

Title:

**Fractional handpiece with CO2 Laser:
Fractional Ablative Laser Treatment of Vulvovaginal
Atrophy
Clinical Study**

Protocol 2016-PM-001

Sponsor: Perigee Medical

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1. SYNOPSIS

Objective:

To assess the feasibility and efficacy of the CO2 fractional handpiece in the treatment of vulvovaginal atrophy (VVA) in post-menopausal women and its effect on the patient VHIS (vaginal health index score). The primary endpoint is to assess the change in the vaginal dryness by means of a visual analogic scale (10 cm VAS).

Study Population:

This is a single center study with 30 patients.

Study Design:

The study design will be a prospective open label study. Up to 30 post menopausal female subjects (absence of menstruation for at least 12 months) exhibiting signs of vulvovaginal atrophy will be recruited. The subjects will be treated 3 times over 12 weeks. Each treatment duration will be approximately 15 minutes. The initial power and number of passes parameters shall be set according to the clinical specifications in this protocol.

Before the first treatment each subject will undergo clinical evaluation. The evaluation includes a medical history, a pelvic exam, a PAP smear per recommendation, a vaginal maturation index a vaginal pH test, and a prolapse evaluation with POPQ (pelvic organ prolapse qualification).

Clinical improvement will be assessed by the investigator physician using a visual analogic scale (10 cm VAS) to assess vaginal dryness. Additionally, patients shall complete a standardized vulvovaginal symptom questionnaire (PISQ-12) at each follow-up visit. Treatment and all results will be documented in a Case Report form. Additional evaluation questionnaires may be used at the discretion of the investigator.

If adverse side effects are observed, the investigator should provide the subject with the proper care and remedy and will document it in the Case Report Form.

2. INTRODUCTION

Vulvovaginal atrophy is an inflammation of the vagina (and the outer urinary tract) due to the thinning and shrinking of the tissues, as well as decreased lubrication. These symptoms are due to a lack of the reproductive hormone estrogen.

The most common cause of vaginal atrophy is the decrease in estrogen which happens naturally during perimenopause, and increasingly so in post-menopause. Vaginal atrophy symptoms usually appear 4-5 years after the onset of menopause and can affect up to 50% of women. The symptoms can include vaginal soreness and itching, as well as painful intercourse, and bleeding after sexual intercourse. The shrinkage of the tissues and loss of flexibility can be extreme enough to make intercourse impossible.

The primary goal of vaginal atrophy treatment is to restore the normal physiological conditions of the vagina, this reducing the symptoms.

Various therapies have been used to treat this condition – herbs, lubricants, and hormonal treatments. However, the results of these treatments are transitory and limited to the vaginal mucosa.

Lasers, particularly fractional CO₂ lasers, have shown much promise as a treatment with a lasting effect. The fractional CO₂ laser can induce permanent molecular changes, stimulating the growth of new collagen and the activation of fibroblasts.

There have been other clinical studies successfully using fractional CO₂ lasers for the treatment of vaginal atrophy.

In a 2013 study, 48 post-menopausal women were treated with a vaginal fractional CO₂ laser from Deka. The data indicated significant improvement in VVA symptoms in women who had undergone 3 fractional CO₂ laser sessions. Overall, 91.7% were satisfied or very satisfied with the procedure and experienced considerable improvement in their quality of life. This study was published in *Maturitas*, the European menopause journal - *Vulvo-vaginal atrophy: A new treatment modality using thermo-ablative fractional CO₂ laser* (Antonino Perino, Alberto Calligaro, Francesco Forlani, Corrado Tiberio, Gaspare Cucinella, Alessandro Svelato, Salvatore Saitta, Gloria Calagna).

In 2014, another study was published in the *Journal of Endometriosis and Pelvic Pain Disorders* 2014: 6(3) 150-156 entitled *Microablative fractional CO₂ laser improves dyspareunia related to vulvovaginal atrophy: a pilot study* (Stefano Salvatore, Umberto Leone Roberti Maggiore, Massimo Origoni, Marta Parma, Lavinia Quaranta, Filomena Sileo, Alice Cola, Ilaria Bainsi, Simone Ferrero, Massimo Candiani, Nicola Zerbinati). In this study, the laser treatment was efficacious in improving dyspareunia in 100% of the 15 patients included in the study. The intensity of dyspareunia significantly decreased from baseline (8.7 ± 1.0) to 12 week follow-up (2.2 ± 1.0 ; $p < 0.001$). In addition, all other VVA symptoms significantly ameliorated at the same follow-up.

Another 2014 study, published in the journal **Climacteric**. 2014 Aug;17(4):363-9 and entitled *A 12-week treatment with fractional CO₂ laser for vulvovaginal atrophy: a pilot study* (Salvatore S, Nappi RE, Zerbinati N, Calligaro A, Ferrero S, Origoni M, Candiani M, Leone Roberti Maggiore U), showed that fractional CO₂ laser treatment for VVA was effective ($p < 0.001$) to improve VVA symptoms in 50 post-menopausal women dissatisfied with previous local estrogen therapies.

3. STUDY OBJECTIVE

This single-center study objective is to assess the safety and efficacy of the Edge One CO₂ laser and laser handpiece in the treatment of vulvovaginal atrophy (VVA), particularly for vaginal dryness.

4. STUDY DEVICE

The CO₂ laser will be provided by Perigee Medical and will be stored in a locked room at the study center site. An accurate record of the module usage and settings should be maintained by the Principal Investigator. Using pre-determined settings, each patient will be treated 3 times over an 12 week period.



Figure 1: CO2 handpiece

Please note that the Edge CO2 laser with the fractional handpiece has an FDA clearance (K100590). The fractional handpiece has a general clearance for ablative skin resurfacing. The handpiece to be used is a variation of the FDA cleared handpiece, and it does not have an FDA clearance. It does bear a CE mark internationally for this indication for use. The purpose of this study is to determine the efficacy and feasibility of the Perigee Medical Edge CO2 laser with fractional handpiece for the treatment of a specific gynecology issue – vulvovaginal atrophy.

5. INVESTIGATIONAL PLAN

5.1 Study Design

The study design will be a prospective study with a total of up to 30 post menopausal subjects clinically diagnosed with vulvovaginal atrophy. The subjects will be treated with the fractional handpiece. Subjects will undergo 3 treatments. (Each treatment duration will be approximately 10-15 minutes.)

Before the initiation of the treatment, each subject will undergo a clinical evaluation as noted before. Each subject's vulvovaginal atrophy will be assessed by the clinical physician.

Clinical improvement will be assessed by the patient using a visual analogic scale (VHIS) to determine vaginal dryness. Additionally, patients shall complete a standardized female sexual function index questionnaire (FSFI) at each follow-up visit. Treatment and all results will be documented in a Case Report form.

If adverse side effects are observed, the investigator should provide the subject with the proper care and remedy and will document it in the Case Report Form.

5.2 Study Population

Subjects for this study will be recruited from the existing patient base at the study site. IRB approved e-mails and fliers may also be used for the recruitment of subjects. Up to 25 healthy

evaluable subjects will participate in this study. An evaluable subject is one who has passed the inclusion and exclusion criteria; given informed consent; received and followed the treatment schedule, and has been adequately followed to establish valid endpoints of efficacy.

5.2.1 Inclusion Criteria

Subjects meeting the following inclusion criteria may participate:

- Healthy non-smoking post menopausal women with absence of menstruation of at least 6 months
- Exhibiting VVA symptoms
- Prolapse staged \leq II, according to the pelvic organ prolapse quantification (ICS-POP-Q) system
- Have not had procedures in the anatomical area through 6 months prior to treatment
- Understand and accept the obligation and is logistically able to present for all scheduled follow-up visits

5.2.1 Exclusion Criteria:

Subjects meeting any of the following criteria will be excluded from participation:

- Acute or recurrent urinary tract infection (UTI), or genital infection (e.g. herpes candida).
- Prolapse staged $>$ II, according to the pelvic organ prolapse quantification (ICS-POP-Q) system
- Any serious disease, or chronic condition, that could interfere with the study compliance
- Previously undergone reconstructive pelvic surgery
- Have used vaginal creams, moisturizers, lubricants or homeopathic preparations for at least 3 months
- Have taken antiviral treatments
- Have a mesh (slings are acceptable)
- A history of thrombophlebitis
- A history of acute infections
- A history of heart failure
- Received or is anticipated to receive antiplatelets, anticoagulants, thrombolytics, vitamin E or anti inflammatories within 2 weeks pre treatment
- Any medical condition, that, in the investigator's opinion would interfere with the patient's participation in the study
- Taking medications that are photosensitive
- A history of keloid formation

5.2.3 Concomitant/Excluded Skin therapies and Medications

Subjects are not allowed to take take Premarin, Estrace 17 Beta Estradiol vaginal cream, Vagifem, or Estring (within 30 days) of the treatments. Subjects cannot have used topical prescription or over the counter meds in the treatment area within 30 days of a treatment. Subjects will be instructed not to take any prescription medications (except those allowed by protocol), without prior consultation with the Investigator. If concomitant therapy must be added then the reason, the name of the drug/product, the daily dose, and date of initiation and/or discontinuation of therapy will be recorded on the Concomitant Medication Page of the Case Report Form.

5.2.4 Informed Consent

At the initial screening, each prospective subject will be given a full explanation of the nature and purpose of the study by qualified staff of the clinical study site. Once the essential information has been provided to the subject and the Investigator is assured that an individual candidate understands the implications of participating in this study, the subject will be asked to give consent to participate in the study by signing an informed consent form. This consent must

be witnessed and dated and retained by the Investigator as part of the study records. Each subject's signed informed consent form will be kept on file by the Investigator. A copy of the informed consent form will be provided by the Investigator to the subject.

5.2.5 Subject Identification and Confidentiality

Subjects will be identified on the study CRFs by their subject number and/or their initials. CRFs are confidential documents and will only be available to the Investigator, Perigee Medical's representative and the IRB.

5.2.6 Subject Compensation

There will be no subject compensation.

6. STUDY CONDUCT

The study will be conducted at a single center associated with Dr. Sherry Thomas, the lead investigator.

6.1 Assignment of Subject Numbers

Each subject who satisfies the inclusion and exclusion criteria will be assigned a number for treatment in accordance with their chronological order of qualification for the study. Once a treatment number has been assigned to a subject it cannot be re-assigned to any other subject.

6.2 Treatment Regimen

A total of up to 30 subjects will be assigned to receive CO2 fractional treatments for vulvovaginal atrophy. Treatments will be repeated every 4 weeks for a total of up to 3 treatments.

Concomitant use of other prescription or OTC medications in the treatment area is not permitted while in the study.

If the subject is unable to tolerate the treatments, then the subject will be discontinued. If the patient is discontinued, they will come in for a 1 month follow up visit after the treatment to ensure patient safety.

If strong reactions occur after any treatment, these subjects should be treated according to the best judgment of the Principal Investigator. This information is to be appropriately documented on the CRFs.

6.3 Subject Instruction

The Investigator or Study Coordinator will thoroughly explain all procedures to the subjects.

Subjects are to be instructed as to the following:

1. Specifics of treatment dosing as discussed above.
2. Not to apply medications of any kind to the treatment area.

6.4 Study Visits

6.4.1. Schematic of Study Visits and Procedures

The evaluations scheduled for each visit are listed below and summarized in the Schematic of Study Visits and Procedures.

Schematic of Study Visits:

Month of visit	BL	1 Tx1	1 FU1	2 Tx2	2 FU2	3 Tx3	3 FU3	4 FU
Eligibility	√							
Informed Consent	√							
Medical History	√							
Medication	√							
Pelvic exam, pap smear, vaginal maturation index, and vaginal pH	√							
Classification	√							
Vulvovaginal symptom questionnaire	√	√	√	√	√	√	√	
Treatment		√		√		√		
Adverse side effects		√	√	√	√	√	√	
Clinical improvement evaluation			√	√	√	√	√	√
Case report form	√	√	√	√	√	√	√	√

BL = baseline

Tx = treatment

FU = follow-up visit

6.4.2 Screening Visit/Baseline

Prior to study initiation, each subject will be screened to ensure they meet all of the inclusion and none of the exclusion criteria outlined above. Potential subjects will be interviewed and examined by Investigator or his designee to establish their eligibility for inclusion in the study. Subjects will be given a full description of the nature and purpose of the study. If a subject is willing to participate, they must provide written informed consent before proceeding with the study. This visit will take approximately 1 hour.

Screening procedures will include the following activities for prospective participants:

1. Investigator, or designee, explains the investigational study and eligibility requirements.
2. Subject signs informed consent prior to any study-related procedures.
3. Investigator determines eligibility criteria.
4. Brief medical history.
5. Investigator assessment of vaginal dryness using a visual analogic scale (10cm VAS)

6.4.3 Treatment will take approximately 10-15 minutes.

1. Query for concomitant products/medications.
2. Exam of the treatment area.
3. Subject will receive treatment for vulvovaginal atrophy
5. Adverse event evaluation.

6.4.4 Follow-Up Visits (months 1,2,3 and 4)

Clinical improvement evaluations will be done at each follow-up visit (weeks 2,5,9 and 43). Each visit will take approximately 30 minutes.

1. Exam of the treatment area.
2. Clinical improvement evaluation using a visual analogic scale (10cm VAS) to determine vaginal dryness
3. Patient assessment of their treatment using the PISQ-12 standardized questionnaire

4. Adverse event evaluation.

6.5 Treatment Procedure:

Every treatment session should include the followings:

6.5.1 Pre-treatment:

- The subject shall sign an informed consent form after the investigator provides the subject with all relevant information and explains the study procedure.
- The investigator will determine subject's eligibility to participate in the study protocol.
- The investigator will perform a medical history assessment of the subject.
- The investigator will determine the vaginal dryness using a visual analogic scale (10 cm VAS)

6.5.2 Treatment Technique:

The treatment technique involves inserting the fractional handpiece (specially designed with an angled mirror) into the vagina to delivery laser energy along the vaginal canal.

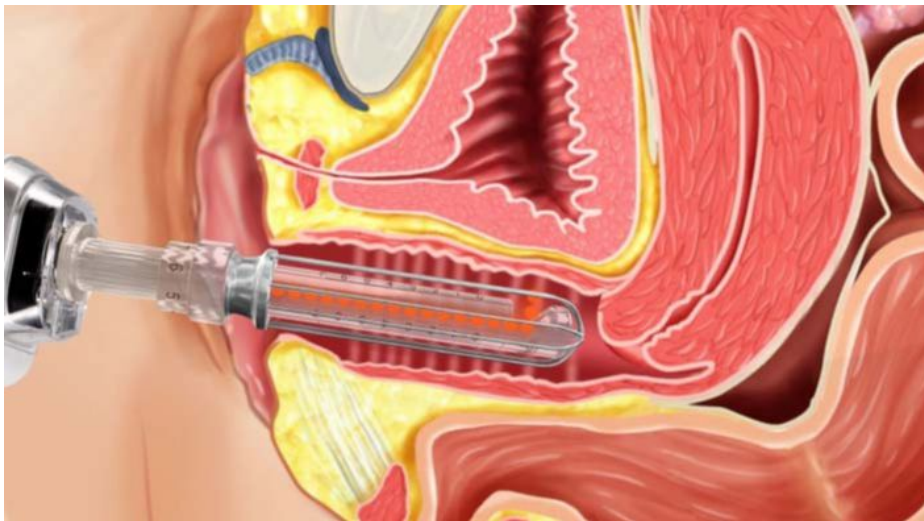


Figure 2: CO2 fractional treatment

The fractional handpiece, when attached to the Perigee Medical Edge CO2 laser, delivers fractionated laser energy through a special lens that divides the energy into a 1 x 1 cm matrix of tiny spots. These spots create thermal damage and are spaced such that the tissue between each is left unaffected. This results in a faster healing process. The fractional laser rays cause thermal damage that reaches the dermis to stimulate collagen growth.

6.5.3 CO2 fractional Treatment Protocol:

- Clean the treated area with a gauze sponge to remove any excessive mucus in the treatment area.
- Make sure the doctor and all medical staff inside the treatment room wear appropriate eye protection. The safety eyewear should be rated with an optical density of OD>7 and be labeled for the 10,600nm CO2 wavelength.

- Insert the speculum into the vagina.
- Insert the handpiece scope into the speculum. Turn the system on and select Fractional Mode from the control panel.
- In **Standby** mode set the initial energy level (startup set recommendations: 30 watts, 90 mJ Pulse energy, 2 stacking, 8x8 pattern. According to the patient's reaction, you can increase up 120 mJ pulse energy and 3 stacking max, pulse mode or repeat mode). **WARNING:** Do not apply energy when inserting the handpiece.
- Insert the handpiece as distally as possible, with the laser energy window oriented to the 12:00 o'clock position. NOTE: There are position markings on the handpiece.
- Set the system to **Ready** mode.
- Trigger a laser pulse by pressing the footswitch.
- Shoot the laser and rotate the probe to each of the 7 numbered increments.
- When you reach the 12:00 o'clock position again, withdraw the handpiece by approximately one centimeter and repeat the rotation treatment procedure.
- Continue pulling back at one centimeter intervals triggering pulses until the handpiece window reaches the entrance of the vagina. Once you reach the entrance of the vagina, stop the treatment.
- Repeat the entire process by 3 passes.
- Repeat if required. NOTE: If necessary, increase or decrease the power to between 80 to 120 MJ, depending on patient comfort.

6.5.5 Clinical End-Points:

The clinical end point is determined when the entire treatment process described above has been completed.

6.5.6 Post Treatment Care:

Following treatment:

Post treatment care: immediately after treatment, patient will refrain from inserting anything into the vagina for 7 days. The patient will be provided with Lidocaine Ointment 5% to apply to outside of vagina every 4 hours as needed for the next 1-2 days.

Subjects must be instructed to avoid vaginal estrogen therapy during, pre- and post-operative period.

If adverse side effects occur the patients will call Dr Sherry Thomas at 818-480-7100 and 818-674-2288

6.6 Premature Discontinuation from Study

A subject may be withdrawn from the study at any time at either the Investigator's or the subject's discretion.

Participation in this research study may be discontinued for any of the following reasons:

1. Normal protocol completion.
2. Severe adverse reactions.
3. Noncompliance with protocol requirements (consistently missed study visits).
4. Subject requests to withdraw from study for whatever reason.

The reason for discontinuance from the study will be documented in the CRF.

Discontinued subjects will be asked to come in for a 1 month follow up after the last treatment.

6.7 Treatment Modification/Toxicity Management

In the event of severe irritation, vaginal bleeding, pain, discomfort, or infection treatment will be stopped. A patient may also discontinue if they cannot tolerate the discomfort that occurs during the treatment. A subject may be removed from the study for untoward or severe adverse reactions at the discretion of the study physician.

6.8 Compliance

At each treatment visit, subjects will be questioned regarding their compliance with the study protocol. Those subjects who consistently miss treatments or study visits, or who use con meds/therapies will be discontinued. Each treatment will be followed up between 30 – 45 days from the previous treatment.

7. STUDY ASSESSMENTS

7.1 Investigator Assessment- Clinical Improvement Evaluation

At baseline, before each treatment and before each follow-up visit, the investigator will evaluate the clinical improvement from the visual appearance of the treated area using a visual analogic scale (10 cm VAS).

8.0 DATA COLLECTION AND ANALYSIS

8.1 Recording of Data

The CRFs for each subject will be created by the research team. All CRFs are to be completed by the personnel administering the tests. All forms must be completed in black ink or typed. If an entry is blank because the item was not done, mark the item not done. If the item is unknown, mark the item UNK. If the item is not applicable to the subject, mark the space N/A. Corrections of data on the CRFs can be made only by crossing out the incorrect data with a single horizontal line and writing the correct values next to those crossed out. Each correction must be initialed and dated by the person making the correction. If corrections are made after review and signature by the Investigator, the Investigator must so document by initialing and dating the changes.

The CRFs will be reviewed by the Investigator who will sign the last page to acknowledge that review. The original completed CRF will be retained by the Sponsor, Perigee Medical.

8.2 Statistical Methods

8.2.1 Population

All subjects who receive treatment and complete the study will be considered evaluable.

8.2.2 Statistical and Analytical Plan (sponsor responsibility)

Upon completion of the research study, the data will be analyzed for tolerance and efficacy at each follow-up interval versus baseline. Only those subjects who satisfy the criteria for an “evaluable subject” will be included in the statistical analysis of efficacy. An evaluable subject is one who meets all entry criteria, not used any unapproved medications or therapies during the study, completed the follow-up visits and evaluations, and complied with the treatment regimen.

Adverse reactions during the study will be summarized using descriptive statistics and percentages whenever it is appropriate. The primary objective of this study is to assess the safety and efficacy of the CO₂ fractional handpiece in the treatment of vulvovaginal atrophy. The primary efficacy endpoint is the change from baseline in the vaginal dryness as determined by a visual analogic scale (10 cm VAS).

9.0 ADVERSE EVENTS

9.1 Introduction

All adverse events occurring during the course of a study will be documented on Adverse Event Forms. A separate Adverse Event Form will be filled out for each adverse event. All items on the form will be completed. For NONSERIOUS events, if information is missing at the initial visit and the subject will be returning for follow-up examination in a reasonably short period of time, the investigator may hold the Adverse Event Form until the scheduled follow-up examination. If the subject will not be returning in a reasonable period of time, the investigator will forward the form to the Sponsor and provide the missing information by letter or telephone call when the information is known. For SERIOUS adverse events, an Adverse Event Form will be returned to the Sponsor as soon as practical, even if it is incomplete, with new information submitted by telephone call as soon as it becomes known.

9.2 Nonserious Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient, or clinical investigation subject, undergoing a test treatment whether or not it is caused by this treatment. An adverse event can, therefore, be any unfavorable and unintended sign, symptom or disease temporarily associated with the use of a device, whether or not considered related to the device.

Events that occur prior to the use of the light device are not considered adverse events.

A non-serious adverse event is defined as a change in a subject's medical health, which is neither life threatening, does not require hospitalization, does not prolong a current hospitalization, and is not disabling.

Possible expected occurrences due to the use of the Edge fractional CO₂ laser may include the following reactions which will not be reported as adverse events:

- **Heating sensation or pain** – subject may experience a heating sensation during or just following the treatment, however, such pain is expected to be mild and to resolve within few minutes.
- **Burns**
- **Chronic Urinary tract infection**
- **Vaginal infections**
- **Moderate to severe vaginal bleeding (more than a menstrual period)**

9.3 Serious Adverse Event

Serious adverse events are defined as any finding which suggests a significant hazard, contraindication, side effect, or precaution. Additionally, any adverse event which results in a fatality, is life threatening, is permanently disabling, requires inpatient hospitalization, prolongs a current hospitalization, or a congenital anomaly is also considered a serious adverse event.

A life threatening adverse event means that the subject was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused a death. Serious, alarming and/or unusual adverse events must be reported to the following individual within 24 hours of the investigator's knowledge of the event:

CONTACT: Sherry Thomas
29525 Canwood Street, Suite 211
Agoura Hills, Ca 91301
818 480-7100 Exchange
Phone: 818 674-2288(mobile)
E Mail: drsherrythomas@yahoo.com – non urgent and non HIPPA compliant

An Adverse Event Form will be completed for all serious adverse events and forwarded to the Sponsor within 24 hours. Additionally, a phone call will be made to confirm delivery of the report. When new significant information is obtained as well as when outcome of an event is known, the Sponsor will be informed by telephone call. Depending on the nature and seriousness of the adverse event, a copy of the medical record of the patient as well as results of laboratory tests performed may be requested. If the subject was hospitalized, a copy of the discharge summary may be forwarded to the Sponsor as soon as it is ready. In all instances, investigators will follow subjects until an outcome to the event is known.

10.0 ADMINISTRATIVE REQUIREMENTS

10.1 Principal Investigator

The Principal Investigator is responsible for insuring the investigation is conducted according to the study protocol and good clinical practice guidelines.

10.2 Study Coordinator

The study coordinator is the contact person at the investigational site who is appointed by the Principal Investigator to assure that all elements of the protocol are faithfully implemented.

10.3 Informed Consent and Institutional Review Board

All subjects in this study will be completely informed, according to informed consent guidelines, about the pertinent details and purpose of the study. A written Informed Consent form will be understood and signed by each subject prior to enrollment into the study. The investigator or his designee will supply the consent form, approved by an Institutional Review Board, and a copy of such provided to the Sponsor. The study site will keep the original signed copies of all consent forms in its files and will provide the subject with a duplicate copy.

This study must be reviewed and approved by an appropriate Institutional Review Board (also known as an Ethics Committee). A copy of the letter indicating IRB approval will be provided to the Sponsor prior to study initiation. Annual updates will be provided to the IRB by the investigator for studies longer than a year. This study will not last more than 1 year.

10.4 Adherence to Protocol

The Investigator is not permitted to deviate from the protocol without proper notification of the Sponsor. Except for an emergency situation in which proper care for the protection, tolerance

and well being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. Any deviation from the protocol must be reported, explained, and documented in the CRF.

10.5 Protocol Amendment

Should amendments to the protocol be required, the amendment must be reviewed and approved by the Sponsor. The written amendment to the Study Protocol must be submitted to the chairperson of the IRB responsible for overseeing the conduct of this study. This amendment must be approved by the IRB prior to its implementation.

10.6 Data Collection

The research facility will maintain detailed records on all study subjects. Data for this study will be recorded on Case Report Forms (CRFs). All data will be recorded completely, promptly, and legibly on the CRFs. Corrections will be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and all corrections on the CRF should be initialed and dated. The testing facility will maintain a copy of all completed CRFs in its study files.

10.7 Test Device Accountability

The principal investigator or his designee, upon receipt of the CO2 fractional handpiece module, will conduct an inventory and complete and sign the Receipt of Clinical Supplies form (Supplied by the Sponsor), mailing it to the Sponsor. A copy will be maintained for the investigator's records.

The clinical staff will keep a current record of the date and time of the use of the module. Additionally, the clinical staff will confirm on the subject's data sheet (or CRF) the date and time of the module use. These records will be made available to the Sponsor's monitor for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency will be recorded, with an explanation. After all subjects have completed the study, the testing facility will return the CO2 fractional handpiece to the Sponsor with a copy module use log.

10.8 Study Monitoring

The study may be monitored at any time. The monitor from the Sponsor will maintain a close liaison with the research facility to clarify any problem(s) that may arise in the study and to ensure that the study is conducted according to the protocol. The liaison ordinarily consists of personal visits and/or frequent communications via telephone, fax and/or email.

The investigator will allow a Sponsor monitor to inspect all Case Report Forms and corresponding portions of a study subject's records, if necessary, to verify that the study was performed according to this protocol and that test results and collected data were faithfully and accurately recorded.

10.9 Information Reporting Responsibilities of Investigator

The Investigator will be responsible for producing a summary of the study that will detail the conduct of the study, protocol deviations, and occurrence of adverse events and any ancillary reports or statistical data generated by the Investigator's team.

10.10 Confidentiality

Subjects will be identified on the study CRFs by their Subject Number and their initials. CRFs are confidential documents and will only be available to the Investigator, the sponsor's

representative, and the IRB. Individual subject's medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited according to federal HIPAA regulations.

10.11 Record Retention

All records relating to the conduct of this study will be held by the investigator for a period of no less than six (6) years in a secure area. Additionally, the Sponsor will be contacted prior to the destruction of any study related records. Should the Sponsor require archiving for longer than 6 years, prior agreement between the Site and the Sponsor must be obtained.