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	procedure results. However, this clinical trial will continue until every enrolled subject has reached 6 months following their procedure. At that time, the trial will be considered complete, the final results will be analyzed, and a final report will be prepared.

2 STUDY ADMINISTRATIVE STRUCTURE

Study Sponsor:

Apyx Medical Corporation
5115 Ulmerton Road
Clearwater, FL 33760-4004
Phone: (800)537-2790
Fax: (800)323-1640

Proprietary Notice:

This document contains mainly unpublished data and is the sole property of the Sponsor. Therefore, it is provided to you in strict confidence as an investigator, potential investigator, or consultant. The information may be reviewed by you, your staff, and your institutional review board. It is understood that this information will not be disclosed to others without written authorization from the study Sponsor except to the extent necessary to obtain informed consent from those persons to whom the investigational device may be implanted.

Ethics Statement:

The study will be completed in accordance with applicable regulations and standards to provide public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

4.3.3 Secondary Safety Endpoint

The secondary safety endpoint is the evaluation of the change in pain and discomfort after treatment (baseline, within 60 minutes following the procedure) experienced in the period up to the 10 (-1/+4) day follow-up visit. Pain or discomfort will be recorded daily by each participant in a diary using an 11-point Visual Analogue Scale (VAS).

4.3.4 Additional Endpoints

Other endpoints to be evaluated include:

1. Whether or not (Yes/No) at least 2 out of 3 blinded Independent Photographic Reviewers (IPRs) correctly identify the 90-day image of a subject from the pair of baseline and 90-day images.
2. Magnitude of improvement measured by the mean change in FWS from baseline to 90-day visit as determined by Investigators.
3. Subject modified GAIS at 90-day FUV.
4. Investigator modified GAIS at 90-day FUV.
5. Subject satisfaction with procedure recorded at the 90-day visit.
6. Achievement of re-epithelialization by facial zone and across all facial zones at the 10 day, 30 days and 90 days follow-up visits as reported by the investigator.
7. Mean duration until study subject feels comfortable going in public after treatment as reported by the study subject.

5 INVESTIGATORS SELECTION AND STUDY POPULATION

5.1 Investigator Selection

Participating Investigators will be qualified based on professionals experienced in treatment of wrinkles, such as dermatologists or plastic surgeons. Investigators will be selected based on interest and availability for participation in the study; ability to provide qualified subjects; adequate support staff; experience conducting clinical research; and willingness to comply with the protocol, IRB requirements, regulatory requirements (including the signed investigator agreement and statements disclosing any financial relationship investigators might have with Apyx Medical Corporation), and FDA regulations.

5.2 Study Population

All subjects requesting a procedure for the purpose of improving facial appearance by reducing facial wrinkles and rhytides from each participating investigator's subject population will be considered as candidates for the study. Those subjects who meet eligibility criteria and agree to provide written informed consent will be invited to participate.

Subjects will be considered enrolled into the study when they have signed an approved informed consent form. Enrolled subjects who meet all study criteria and have undergone a procedure with the Renuvion Dermal System will be part of the full analysis set.

5.2.1 Inclusion Criteria

Potential subjects must meet all of the following inclusion criteria:

1. Male or female subjects ≥30 years of age.
2. Subject is seeking improvement of facial appearance by reducing facial wrinkles and rhytides.
3. Subject with a facial wrinkle score rating of at least 4 on the FWS.
4. Subject with a Fitzpatrick Skin Scale score ≤III.
5. Subjects who are willing and able to take protocol allowed medications prescribed at investigator discretion which may include Keflex or Z-pack as an antibiotic, Acyclovir or Valtrex as an antiviral, Diflucan as an antifungal, Ativan or Valium for anxiety during treatment, Norco or Ultram for pain control during or post-procedure, Gabapentin, Tylenol with Codeine or NSAIDS for post-procedure pain control, and/or Antihistamines for itching during healing.
6. Subjects who are willing to have polycarbonate eye shields placed for study treatment.
7. Subject is willing and able to provide written informed consent.
8. Subject is willing and able to comply with protocol requirements, including obtaining study-required images/photos and assessments, post-care instructions, and returning for follow-up visits.
9. Subject is willing to maintain baseline skin care regimen during study participation with the exception when protocol specified ointments, moisturizers, and cleansers are required during healing stage (through approximately the 30-day follow-up). Sunblock is required throughout the study starting on approximately day 10.

assessment tool used to assess skin wrinkle severity and elastosis on a scale from 1 through 9, where the lower score is considered better. Three Independent Photographic Reviewers will be blinded to the study subject's visit (baseline and follow-up visit) and will perform photographic assessments of each subject's wrinkle depth in the treated zones (identified only as "Zones to Evaluate" to the IPRs) using FWS and ignoring nasolabial folds and marionette lines (effects of gravity), and artifacts from the chin rest. The IPRs will assign a single FWS score per subject for both the right and left photo. Each photograph will have a unique identification number but sets of images will not be arranged in any specific order (i.e., randomized order).

Independent Photographic Review Evaluation Process for FWS:

1. Each blinded assessor will be provided with identical photos to be assessed. The pre-treatment and follow-up photos will be consistent in lighting, subject positioning and focus. Each photo's visit interval, i.e., pre-treatment and follow-up, will NOT be marked. The images placement (right or left) will be randomly ordered for pre-treatment and follow-up images. Images for each subject will be grouped together into one set with all pre-treatment and follow-up images in the same location (right/left) for the subject set.
2. Each blinded assessor will conduct their assessment independently with no input from another blinded assessor.
3. Each blinded assessor reviews the Left photo and assigns a FWS score.
4. Each blinded assessor reviews the Right photo and assigns a FWS score.
5. Enough time should be allowed to do this for each image, so the assessments are not rushed.
6. The change between FWS scores will be calculated during data analysis after assessments are complete.
7. Success will be determined by at least 1-point improvement in FWS by at least two out of three blinded, independent reviewers.

Table 3: Fitzpatrick Wrinkle and Elastosis Scale

Table 3: Fitzpatrick Wrinkle and Elastosis Scale			
Class	**Description**	**Score**	**Description**
I	Fine wrinkles	**1-3**	**Mild:** Fine texture changes with subtly accentuated skin lines.
II	Fine to moderate depth wrinkles, Moderate number of lines	**4-6**	**Moderate:** Distinct papular elastosis (individual papules with yellow translucency under direct lighting) and dyschromia.
III	Fine to deep wrinkles, numerous lines, with or without redundant skin folds	**7-9**	**Severe:** Multipapular and confluent elastosis (thickened, yellow and pallid) approaching or consistent with cutis rhomboidalis.

lasting up to a typical maximum duration. All ETEs and AEs will be collected during the conduct of this trial.

A preexisting condition (one that is present at the start of the study) will be recorded as an AE only if the frequency, intensity, or the character of the condition worsens during the study period.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances: hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

8.3 Serious Adverse Event (SAE) Definition

Serious Adverse Event (SAE) is an adverse event that:

- Led to a death or
- Led to a serious deterioration in the health of a subject that:
  - Resulted in a life-threatening illness or injury,
  - Resulted in a permanent impairment of a body structure or body function,
  - Required in-patient hospitalization or prolongation of existing hospitalization,
  - Resulted in medical or surgical intervention to prevent impairment to body structure or a body function
  - Led to fetal distress, fetal death or a congenital abnormality or birth defect, or
  - Other serious (important) medical events that may jeopardize the subject and may require medical or surgical intervention to prevent on of the other outcomes.

All SAEs that occur during the study period, whether considered to be related to the investigational product or not, must be reported to the Sponsor within 24 hours of knowledge of the event. IRB reporting requirements may also apply for SAEs.

8.4 Unanticipated Adverse Device Effect (UADEs) Definition

An **unanticipated adverse device effect** (**UADEs)** is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

In addition, any **UADEs** will be reported to the Sponsor and the reviewing IRB as soon as possible, but no later than within 24 hours of knowledge of the event.

All adverse events, anticipated or unanticipated, will be monitored until they are adequately resolved or explained.

8.5 Reporting Requirements

All adverse events (AEs) observed by study subjects, investigators or other study staff from first exposure to the study product through last study follow-up visit will be recorded. If a device-related AE, SAE, or unanticipated serious device related effect is ongoing at the final study visit,

the subject will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The investigator should make every effort to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate, as completely as practical, the nature and/or causality of the AE or SAE. This may include unscheduled follow up visits for AE assessment.

Study subjects will be instructed to report all AEs to the clinical study staff. AE information will be collected throughout the study and recorded on CRFs.

8.6 Severity of Adverse Events

The **severity of adverse events** will be categorized using the following criteria:

- **Mild:** easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. These events generally do not require treatment.
- **Moderate:** sufficiently discomforting to interfere with normal everyday activities. These vents are usually relieved by simple therapeutic measures.
- **Severe:** prevents normal, everyday activities. These events may require systemic drug therapy or other medical treatment.

8.7 Relationship to the Study Device and/or Procedure

The **relationship to the study device and/or procedure** will be determined by the investigator utilizing the following categories:

- **Not Related:** An event for which an alternative explanation is conclusively identified – e.g., concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is highly unlikely.

- **Related:** The adverse event follows a reasonable temporal sequence related to treatment by the device, follows a known or suspected response pattern and a plausible alternative etiology cannot be identified.

- **Undetermined:** The relation of the adverse event has some temporal relationship to the device and/or device procedure, is not clearly due to another condition and the involvement of the study device is unknown.

8.8 Stopping Guidelines / Stopping Rules: Safety

The Sponsor and/or investigator may recommend termination or modification of the study if there is an occurrence of any device- or treatment-related Serious Adverse Event, using the clinical protocol definitions of Serious Adverse Event in **Section 8.3** of this protocol. In addition, termination or modification may be recommended for any other perceived safety concern based on clinical judgment, including but not limited to a severe burn (anticipated or unanticipated), a higher than anticipated rate for any component of the safety measures, device failures resulting in Adverse Events, or unexpected SAEs.

9 RISK AND BENEFITS

9.1 Benefits

A possible benefit of using the Renuvion Dermal System is the potential for improvement in wrinkle severity. Additional potential benefits of improving the appearance of wrinkles could include enhanced well-being, with improved satisfaction with the appearance of less facial wrinkles or the perception of a having a more youthful appearance.

9.2 Risks

The following are expected treatment effects (ETE) with the Renuvion Dermal System:

- Pain & tenderness immediately after the procedure, decreasing substantially by 10 days post-procedure; and
- Erythema, swelling, induration (crusting) and/or urticaria (itching) persisting approximately 7-14 days.
- Pin-point bleeding during reepithelialization resolving by 14 days.
- Temporary post-inflammatory hyperpigmentation resolving by 90 days,

Potential risks with the Renuvion Dermal System are similar to those that are encountered for many routine facial soft tissue reductions. These include but are not limited to:

- pain,
- tenderness,
- itching,
- bleeding,
- bruising/hematoma/seroma,
- allergic reaction,
- hypersensitivity to the treatment (resulting in erythema, swelling, induration and/or urticaria),
- temporary or permanent post-inflammatory hyperpigmentation,
- telangiectasias,
- skin overheating/burn,
- hypertrophic scarring
- discoloration/permanent hypopigmentation,
- vessel laceration or occlusion,
- abscess (infection) at treatment site which may result in induration and/or scar formation, and
- prolonged wound healing.

Subjects using drugs that reduce coagulation (aspirin or NSAIDs) may experience increased bruising or bleeding at the treatment site.

Side effects of nerve blocks and tumescent local anesthesia containing lidocaine or epinephrine include:

- Nausea
- Vomiting
- Mild sleepiness

Common side effects of Tylenol with Codeine include:

- nausea,
- vomiting,
- upset stomach,
- constipation,
- headache,
- lightheadedness,
- dizziness,
- drowsiness,
- blurred vision, or
- dry mouth
- Inform your doctor if you experience unlikely but serious side effects of Tylenol with Codeine including mental/mood changes, severe stomach/abdominal pain, or difficulty urinating.

- **NSAIDS**

  The most common side effects are:

  - vomiting,
  - nausea,
  - constipation,
  - diarrhea,
  - reduced appetite,
  - headache,
  - dizziness,
  - rash, and
  - drowsiness.

  NSAIDs also may cause swelling of the arms and legs due to the retention of fluid from their renal effects.

  The most serious side effects are ulcers, bleeding, kidney failure, and, rarely, liver failure.

11.4.1 Primary Safety Endpoint

The primary safety endpoint is the enumeration of each subject's adverse events (AE) up to the 90-day visit after treatment. Each AE will be categorized by cause, severity, seriousness, and relatedness to the procedure, the device, and the therapy.

11.4.2 Secondary Safety Endpoint

The secondary safety endpoint is the evaluation of the change in pain and discomfort after treatment (baseline, within 60 minutes following the procedure) experienced in the period up to the 10-day follow-up visit. Pain or discomfort will be recorded daily by each participant in a diary using an 11-point Visual Analogue Scale (VAS).

11.5 Effectiveness Endpoints

11.5.1 Primary Effectiveness Endpoint

Primary Effectiveness Endpoint

On each subject, the appearance of facial wrinkles and rhytides at baseline and the 90-day images will be assessed by three blinded Independent Photographic Reviewers using the FWS. Each subject will have three change scores; if 2 or more of the 3 change scores are one point or higher, the subject will be considered a success (Y or 1) and if 2 or more of the 3 change scores are less than one point, the subject will be considered a failure (N or 0).

11.6 Additional Endpoints

Other endpoints to be evaluated include:

1. Whether or not (Yes/No) at least 2 out of 3 blinded Independent Photographic Reviewers (IPRs) correctly identify the 90-day image of a subject from the pair of baseline and 90-day images.
2. Magnitude of improvement measured by the mean change in FWS from baseline to 90-day visit as determined by the Investigators.
3. Subject modified GAIS at 90-day FUV.
4. Investigator modified GAIS at 90-day FUV.
5. Subject satisfaction with procedure recorded at the 90-day visit.
6. Achievement of re-epithelialization by facial zone and across all facial zones at the 10 day, 30-day and 90-day follow-up visits as reported by the investigator.
7. Mean duration until study subject feels comfortable going in public after treatment as reported by the study subject.

11.7 Statistical Analysis of Safety Endpoints

All statistical analyses will be described in detail in an accompanying statistical analysis plan (SAP).

Primary Safety Endpoint

Adverse event rates will be estimated using Kaplan-Meier time-to-event analyses. The monthly event rates and their 95% confidence intervals (CIs) will be reported by their type, severity, and relationship to the study procedure, device, and therapy.

Secondary Safety Endpoint

The mean VAS score will be reported at each measurement along with it 95% CI, its SD and its minimum and maximum. The change from baseline will be similarly reported.

11.8 Statistical Analysis of the Effectiveness Endpoint

All statistical analyses will be described in detail in an accompanying statistical analysis plan (SAP).

For the primary effectiveness endpoint, the proportion of successful patients (P) will be tested against the PG. If the lower bound of the 95% confidence interval of the proportion of subject achieving treatment successes is greater than the Performance Goal, the effectiveness endpoint would be met. The statistical test will be a one-sided Fisher's Exact Test at $\alpha = 0.05$. For the effectiveness endpoint to be met, Ho must be rejected.

$$\text{Ho: } P \leq 50\% \quad \text{vs.} \quad \text{Ha: } P > 50\%$$

11.9 Statistical Analysis of Additional Endpoints

These analyses will be described in the accompanying SAP.

11.10 Subgroup Analysis

Subgroup analyses will include modeling (using linear regression analysis) the effect of on age, gender, race/ethnicity, and Fitzpatrick Skin Scale (FSS) on the ΔFWS. (Age *et al* are called "independent variables".) The goal is to determine whether certain types of subjects are more likely to have a better response than other types. If any of the independent variables are significant, the effect size and better responders will be reported. This is examined in greater depth in the SAP.

12 DATA HANDLING AND RECORDKEEPING

12.1 Investigator Records

The Investigator is responsible for the preparation, review, signature, and retention of the records listed below:

- signed Clinical Trial Agreement and Curriculum Vitae
- all correspondence pertaining to the investigation with other investigators, the reviewing IRB, the study Sponsor, the Monitor and FDA,
- investigational device receipt, use and disposition records,
- subject case history records relating to use of the device, including Case Report Forms, medical records, progress notes, nurses' notes, etc.,
- all signed informed consent forms,
- all shipping and disposition records for investigational devices and relevant observations relating to the device, and
- the protocol and documentation of date and reason for any deviation from investigational plan.

Records are subject to FDA inspection and must be retained for a period of at least two years after the latter of two dates:

1. date on which the investigation is terminated or completed, or
2. date that the records are no longer required for purposes of supporting an application to the FDA to market the device.

12.2 Investigator Reports

The Investigator is responsible for the preparation, review, signature, and submission of the reports listed in Table 6. These are also subject to the FDA inspection and the retention requirements described above for the Investigator's Records.

LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CRO	Clinical Research Organization
DCF	Data Clarification Form
DRM	Data Review Meeting
ESU	Electrosurgical Generator Unit
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSS	Fitzpatrick Skin Scale
FWS	Fitzpatrick Wrinkle and Elastosis Scale
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
ICH	International Conference for Harmonization of Technical Requirements of Pharmaceuticals for Human Use
IFU	Instructions for Use
IPR	Independent Photographic Reviewer
IRB	Institutional Review Board
ITT	Intent-to-Treat
NSAID	Non-steroidal Anti-Inflammatory Drug
PP	Per Protocol
PSR	Plasma Skin Resurfacing
PPS	Per Protocol Set
RF	Radiofrequency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analog Scale

3 INTRODUCTION

3.1 Study Background

Physiological skin aging is multi factorial and results from both intrinsic and extrinsic factors. Genetics is one example of an intrinsic factor; others include hormone and metabolic processes that can cause the skin to age. Exposure to chronic light, radiation, pollution, chemicals and toxins, are examples of extrinsic factors. Since skin health and beauty is contemplated as one of the representations of overall "well-being" and "health", several anti-aging therapies have been developed during the recent years. The goal of these therapies is to achieve a healthy, smooth, blemish-free, translucent and resilient skin. [1]

Skin resurfacing or peel procedures have become an established non-surgical method for reducing certain skin imperfections such as wrinkles, rhytides, dark spots, scars, or blemishes. Traditional fully ablative and fractional lasers are the most commonly used devices for skin resurfacing.

The skin is composed of three layers: the epidermis, the dermis, and the hypodermis. The dermis contains well-organized and oriented collagen fibers that contribute to the firmness and smoothness of the skin. As people age, these collagen fibers reduce in number and become less organized, resulting in sagging and/or wrinkled skin. When esthetic procedures are scheduled for older adults, the rate of the epidermal turnover associated with a slower wound healing and less effective desquamation (shading of outer layers of the skin), needs to be taken into consideration.[1]

In most skin resurfacing procedures, an energy source (heat, radiofrequency energy, etc.) is used to selectively damage the skin and prompt a healing response that stimulates the growth of new collagen fibers in the dermis that are well-organized. The healing response and new collagen formation results in skin that is smoother and firmer.

There are numerous traditional fully ablative and fractional lasers on the market today used for skin resurfacing. Traditional and fractional lasers differ in their method of treatment. Traditional lasers have a single beam that burns or damages all of the epidermis within the treatment area of the beam. Fractional lasers divide the beam into multiple smaller beams and treat only a "fraction" of the epidermis to affect changes in the deeper epidermis or dermis. This results in multiple small cores of laser damage surrounded by areas of healthy tissue. When compared to traditional lasers, fractional lasers deliver a more superficial treatment resulting in less risk for complications and reduced time for healing. However, this also means more treatments may be required to achieve the desired results especially in areas of deep lines or wrinkles. Healing times vary by amount of treatment, but fractional laser recovery time is typically one week compared to three to four weeks for traditional lasers.

In the wake of the demonstrated safety and effectiveness of laser skin resurfacing, multiple additional treatment modalities have been developed for this application including the use of radiofrequency (RF) energy. The fractionated radiofrequency results in epidermal and subepidermal ablation under the conductive pins that reproduces similar effects as a fractional CO_2 laser with dermal heating, seen in the non-ablative lasers and devices.[2] The combination of epidermal ablation and dermal heating with radiofrequency, called sublative resurfacing in some studies, is suitable for skin types I–IV, for the treatment of skin laxity, wrinkles, enlarged pores, pigmented lesions, acne, telangiectasias, and scarring from trauma or acne. Subject recovery and

10. Subject is willing to release rights to study Sponsor for the use of the photos, including in potential publication.
11. Subject is willing to abstain from other facial cosmetic procedures through the 6-month follow-up visit; examples include, but are not limited to, laser or chemical re-surfacing, dermabrasion, neuromodulator and/or filler injections, aesthetic facial surgery, etc.

5.2.2 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Subject with a Fitzpatrick Skin Scale score ≥IV.
2. Subject is pregnant or lactating.
3. Active HSV-1 or diabetes mellitus.
4. Active cut, wound, or infection on the skin of the face.
5. Subject has used, within 30 days prior to screening or plans to use during study participation, Accutane, Retinol, or any medication that can cause dermal hypersensitivity.
6. Subject has used, within 10 days prior to study treatment, aspirin or NSAIDs.
7. Subject has a history of autoimmune disease (excluding Hashimoto's thyroiditis).
8. Subject with a known bleeding disorder or who is on blood thinning medication that may be at risk for bleeding.
9. Subject has a known adverse reaction to lidocaine and/or epinephrine.
10. Subjects with active skin disease of the facial area or known connective tissue disease.
11. Subjects with known susceptibility to keloid formation or hypertrophic scarring.
12. Subjects with present cancerous or pre-cancerous lesions in the area to be treated.
13. Subject who, for any reason, suspects that they will not be able to complete the prescribed follow-up assessment(s).
14. Subject has had concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety and effectiveness of the study treatment method.
15. Subject is not willing to release rights to study Sponsor for the use of the photos, including in potential publication.
16. Subject is enrolled in another investigational (drug or device) clinical trial that can interfere with this study's assessments.
17. Subject has undergone a facelift procedure within 12 months prior to the screening visit.
18. Subject has received IPL, microneedling, or chemical peels within 3 months prior to the screening visit.
19. Subject has received microneedling with RF or any facial treatment with an energy-based device within 6 months prior to the screening visit.
20. Subject has received facial injections with BOTOX® or other toxins within 6 months prior to the screening visit.
21. Subject has received hyaluronic acid or calcium hydroxylapatite fillers within 4 months prior to the screening visit.
22. Subject who is a family member or employee of the investigator or sponsor.
23. Participation in any other investigational study within 30 days prior to consent.
24. Subject who, in the opinion of the investigator, is not an appropriate candidate for the study.

7.3 Modified Global Aesthetic Improvement Scale (GAIS)

The Global Aesthetic Improvement Scale (GAIS) is a subjective rating of improvement in treatment results compared to pre-treatment. A modification of the GAIS to include "much worse" and "very much worse" as rating options will be used in this study. The Investigator will grade the overall improvement of treatment area as indicated in Table 4a by comparing the subject's appearance at follow-up visits against a photograph taken prior to procedure. Likewise, the subject will also rate their improvement compared to pre-treatment as shown in Table 4b.

The modified GAIS results will be collected at the 30, 90, and 180-day follow-up visits.

Table 4: Modified Global Aesthetic Improvement Scale Evaluation

Table 4a: Modified Global Aesthetic Improvement Scale Evaluation (GAIS): Investigator	
Rating	**Description**
Very much improved	Optimal cosmetic result from this procedure in this subject
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject
Improved	Obvious improvement in appearance from the initial condition
No change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition
Much worse	The appearance is much worse than the original condition
Very much worse	The appearance is very much worse than the original condition

Table 4b: Modified Global Aesthetic Improvement Scale Evaluation (GAIS): Subject	
Rating	
Very much improved	□ Optimal cosmetic result.
Much improved	□ Marked improvement in appearance from the initial condition, but not completely optimal.
Improved	□ Obvious improvement in appearance from initial condition.
No change	□ The appearance is essentially the same as the original condition
Worse	□ The appearance is worse than the original condition.
Much worse	□ The appearance is much worse than the original condition.
Very much worse	□ The appearance is very much worse than the original condition.

7.4 Re-epithelization and Down Time

The study investigators and/or Independent Photographic Reviewers (as applicable) will be required to obtain and document re-epithelization and down time defined as per below:

- Confusion
- Convulsions
- Respiratory depression and/or respiratory arrest
- Cardiovascular stimulation or depression
- Cardiac arrest
- Lightheadedness or dizziness
- Nervousness
- Apprehension
- Euphoria
- Tinnitus
- Blurred or double vision
- Sensations of heat, cold or numbness
- Twitching
- Tremors
- Unconsciousness
- Anaphylactic response (hypotension, difficulty breathing, tightness in chest, and/or shortness of breath)

Side effects and subject instructions for medications that are at investigator discretion include:

- **Keflex**

  If any of these effects persist or worsen, tell your doctor or pharmacist promptly:

- Diarrhea
- Nausea
- Vomiting
- Upset stomach

  This medication may rarely cause a severe intestinal condition due to resistant bacteria. This condition may occur during treatment or weeks to months after treatment has stopped. Do not use anti-diarrhea or opioid medications if you have any of the following symptoms because these products may make them worse. Tell your doctor right away if you develop:

- Persistent diarrhea
- Abdominal or stomach pain/cramping
- Blood/mucus in your stool

  A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including:

- Rash

Individuals allergic to NSAIDs may experience shortness of breath after taking an NSAID and may experience a similar reaction when other NSAIDs are taken.

People with asthma are at higher risk for experiencing serious allergic reactions to NSAIDs.

NSAIDs (except aspirin) may increase the risk of heart attacks, stroke, and related conditions, which can be fatal. This risk may increase with duration of use and in patients who have underlying risk factors for disease of the heart and blood vessels.

NSAIDs, particularly non-selective NSAIDs, cause an increased risk of serious, even fatal, stomach and intestinal adverse reactions such as bleeding, ulcers, and perforation of the stomach or intestines. These events can occur at any time during treatment and without warning symptoms. Elderly patients are at greater risk for these types of reaction.

- **Antihistamines**
    - Less common or rare

- Abdominal or stomach pain
- burning
- chills
- clay-colored stools or dark urine
- cough
- diarrhea
- difficulty swallowing
- dizziness
- fast or irregular heartbeat
- fever
- headache
- hives
- itching
- prickly sensations
- puffiness or swelling of the eyelids or around the eyes, face, lips or tongue
- redness of skin

Table 6: Required Investigator Reports

Table 6: Required Investigator Reports		
Report	**Submit to**	**Description**
Unanticipated Adverse Device Effect (UADE)	Sponsor and IRB	The Investigator must submit to the Sponsor and reviewing IRB a report of any UADE as soon as possible but not less than 10 working days after the Investigator first learns of the effect.
Withdrawal of IRB Approval	Sponsor	The Investigator must report a withdrawal of the reviewing IRB approval within 5 working days.
Progress Report	Sponsor, Monitor and IRB	The Investigator must submit this report at regular intervals, but not less than once per year to the IRB, Sponsor and Monitor.
Deviation from Protocol in Emergency	Sponsor and IRB	Deviation from the study protocol that is made to protect the life or physical well-being of a subject in an emergency situation must be reported within 5 working days after the emergency occurred.
Deviation from Protocol that affect the scientific soundness of the study plan or the rights, safety or welfare of human subjects	Sponsor	Prior approval by the Sponsor is required when a deviation of this nature is anticipated.
Failure to obtain informed consent	Sponsor and IRB	If a study device was used without obtaining informed consent, the Investigator must notify the Sponsor and IRB within 5 working days of the use of the device.
Final Report	Sponsor and IRB	The Investigator must submit this report to the Sponsor and IRB within 3 months after the termination or completion of the study, or after the Investigator's participation in the study is complete.

12.3 Data Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site Principal Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.