Document: "Guidance for Clinical Trial Sponsors on the Establishment of Clinical Trial Data Monitoring Committees"

15.4 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

15.5 Case Report Forms (CRFs)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.