CLINICAL TRIAL PROTOCOL NUMBER: APX-21-02

A PILOT STUDY OF THE RENUVION APR SYSTEM WHEN USED AS AN ADJUNCT PROCEDURE IN GYNECOMASTIA SURGERY

SPONSOR: APYX MEDICAL

FUNDED BY: APYX MEDICAL

DATE: JULY 21,2021

DRAFT OR VERSION: 1.0

CONFIDENTIAL – PROPRIETARY INFORMATION

SPONSOR STATEMENT AND SIGNATURE PAGE

Company Name:	Apyx Medical
Address:	5115 Ulmerton Rd. Clearwater, FL 33760
Telephone:	800.537.2790
Study Device:	Apyx Plasma RF
Protocol Title:	A Pilot Study of the Renuvion APR System when Used as an Adjunct Procedure In Gynecomastia Surgery
Protocol Number:	APX-21-02
Draft Revision / Date:	v.0.1 June 24, 2021
Final Protocol Version / Date:	v.1.0 July 21, 2021

The investigation will be conducted in compliance with the clinical investigation plan (CIP), GCP, EN ISO 14155, the Declaration of Helsinki, and regulatory authority requirements.

Apyx Medical (hereinafter "Study Sponsor") maintains responsibility for the ongoing safety of this clinical trial involving the evaluation of the Renuvion system. Study Sponsor will promptly notify all investigators, the responsible IRB(s), and the regulatory authorities of any findings from ongoing trial monitoring activities that could adversely affect the safety of subjects, impact the conduct of the clinical study, or alter the IRB's approval to continue the study, specifically within 5 working days of making an Unanticipated Adverse Device Effect (UADE) determination or 15 working days after first receiving notice of the UADE, within 10 days for Serious Adverse Event reports, and at least annually for routine reports. In the event that participant safety could be directly affected by study results after the study has ended, Study Sponsor will notify all investigators of these results to enable investigators to consider informing participants as soon as possible or at least within one year of study closure.
The following individuals are responsible for the content of the CIP:

_____ _____

Samantha Hannon
Sr. Manager, Clinical Affairs Date

_____ _____

Kari Larson, MBA Date
Sr. Director, Clinical Affairs

_____ _____

Shawn Roman Date
Vice-President, R&D

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Kim Hanson, BSN, RNFA Date
Director, Clinical Operations & Medical Affairs

_____ _____

Topaz Kirlew Date
Vice-President, Quality Assurance & Regulatory Affairs

STATEMENT OF COMPLIANCE

I have thoroughly read and reviewed this clinical investigation plan (CIP) and hereby agree to participate in this clinical trial sponsored by Study Sponsor. I agree to conduct this investigation according to the requirements of the CIP provided by the Study Sponsor and in accordance with Good Clinical Practice (GCP) as required by EN ISO 14155, the Declaration of Helsinki, Investigational Device Exemption (21 CFR Part 812), Protection of Human Subjects (45 CFR Part 46), and other applicable FDA regulations, and regulations of other relevant regulatory authorities and conditions imposed by the reviewing Institutional Review Board (IRB) or Ethics Committee (EC). I agree that no deviation from, or changes to the CIP will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. I agree to ensure that appropriate informed consent is obtained from all subjects prior to inclusion in this study. I also agree to supervise all testing of the device involving human subjects, and to report to the Study Sponsor, within 24 hours, any adverse event that is serious, whether considered treatment-related or not. I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee employed by the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor.

All study data will be entered within 3 days after the study visit.

I am also aware that I may be inspected by a representative of the relevant regulatory authorities, including the United States Food and Drug Administration, to verify compliance with applicable regulations related to clinical research on human subjects.

My current curriculum vitae in this study will be provided to the Study Sponsor. The curriculum vitae will include the extent and type of our relevant experience with pertinent dates and locations. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I certify that I have not been involved in an investigation that was terminated for non-compliance at the insistence of the Study Sponsor, the IRB or EC, or other regulatory authorities. I agree to provide the Study Sponsor sufficient, accurate financial disclosure information. I also agree to update financial disclosure information if any relevant changes occur during the investigation and for one year following the completion of the study.

I understand that this CIP and the trial results are confidential, and I agree not to disclose any such information to any person other than a representative of the Study Sponsor or the relevant competent authorities without the prior written consent of the Study Sponsor.

Accepted by:

Principal Investigator Signature	Principal Investigator Name	Date

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
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
NRS	Numeric Rating Scale
NSAID	Non-steroidal Anti-Inflammatory Drug
PP	Per Protocol
PPS	Per Protocol Set
RF	Radiofrequency
SAE	Serious Adverse Event
SAL	Suction-Assisted Liposuction
UADE	Unanticipated Adverse Device Effect

PROTOCOL SYNOPSIS

Protocol Title:	A Pilot Study of the Renuvion APR System when Used as an Adjunct Procedure in Gynecomastia Surgery
Investigational Device:	The Renuvion APR Handpiece (K191542) is a sterile, single use electrosurgical (monopolar) device intended to be used in conjunction with compatible generators for the percutaneous delivery of radiofrequency energy and/or helium plasma for cutting, coagulation and ablation of soft tissue. The Renuvion APR Handpiece is compatible with the Electrosurgical Generators BVX-200H/P (K170188), and APYX-JS3/RS3 (K192867) owned by Apyx Medical that are indicated for delivery of radiofrequency energy and/or helium gas plasma to cut, coagulate, and ablate soft tissue during open and laparoscopic surgical procedures.
Development Phase:	Pilot
Study Purpose:	To evaluate the use and safety of the Renuvion APR System as an adjunct procedure to bilateral gynecomastia surgery.
Brief Study Overview:	This is a prospective, multi-center, single-blinded, randomized study of up to 10 study subjects undergoing bilateral gynecomastia surgery with Renuvion APR System used as an adjunct procedure on one side. The study will be conducted at up to 3 investigational centers in the United States. At baseline, the grade of gynecomastia will be recorded by side, male chest measurements will be taken, and pre-surgery photographs taken in the frontal, lateral, and oblique views. The gynecomastia surgery and Renuvion APR System use will be as per investigator's standard clinical practice. During the procedure, fat transfer and treatment of the lateral chest and/or axilla is not allowed. The Renuvion APR System will be used on one side only. The treated side will be randomized and the patient will be blinded as to which side of the chest received Renuvion. Procedure data and adverse events will be captured. Endermology is not allowed post-procedure. Post-procedure compression will be used for 2-3 weeks with a standard compression vest for all subjects. Follow-up images, grade of gynecomastia, and male chest measurements will be taken at D30/D90/D180. All images will be assessed for correct identification of Renuvion-treated side by blinded Independent Photographic Reviewers (IPR) following the D180 visit. Following study participation, the subject will be offered an optional balancing treatment to the side not previously treated with Renuvion.
Number of Sites Enrolling Participants:	Subjects will be recruited from up to 3 study sites in the US.
Sample Size:	N = Up to 10 treated subjects; subjects enrolled may be greater than subjects treated.
Subject Population:	Healthy, male adult subjects, ages 18 – 75 years old who meet the inclusion/exclusion criteria.
Inclusion Criteria:	1. Male subjects, ages 18 – 75 years old. 2. ASA Physical Status Classification System Class I and Class II subjects. 3. Clinical diagnosis of primary or secondary Gynecomastia.

	4. Gynecomastia Rohrich Grade IIA or higher. 5. Symmetrical gynecomastia Rohrich grades. 6. Symmetrical chest measurements (no more than 3% variance between sides). 7. Scheduled for Gynecomastia surgery. 8. Willing to have Renuvion APR System as an adjunct procedure on one side understanding that an optional balancing procedure may be provided post-study exit. 9. Understands and accepts the obligation not to undergo any other procedures or treatments in the areas to be treated during study participation. 10. Absence of physical conditions unacceptable to the investigator. 11. Willing and able to comply with protocol requirements, including study-required images/photos, assessments/measurements, and returning for follow-up visits. 12. Willing to release rights for the use of study photos, including in publication. 13. Able to read, understand, sign, and date the informed consent.
Exclusion Criteria:	1. Subjects without clinical diagnosis of primary Gynecomastia and/or a clinical diagnosis of gynecomastia with secondary causes such as medications, drugs, or testicular tumors. 2. Subjects presenting with ASA Physical Status Classification System Classes III or higher. 3. Gynecomastia Rohrich Grade I. 4. Non-symmetrical gynecomastia Rohrich grades. 5. Non-symmetrical chest measurements (more than 3% variance between sides). 6. Previous treatment or surgery in the breast area. 7. Active systemic or local skin disease that may alter wound healing. 8. Significant or uncontrolled medical condition that in the opinion of the investigator participation in the study may compromise the patient's health. 9. History of autoimmune disease (excluding Hashimoto's thyroiditis). 10. Known susceptibility to keloid formation or hypertrophic scarring. 11. Cancerous or pre-cancerous lesions in the area to be treated. 12. Possesses a surgically implanted electronic device (i.e. pacemaker). 13. Serious mental health illness such as dementia or schizophrenia; psychiatric hospitalization in the past two years. 14. Use of endermology post-procedure for the duration of the study. 15. Participation in any other investigational study within 30 days prior to consent and throughout study participation. 16. Subject who, in the opinion of the investigator, is not an appropriate candidate for the study.
Primary Safety Endpoint:	Analysis of bilateral occurrence of adverse events (both sides).
Outcome Measures:	1. Bilateral analysis of change to STPTUP (Tebbetts & Adams High 5 Measurements) from baseline to day 30, 90, and 180. 2. Bilateral analysis of change to STPTIMF (Tebbetts & Adams High 5 Measurements) from baseline to day 30, 90, and 180. 3. Bilateral analysis of male chest measurements (Murphy) from baseline to day 30, 90, and 180. 4. Bilateral analysis of skin excised during the procedure by Gynecomastia Grade (Rohrich Classification).

	5. Bilateral analysis of gland tissue removal methods (Longheu) during the procedure by Gynecomastia Grade. 6. The Principal Investigator, sub-investigator or qualified clinician delegated by the principal investigator, will complete a bilateral PGAIS assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment. 7. The subject will complete a bilateral SGAIS assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment. 8. The subject will complete a bilateral Patient Satisfaction Questionnaire (PSQ) at the 180-day follow-up visit. 9. Baseline images compared to Day 30, 90, and 180 images will be assessed for correct identification of Renuvion-treated side by blinded Independent Photographic Reviewers.
Safety Variables:	1. Prior to treatment, the subject's medical history will be reviewed, and a physical examination will be conducted. 2. Following study treatment and at each subsequent visit, the subject will be queried about adverse events, expected treatment effects, and changes in concomitant medications, and the treatment area will be visually examined.
Study Duration:	The duration from when the study opens to enrollment until completion of data analyses is anticipated to be 12 months.

TABLE OF CONTENTS

1. KEY ROLES

Persons, companies, and/or groups serving in key roles in the conduct or oversight of this clinical trial are listed in **Table 1** below, including sponsor, clinical project manager for the trial, investigator responsible for conducting the trial.

1.1 INTERNAL RESPONSIBILITIES

TABLE 1 INTERNAL RESPONSIBILITIES

Name	Function	Address
Apyx Medical	Sponsor	5115 Ulmerton Road Clearwater, FL
Shawn Roman	Research & Development	Phone: (904) 382-4857 Email: shawn.roman@apyxmedical.com
Kari Larson	Clinical Affairs	Phone: (801) 244-0058 Email: Kari.Larson@apyxmedical.com
Samantha Hannon	Clinical Affairs	Phone: (386) 748-4891 Email: sam.hannon@apyxmedical.com
Topaz Kirlew	Regulatory Affairs	Phone: (727) 803-8617 Email: topaz.kirlew@apyxmedical.com
Kim Hanson	Medical Affairs	Phone: (720)480-6584 Email: kim.hanson@apyxmedical.com

2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION & RATIONALE

Energy has been applied in some form to tissue since the beginning of recorded history. The practice of applying heat to tissue through the use of cauteries was used for thousands of years as an invaluable method of controlling hemorrhage. Continuous improvement of methods for utilizing the beneficial effects of heat on tissue eventually led to the development of the basic concepts of electrosurgery we know today. In October of 1926, Dr. Harvey Cushing used an electrosurgical unit developed by Dr. William T. Bovie to successfully remove a highly vascularized brain tumor from a patient after previous failed attempts. Today, electrosurgical instruments are used in almost every surgical procedure performed worldwide.[1]

Through this long history, the heat effects of the radiofrequency (RF) alternating current used in electrosurgery on cells and tissue have been well established. Normal body temperature is 37°C and, with normal illness, can increase to 40°C without permanent impact or damage to the cells of our body. However, when the temperature of cells in tissue reaches 50°C, cell death occurs in approximately 6 minutes.[2] When the temperature of cells in tissue reaches 60°C, cell death occurs instantaneously.[3] Between the temperatures of 60°C and just below 100°C, two simultaneous processes occur.[1] The first is protein denaturation leading to coagulation which will be discussed in more detail below. The second is desiccation or dehydration as the cells lose water through the thermally damaged cellular wall. As temperatures rise above 100°C, intracellular water turns to steam and tissue cells begin to vaporize as a result of the massive intracellular expansion that occurs. Finally, at temperatures of 200°C or more, organic molecules are broken down into a process called carbonization. This leaves behind carbon molecules that give a black and/or brown appearance to the tissue.

Understanding these heat effects of RF energy on cells and tissue can allow the predictable changes to be used to accomplish beneficial therapeutic results. Protein denaturation leading to soft tissue coagulation is one of the most versatile and widely utilized tissue effects. Protein denaturation is the process in which hydrothermal bonds (crosslinks) between protein molecules, such as collagen, are instantaneously broken and then quickly reformed as tissue cools. This process leads to the formation of uniform clumps of protein typically called coagulum through a subsequent process known as coagulation. In the process of coagulation, cellular proteins are altered but not destroyed and form protein bonds that create homogenous, gelatinous structures. The resulting tissue effect of coagulation is extremely useful and most commonly used for occluding blood vessels and causing hemostasis.

In addition to causing hemostasis, coagulation results in predictable contraction of soft tissue. Collagen is one of the main proteins found in human skin and connective tissue. The coagulation/denaturation temperature of collagen is conventionally stated to be 66.8°C, although this can vary for different tissue types.[4] Once denatured, collagen rapidly contracts as fibers shrink to one-third of their overall length.[5] This principal of thermally-induced contraction of collagen through denaturation and coagulation of soft tissue is well known in medicine and is used to achieve beneficial results in ophthalmology, orthopedic applications, and the treatment of varicose veins. Once tissue is heated to the appropriate temperature, protein denaturation and collagen contraction occur resulting in a reduction of volume and surface area of the heated tissue. Noninvasive use of RF devices, lasers, and plasma devices have been used for the reduction of facial wrinkles and rhytides caused by thermal-induced collagen/tissue contraction since the mid-1990s.[6-11]

Recently, the use of thermal-induced collagen/tissue contraction has been expanded to minimally invasive procedures. Laser-assisted lipolysis (LAL) and radiofrequency-assisted lipolysis (RFAL) devices have combined the removal of subcutaneous fat with soft tissue heating to address the skin laxity that often results from fat volume

removal. These devices are placed in the same subcutaneous tissue plane as a standard suction-assisted lipolysis (SAL) cannula and are used to deliver thermal energy to coagulate the subcutaneous tissue including the underside of the dermis, the fascia, and the septal connective tissue. The coagulation of the subcutaneous tissue results in collagen/tissue contraction.

Apyx Medical Corporation's product family of helium-based plasma technology (Renuvion/J-Plasma family of devices) has FDA clearance for the cutting, coagulation, and ablation of soft tissue. The Renuvion APR Handpiece is a new device designed to be a part of this helium-based plasma technology family. All devices in the product family are part of a system that consists of an electrosurgical generator unit, a handpiece, and a supply of helium gas. RF energy is delivered to the handpiece by the generator and used to energize an electrode. When helium gas is passed over the energized electrode, a helium plasma is generated which allows heat to be applied to tissue in two different and distinct ways. First, heat is generated by the actual production of the plasma beam itself through the ionization and rapid neutralization of the helium atoms. Second, since plasmas are very good electrical conductors, a portion of the RF energy used to energize the electrode and generate the plasma passes from the electrode to the patient and heats tissue by passing current through the resistance of the tissue, a process known as Joule heating. These two sources of tissue heating give the Renuvion APR device some advantages during use as a surgical tool for the coagulation and contraction of subcutaneous soft tissue.

These advantages are as follows:

1. The Renuvion APR Handpiece device achieves soft tissue coagulation and contraction by rapidly heating the treatment site to temperatures greater than 85°C for between 0.040 and 0.080 seconds.
2. The tissue surrounding the treatment site remains at much cooler temperatures resulting in rapid cooling after the application of the energy through conductive heat transfer.
3. Focused delivery of energy on immediate heating of the fibroseptal network resulting in immediate soft tissue coagulation and contraction without unnecessarily heating the full thickness of the dermis.
4. 360° tissue treatment without the need for the user to redirect the flow of energy due to electrical energy taking the path of least resistance.
5. Unencumbered delivery of power regardless of the tissue impedance due to the unique power output from the electrosurgical generator.
6. Low current RF energy resulting in minimal depth of thermal effect and prevention of over-treating tissue when performing multiple passes.

Gynecomastia is a benign enlargement of the male breast due to proliferation of the glandular tissue. It affects up to 65% of males at all stages of life, however, not all require surgical intervention.[17] Typically, gynecomastia presents as asymmetric and mostly bilateral. Treatment options are varied, but liposuction, either alone or in conjunction with removal of the glandular tissue, is most commonly utilized.[18] This study aims to evaluate the use and safety of the Renuvion APR System as an adjunct procedure to bilateral gynecomastia surgery.

2.1.1 Device Name and Indications for Use

The Renuvion APR Handpiece is a sterile, single use electrosurgical (monopolar) device intended to be used in conjunction with compatible generators for the percutaneous delivery of radiofrequency energy and/or helium plasma for cutting, coagulation and ablation of soft tissue. The compatible Generators operate at an adjustable power of up to 40W (expressed as 0-100% where 100% is 40W) and provide an adjustable helium gas flow of 1-5 LPM.

Radiofrequency energy is delivered to the handpiece by the generator and used to energize the electrode. When helium gas is passed over the energized electrode, a helium plasma is generated for soft tissue cutting, coagulation

or ablation. The Renuvion APR system consists of a handpiece (Figure 1), an electrosurgical unit (ESU, Figure 2), and a supply of helium gas (Figure 2). RF energy is delivered to the handpiece by the ESU and used to energize an electrode. When helium gas is passed over the energized electrode, a helium plasma is generated which allows for conduction of the RF energy from the electrode to the subject in the form of a precise helium plasma beam.

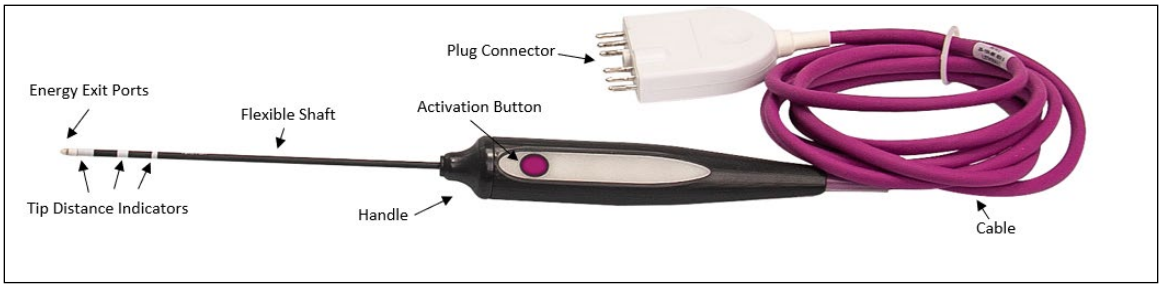

FIGURE 1: RENUVION APR HANDPIECE

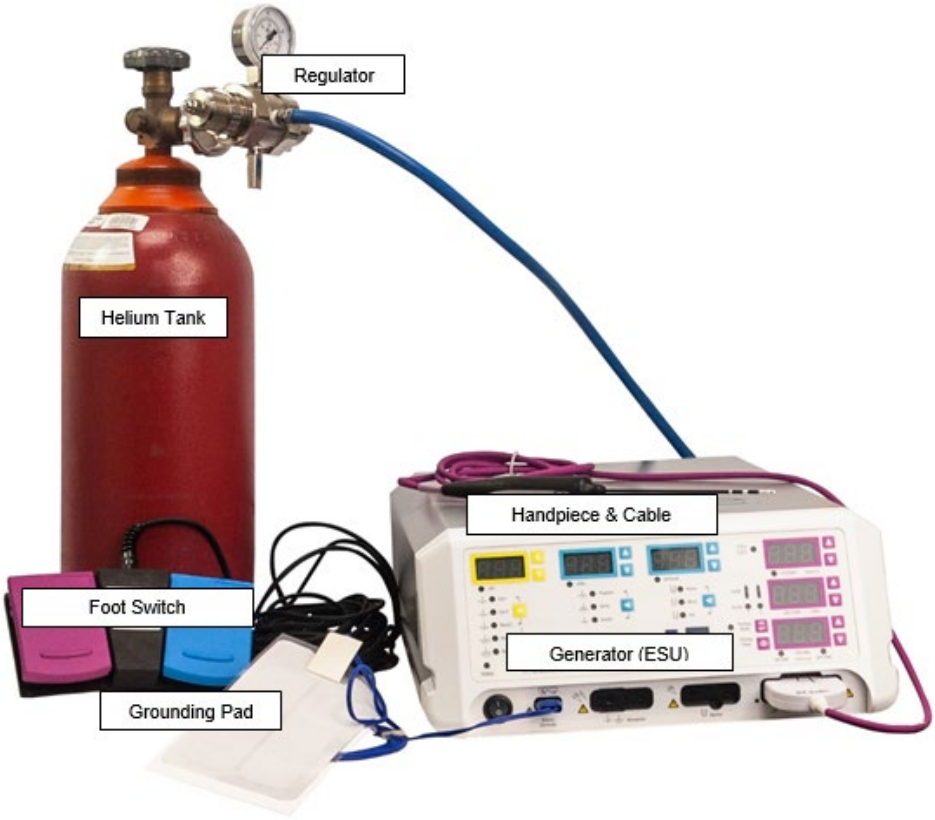

FIGURE 2: ELECTROSURGICAL UNIT AND HELIUM TANK

The Apyx Medical Corporation Renuvion/J-Plasma helium plasma family of products has received FDA clearance under 510(k) numbers K090586, K112233, K142975, K151325, K152570, K170188, K170777, K183610, K191484, K191542, K192867, K202880 for the cutting, coagulation, and ablation of soft tissue.

2.1.2 PRECLINICAL STUDIES

Pre-Clinical Studies to Support Safe Tissue Temperatures during Device Use

During the use of the Renuvion system in open surgical procedures involving subdermal tissue coagulation, the tip of the Renuvion handpiece is placed in the subcutaneous tissue plane through the same access ports used during suction assisted lipolysis procedures (liposuction). In this use, it is important to establish that both the external epidermal tissue temperatures and the internal subdermal tissue temperatures remain within safe limits. The following pre-clinical studies were conducted to measure these temperatures on both live porcine skin tissue and ex vivo human skin tissue:

1. **RP-18032301: Evaluation of Porcine Skin Tissue Epidermal Temperature During Subdermal J-Plasma (Renuvion) Application (Non-GLP)**
   This was a pre-clinical study in which the Renuvion system was used to coagulate the subdermal tissue of porcine skin at various treatment parameters in order to measure the maximum temperature on the surface of the epidermis. In this study, the maximum recorded epidermal surface temperatures were 39.1°C and 40.2°C. These temperatures were recorded after performing six consecutive passes of the Renuvion system under the same area of tissue. Six consecutive passes under the same tissue was included in the study to represent a "worst case" scenario. Six passes are not commonly performed clinically. However, even in this "worst case" scenario the epidermal surface temperature remained within safe limits. Pedroso, et.al, reported that because of superficial thermal safety concerns, the skin surface temperature should be maintained below 45°C. This study was subsequently published[1]. The summary of the published study is as follows:
   J-Plasma helium was used in porcine, liver, kidney and muscle tissue at 20%, 50% and 100% power and 1 L/min and 3 L/min gas flow at 1, 5, and 10 second intervals. J-Plasma was then used in ovarian and uterine tissue at maximum power and gas flow settings in intervals of 1, 5, 10 and 30 seconds. Concluded that J-Plasma has predictable thermal spread in a variety of tissue types. Thermal depth of spread increased linearly with increased power setting, gas flow rate, and exposure time. Even at settings that greatly exceeded the manufacturer's recommendation, the depth of thermal spread associated with the J-Plasma device was less than 3 mm (regardless of the type of tissue) and the diameter of lateral spread was 12 mm or less.

2. **RP-18040201: A Study Evaluating Tissue Contraction, External Tissue Temperature, and Internal Tissue Temperature When Using J-Plasma (Renuvion) on Ex Vivo Abdominoplasty Tissue (non-GLP)**
   This was a pre-clinical study that was performed on ex vivo human tissue collected by a surgeon during previously conducted abdominoplasty procedures. The Renuvion system was used to coagulate the subdermal tissue of the human skin samples at various treatment parameters. During treatment, both the maximum external epidermal tissue temperatures and the maximum internal subdermal tissue temperatures were measured and recorded. The maximum external tissue temperatures ranged from 24.9°C to 37.8°C. This data serves to validate the maximum external tissue temperatures of 39.1°C and 40.2°C reported in RP-18032301 measured in a live porcine model. The maximum internal tissue temperatures ranged from 40°C to 80°C. It is known from the literature that the reported range of temperatures causing collagen shrinkage varies from 60°C to 80°C. Therefore, in order to cause soft tissue coagulation and collagen contraction, the target internal tissue temperature should be within this range. Both the external and internal temperatures remained within safe limits when using the Renuvion system to coagulate the subdermal tissue of human skin samples.

   The results of the above summarized pre-clinical testing support the safe and effective use of the Renuvion® system in dermatological and general surgical procedures involving subdermal tissue coagulation.

2.2 Potential Risks and Benefits

2.2.1 Potential Risks

This treatment modality was designed to inherently minimize the risk to the subject. However, treatment with energy-based modalities (laser, radiofrequency, and plasma devices) produce subsequent heating of the soft tissue that could involve the following commonly Expected Treatment Effects (ETEs): discomfort/pain, edema, erythema, ecchymosis, hypoesthesia, temporary sensory nerve injury (touch sensitivity, itching, temporary numbness/tingling), transient migratory firmness, and temporary and/or transient crepitus.

In addition to commonly expected treatment effects, treatment with the Renuvion APR device could involve the following risks: helium embolism into the surgical site due to inadvertent introduction into the venous or arterial blood supply system, unintended burns (deep or superficial), pneumothorax, pneumomediastinum, temporary or permanent motor nerve injury, ischemia, fibrosis, infection, gas buildup, bleeding, hematoma, seroma, subcutaneous induration, pigmentation changes, increased healing time, unsatisfactory scarring, asymmetry and/or unacceptable cosmetic result.

Risks associated with tumescent anesthesia (lidocaine and epinephrine) include blurred vision, mental/mood changes, drowsiness, dizziness, unusually slow heartbeat, rash, itching, swelling, anxiety, apprehensiveness, restlessness, tremor, weakness, sweating, palpitations, pallor, nausea and vomiting, headache, and respiratory difficulties.

Subjects using drugs that reduce coagulation (aspirin or NSAIDs) may experience increased bruising or bleeding at the treatment site. Any other medications prescribed for the procedure or after-procedure by the investigator have their own risks; these risks should be discussed with the subject.

A grounding pad is used to ground/neutralize the electrical current. Subjects undergoing radiofrequency treatment will be kept away from contact with metal parts which are grounded, or which have appreciable capacitance to earth.

As the Investigator will be treating the subjects per their Standard Practice of Care, there may be additional risks associated with the gynecomastia procedure. The Investigator will be responsible for properly reviewing all potential risks with the patient prior to treatment.

Any unexpected or unforeseen complications will be managed by the investigator throughout the conduct of the study. Unforeseen or unexpected side effects not listed above will be reported to the sponsor and regulatory representatives (IRB) as they occur.

2.2.1.1 Minimization of Potential Risks

These risks are mitigated by utilizing qualified clinical Investigators who have training and are experienced in gynecomastia procedures and Renuvion procedures. In addition, risks are mitigated by including only those subjects that meet the study eligibility criteria.

2.2.2 Potential Benefits

This study is being conducted to determine if there is a possible benefit of using the Renuvion APR device as an adjunct procedure to Gynecomastia surgery.

3. STUDY PURPOSE

The purpose of this pilot study is to assess the safety and effectiveness of the Renuvion APR device, when used as an adjunct procedure in gynecomastia surgery. This study may provide data to support a future pivotal study.

4. STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This study is a prospective, multi-center, single-blinded, randomized pilot clinical trial to be conducted at up to 3 clinical site(s). Up to 10 subjects will be enrolled and treated if they meet the inclusion/exclusion criteria and provide written informed consent. A higher number of subjects than 10 may be enrolled due to screen failures or withdrawal of consent.

Subjects meeting all entrance criteria and confirmed eligible will be enrolled. The gynecomastia surgery and Renuvion APR System will be used as per the Investigator's standard clinical practice. During the procedure, fat transfer and treatment of the lateral chest and/or axilla is not allowed. Subjects will only be treated on one size utilizing the Renuvion APR System. Images will be taken prior to treatment and during each follow-up visit. These images will be assessed for correct identification of the Renuvion-treated side by blinded Independent Photographic Reviewers (IPRs) following the D180 visit. Baseline assessments and pre-treatment images should be obtained within the 30 days prior to study treatment. Endermology is not allowed post-procedure. Post-procedure compression will be used for 2-3 weeks with a standard compression vest for all subjects.

Following study participation, the subject will be offered an optional balancing treatment to the side not previously treated with Renuvion.

4.2 DURATION OF STUDY

Recruitment for this study is estimated to take 6 months. Following the treatment visit, subjects will be followed for a total duration of 180-days. Therefore, the anticipated total duration of the study is approximately 12 months.

4.3 STUDY ENDPOINTS

4.3.1 PRIMARY SAFETY ENDPOINT

The primary safety endpoint is the bilateral occurrence of adverse events.

4.3.2 ADDITIONAL ENDPOINTS

Other additional endpoints for this study are as follows:

1. Bilateral analysis of change to STPTUP (Tebbetts & Adams High 5 Measurements)[19] from baseline to day 30, 90, and 180.
2. Bilateral analysis of change to STPTIMF (Tebbetts & Adams High 5 Measurements)[19] from baseline to day 30, 90, and 180.
3. Bilateral analysis of male chest measurements (Murphy)[20] from baseline to day 30, 90, and 180.
4. Bilateral analysis of skin excised during the procedure by Gynecomastia Grade (Rohrich Classification)[21].
5. Bilateral analysis of gland tissue removal methods (Longheu)[22] during the procedure by Gynecomastia Grade.
6. The Principal Investigator, sub-investigator or qualified clinician delegated by the principal investigator, will complete a bilateral PGAIS assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment.
7. The subject will complete a bilateral SGAIS assessing overall aesthetic improvement in the treatment area at day 30, 90, and 180 post-treatment.
8. The subject will complete a bilateral Patient Satisfaction Questionnaire (PSQ) at the 180-day follow-up visit.

9. Baseline images compared to Day 30, 90, and 180 images will be assessed for correct identification of Renuvion-treated side by blinded IPRs.

4.3.3 Evaluation Tools

The following evaluation tools will be used in this study:

4.3.3.1 Soft Tissue Pinch Thickness of the Upper Pole (STPTUP)

The STPTUP is a measure of the soft-tissue pinch thickness of the upper pole, by isolating skin and subcutaneous tissue superior to the breast parenchyma, pinching firmly, and measuring the thickness with a caliper[19]. See **Figure 3**.

This will be performed at Baseline, Day 30, 90, and 180.

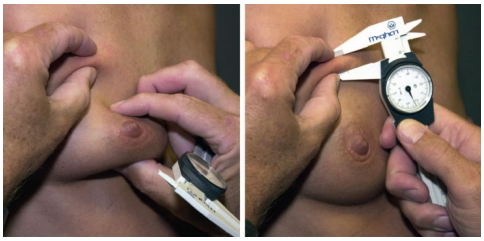

FIGURE 3: STPTUP

4.3.3.2 Soft Tissue Pinch Thickness at the Inframammary Fold (STPTIMF)

The STPTIMF measures soft-tissue pinch thickness at the inframammary fold by isolating skin and subcutaneous tissue at the inframammary fold, pinching firmly, and measuring the thickness with a caliper[19]. See **Figure 4**.

This will be performed at Baseline, Day 30, 90, and 180.

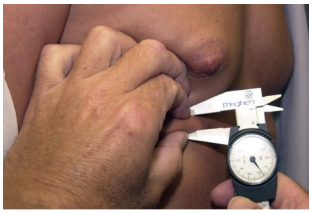

FIGURE 4: STPTIMF

4.3.3.3 Bilateral Male Chest Measurements (Murphy)[20]

Measurements of the male chest will be taken for each patient prior to procedure and at days 30, 90 and 180 as indicated in **Table 2**.

TABLE 2: CHEST MEASUREMENTS (MURPHY)

Measurement	Description
A	Suprasternal notch to nipple
B	Internipple distance
C	Suprasternal notch to nipple plane
D	Midclavicular point to nipple
E	Nipple plane to umbilicus
F	Umbilicus to pubic symphysis
G	Coracoid process to nipple plane
H	Nipple plane to medial epicondyle
I	Coracoid process to medial epicondyle

4.3.3.4 Gynecomastia Grade (Rohrich Classification)[21]

This classification of gynecomastia is based on the amount and character of breast hypertrophy and degree of ptosis. This will be performed at Baseline and all follow-up visits. See **Table 3**.

TABLE 3: ROHRICH CLASSIFICATION

Classification	Description
Grade I I A: Primarily glandular* I B: Primarily fibrous*	Minimal hypertrophy (<250g of breast tissue) without ptosis
Grade II I A: Primarily glandular* I B: Primarily fibrous*	Moderate hypertrophy (250-500g of breast tissue) without ptosis
Grade III Glandular or fibrous*	Severe hypertrophy (>500g of breast tissue) with grade I ptosis
Grade IV Glandular or fibrous*	Severe hypertrophy with grade I or III ptosis

*Fatty and glandular tissue is determined by a pinch test medially, laterally, and beneath the nipple-areola complex

4.3.3.5 Modified Global Aesthetic Improvement Scale (GAIS) (Additional Endpoint)

The Modified Global Aesthetic Improvement Scale (GAIS) is a subjective rating of improvement in treatment results compared to pre-treatment. The Investigator will grade the overall improvement of the treatment area as indicated in **Table 4** 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 5**.

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

TABLE 4: MODIFIED GLOBAL AESTHETIC IMPROVEMENT SCALE EVALUATION - 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 5: MODIFIED GLOBAL AESTHETIC IMPROVEMENT SCALE EVALUATION - SUBJECT

Rating	
Very much improved	☐
Much improved	☐
Improved	☐
No change	☐
Worse	☐
Much worse	☐
Very much worse	☐

The Global Aesthetic Improvement Scale (GAIS) is a 5-point scale that rates global aesthetic improvement from the pretreatment appearance. The ratings are worse, no change, improved, much improved, and very much improved. It was validated by Dr. Carutthers, et al. for this use. In this study both live observation and photo review are utilized by the physician or a qualified, delegated clinician and subject in order to assign a score. The PGAIS must be performed by the principal investigator, sub-investigator or qualified clinician delegated by the principal investigator. Both the PGAIS and SGAIS should be completed in two steps:

- Based on a live assessment of the subject while referring to the subject's pre-treatment photographs (subjects should be given a hand mirror for assessment); and
- Based on a comparison of the subject's pre-treatment photographs to the current post-treatment photographs.

4.3.3.6 Patient Satisfaction Questionnaire (PSQ)

The study subjects will be asked to complete Subject Satisfaction Surveys (see **Attachment A**) at the 180-day follow-up visit.

4.3.3.7 Independent Photographic Review

Three experienced, blinded photographic reviewers will perform a qualitative analysis/review of pre-treatment and post-treatment sets of images for each subject. Images will be provided in a blinded and randomized order. Each blinded reviewer will choose which side of the chest was treated with Renuvion. Success will be correct identification of treated side of the chest by at least 2 of the 3 reviewers.

4.3.3.8 Adverse Event Reporting

The definitions of Adverse Events (AEs) and the subtypes are provided in **Section 8** of this study protocol. Adverse events will be classified by the investigator as to:

- Anticipated vs unanticipated
- Serious vs not serious
- Expected Treatment Effect (ETE) vs Adverse Event (AE)
- Severity: mild, moderate, severe
- Device causality: not related, related, undetermined
- Procedure causality: not related, related, undetermined.

5. SUBJECT ENROLLMENT AND WITHDRAWAL

5.1 Study Population

The study population will consist of males between 18-75 years of age who have chosen to participate in this clinical trial as evidenced by execution of the informed consent document and who meet eligibility criteria defined in this protocol. Subjects will be considered enrolled into the study when they have signed an approved informed consent form. Subjects who are enrolled and do not meet eligibility criteria will be exited as a screen fail without study treatment.

5.1.1 Informed Consent

Informed consent will be obtained from all subjects prior to study participation. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to each participant.

Investigators have ethical and legal responsibilities to ensure that the protocol is clearly explained to each subject considered for enrollment in the study. Compliance with this requirement should be documented on a written Informed Consent Form approved by the reviewing IRB. Each Informed Consent Form will include the elements required by FDA regulations in 21 CFR Part 50.

Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator, or investigator-delegated study personnel, will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The IRB-approved Informed Consent Form will be signed by the study personnel obtaining consent. A copy of the informed consent document will be given to the participants for their records. The investigative site will keep the

original on file. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The participants may withdraw consent at any time throughout the course of the trial without any penalty or loss of benefits to which the subject is otherwise entitled. An Investigator may also discontinue a subject from the study without the subject's consent, if the Investigator feels it is in the best medical interest of the subject.

5.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study device, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

5.1.2 Pre-treatment Recruiting/Screening

Subjects will be recruited from the study site's patient database and/or with the use of an IRB-approved form of advertising. Study site personnel will explain the design and purpose of the study to potential study subject. Subjects interested in participating and who qualify will visit the study site where informed consent will be obtained.

5.1.2.1 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (i.e., subject signs an Informed Consent Form), but who does not receive a study treatment because of failure to meet all the eligibility criteria. Screen failure subjects will be included in the total number of subjects enrolled (i.e., all subjects consented), but not counted towards the total subjects treated.

5.2 Inclusion Criteria

Subjects must meet all the following criteria for study enrollment:

- Male subjects, ages 18 – 75 years old.
- ASA Physical Status Classification System Class I and Class II subjects.
- Clinical diagnosis of primary Gynecomastia.
- Gynecomastia Rohrich Grade IIA or higher.
- Symmetrical gynecomastia Rohrich grades.
- Symmetrical chest measurements (no more than 3% variance between sides).
- Scheduled for Gynecomastia surgery.
- Willing to have Renuvion APR System as an adjunct procedure on one side understanding that an optional balancing procedure may be provided post-study exit.
- Understands and accepts the obligation not to undergo any other procedures or treatments in the areas to be treated during study participation.
- Absence of physical conditions unacceptable to the investigator.
- Willing and able to comply with protocol requirements, including study-required images/photos, assessments/measurements, and returning for follow-up visits.
- Willing to release rights for the use of study photos, including in publication.
- Able to read, understand, sign, and date the informed consent.

5.3 Exclusion Criteria

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

- Subjects without clinical diagnosis of primary Gynecomastia and/or a clinical diagnosis of gynecomastia with secondary causes such as medications, drugs, or testicular tumors.
- Subjects presenting with ASA Physical Status Classification System Classes III or higher.
- Gynecomastia Rohrich Grade I.
- Non-symmetrical gynecomastia Rohrich grades.

- Non-symmetrical chest measurements (more than 3% variance between sides).
- Previous treatment or surgery in the breast area.
- Active systemic or local skin disease that may alter wound healing.
- Significant or uncontrolled medical condition that in the opinion of the investigator participation in the study may compromise the patient's health.
- History of autoimmune disease (excluding Hashimoto's thyroiditis).
- Known susceptibility to keloid formation or hypertrophic scarring.
- Cancerous or pre-cancerous lesions in the area to be treated.
- Possesses a surgically implanted electronic device (i.e. pacemaker).
- Serious mental health illness such as dementia or schizophrenia; psychiatric hospitalization in the past two years.
- Use of endermology post-procedure for the duration of the study.
- Participation in any other investigational study within 30 days prior to consent and throughout study participation.
- Subject who, in the opinion of the investigator, is not an appropriate candidate for the study.

5.4 Strategies for Recruitment and Retention

Subjects will receive compensation for completion of the 30, 90, and 180-day visits. This small stipend will be outlined in the site specific ICF and approved by the IRB prior to subject enrollment.

5.5 Participant Withdrawal or Termination

5.5.1 Reasons for Withdrawal or Termination

All subjects have the right to withdraw at any point during the study without prejudice. The investigator can discontinue any subject, at any time, if medically necessary. Subjects must be discontinued from the investigation by the investigator at any time for any of the following reasons:

- Withdrawal of informed consent.
- Any AEs for which treatment continuation would constitute an unacceptably high risk for the subject.

5.5.2 Handling of Withdrawals or Termination

The subject must undergo the recommended follow-up assessments specified for the last study visit unless contraindicated due to a medical condition. Withdrawn subjects who have been treated will not be replaced.

Subjects who are discontinued from the study due to an AE(s) will be treated according to standard clinical practice and this protocol and will be followed-up until the final study visit/safety visit as described in **Section 7.3**. All pertinent information concerning the AE will be documented on the appropriate study specific CRF.

A subject may discontinue from the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled. An Investigator may also discontinue a subject from the study without the subject's consent, if the Investigator feels it is in the best medical interest of the subject. The date and the reason for study withdrawal will be indicated on the Study Exit CRF.

5.6 Premature Termination or Suspension of the Study or a Study Site

The study or a study site can be prematurely terminated or suspended by the sponsor. Reasons for termination of the study or a study site may include, but are not limited to, the following:

- Subject enrollment is unsatisfactory.

- The risks and benefits of continuing the study have been reassessed, and the risks outweigh any potential benefits.
- The incidence of AEs constitutes a potential health hazard to the subjects.
- New scientific data do not justify a continuation of the study.
- The investigator or study site exhibit serious and/or persistent non-adherence to the protocol, the Declaration of Helsinki, EN ISO 14155, and/or applicable regulatory requirements.
- The sponsor decides to terminate the study at any time for any other reason.

Furthermore, the study may be prematurely ended if the regulatory authority or the IRB has decided to terminate or suspend approval for the study, the study site, or the investigator.

If the study is prematurely terminated or suspended for any reason, the investigator must inform the subjects and assure appropriate follow-up treatment. Within the timeframes noted in applicable regulations, the sponsor will promptly inform the investigators, study sites, the IRB, and regulatory authorities of the termination or suspension of the study, as well as provide reasons for the action.

6. STUDY DEVICE

Cleared devices (K191542) shipped for use in clinical investigations conform to the applicable general safety and performance requirements (GSPR) apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution is taken to protect the health and safety of the subjects. This includes, where appropriate, technical, and biological safety testing and pre-clinical evaluation as well as provisions in the field of occupational safety and accident prevention and taking into consideration the state of the art. Apyx Medical will provide devices for use in this clinical investigation.

6.1 PACKAGING & STORAGE

The sponsor will provide appropriate packaging and storage instructions to the study sites.

6.2 ACCOUNTABILITY

The investigator, or designee, must maintain an inventory record using the site-specific Device Disposition Form of study devices received, used for treatment, and returned to the Sponsor to ensure that the device will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol. There will be 100% accountability for all devices. The clinical study site shall maintain all devices received for clinical trial use in a locked, limited access cabinet or room until the end of the study unless they are returned to Apyx while the study is being conducted, such as at the end of study treatments. Each site will use their existing generators for this study.

6.3 DEVICE MALFUNCTION/OBSERVATION

All malfunctions of, or defects of the delivery system will be reported to the Sponsor by the investigational sites. This will include situations where the delivery system did not perform as intended; user errors; study device/component being physically defective, including out of the box failure.

7. STUDY PROCEDURES AND SCHEDULE

7.1 PRE-PROCEDURE

Study subjects will have verification of eligibility criteria, a brief general examination including medical history, and pre-procedure assessments as detailed below completed within 30 days prior to undergoing the study procedure. In response to the ongoing coronavirus disease (COVID-19) pandemic, preoperative testing can be completed at the Investigator's discretion. Pre-operative testing should be performed as close to the scheduled study procedure as feasible, but in time to get the results.

The following pre-treatment assessments will be performed:

- Subject Gynecomastia Grade will be determined.
- Baseline imaging – frontal, lateral, and oblique views.
- Brief medical history and physical examination per the Investigator's standard of care.
- STPTUP (**Figure 3**).
- STPTIMF (**Figure 4**).
- Bilateral chest measurements (**Table 2)**

Medications that the subject is taking upon entry into the study should also be documented in the Case Report Forms (CRF). All concomitant prescription medications taken during study participation will be recorded on the appropriate study specific CRF. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported on the CRF and entered on the eCRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

Medication used for analgesia and/or anesthesia should be recorded as concomitant medication as well. To ensure the capture of the foregoing information on pre-existing conditions, sites should also be attentive to the need to document without limitation and whenever discovered: (1) all chronic, episodic or 'as needed' medications used before study enrollment; (2) prior episodic or 'as needed' therapeutic interventions, procedures, or hospitalizations; and (3) recent or planned surgical procedures.

7.2 Study Procedure

The bilateral gynecomastia surgery and Renuvion APR System use will be as per investigator's standard clinical practice. During the procedure, fat transfer and treatment of the lateral chest and/or axilla is not allowed. The Renuvion APR System will be used on one side only, and alternate consecutively between patients, starting on the right side. For example, subject 001 will be treated with Renuvion on the right side, subject 002, will be treated on the left, subject 003 will be treated on the right, etc. This treatment scheme will continue until enrollment has completed at each site. The subjects will be blinded as to which side has been treated with Renuvion.

Procedure data and adverse events will be captured.

Endermology is not allowed post-procedure for the duration of the study.

7.3 Follow-up Procedures

7.3.1 Immediately Post-Procedure

All subjects will be required to wear a Sponsor-provided compression vest for 2-3 weeks.

7.3.2 Follow-up Visits & Subject Contact outside of Follow-up Visits

Investigators will follow-up with the study subjects, per their Standard of Care (SOC), at the following time-points:

- 30 (±7) days,
- 90 (±10) days, and
- 180 (±15) days.

TABLE 3: STUDY REQUIRED PROCEDURES

	Baseline/ Pre-Procedure Screening[1]	**Procedure (Day 0)**	**30 Days** 23-37 days	**90 Days** 80-100 days	**180 Days** 165-195 days
Informed Consent	X				
Assess Inclusion/Exclusion Criteria	X				
Medical History	X				
General Physical Exam	X				
Review Medications	X		X	X	X
Patient Treatment Survey	X				
Imaging (front, lateral, and oblique)[3]	X		X	X	X
Gynecomastia Grade	X		X	X	X
STPTUP	X	X	X	X	X
STPTIMF	X	X	X	X	X
Chest Measurements	X	X	X	X	X
Study Procedure		X			
Adverse Event Assessment		X	X	X	X
Modified Global Aesthetic Improvement Scale (GAIS) [2]			X	X	X
Subject Satisfaction Survey					X

[1] Pre-procedure Screening assessments to take place within 30 days prior to undergoing the procedure.

[2] To be completed by Investigator and study subject at day 30, day 90 and day 180 follow-up visits.

[3] Images used for IPR Assessment.

7.4 SUBJECT RANDOMIZATION AND TREATMENT GROUP ASSIGNMENT

All subjects will be treatedper standard of care.). They will be blinded as to which side of the chest is receiving Renuvion.

7.5 Study Schedule

7.5.1 Screening

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify all preliminary/screening inclusion/exclusion criteria are met.

7.5.2 Baseline Assessment

- Obtain protocol-required baseline measures
- Document medical history.
- Perform baseline photography
- Document concurrent medications.
- Obtain height and weight.

7.5.3 Treatment Visit

- Greater than 30 days between baseline and treatment visits will require that the subject be re-screened to confirm enrollment eligibility.
- Perform study treatment.

7.5.4 Follow-up

Subjects will be asked to return to the clinic for in-person follow-up visits at 30, 90, and 180 days post-treatment. At all visits, subjects will be assessed for safety and efficacy, images will be taken, adverse events and protocol deviations will be assessed, and study outcome measures (Gynecomastia Grade, STPTUP, STPTIMF, GAIS) will be completed. At the 180-day follow-up appointment in addition to the above referenced assessments, the subject will complete a Patient Satisfaction Questionnaire. Following study participation, the subject will be offered an optional balancing treatment to the side not previously treated with Renuvion. Virtual visits are not allowed for D30, D90, and D180 as images and measurements are required that are not able to be completed virtually.

7.5.5 Safety Assessments

Adverse events will be assessed immediately post-treatment and at all follow-up visits.

7.5.6 Unscheduled Visits

Investigators may see subjects for visits in addition to the Day 30, Day 90, and D180 at their discretion. Any unscheduled visit or examination should be documented in the subject's medical record and adverse event form (if applicable) stating the reason for the visit and any actions taken. The Sponsor should be notified of the unscheduled visit.

7.5.7 End of Study (Completion)

All subjects who have signed an Informed Consent Form will be considered enrolled in the study. Subjects who complete the study duration will be considered to have completed the study. The end of study will be defined as completion of all study visits by all enrolled subjects. 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.

A study closure visit may be conducted at the study site to review record retention requirements, device disposition requirements, etc., with site personnel. The Sponsor may choose to conduct the closure visit via telephone contact or online conference if appropriate.

8. ASSESSMENT OF SAFETY

8.1 SPECIFICATIONS OF SAFETY PARAMETERS

8.1.1 DEFINITION OF AN EXPECTED TREATMENT EFFECT (ETE) AND AN ADVERSE EVENT (AE)

An expected treatment effect is defined as any typical treatment side-effect of Renuvion APR System of mild to moderate severity and lasting up to a typical maximum duration. An adverse event is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered device-related by the investigator.

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.

All ETEs and AEs will be collected during the conduct of this trial.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENT (SAE)

Each adverse event should be assessed for its seriousness. The definition below should be used for this assessment. Please note that the term serious adverse event is not synonymous with a “severe” adverse event, which may be used to describe the intensity of an event experienced by the subject.

An adverse event should be classified as serious if it meets any of the following criteria:

a. Death
   Death was an outcome of the adverse event.
b. Life-threatening
   The subject was at substantial risk of dying at the time of the adverse event or use or continued use of the device.
c. Hospitalization (initial or prolonged)
   Admission to the hospital or prolongation of hospitalization was a result of the adverse event.
d. Disability or Permanent Damage
   The adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
e. Congenital Anomaly/Birth Defect
   Exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
f. Required Intervention to Prevent Permanent Impairment or Damage (Devices)
   Medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
g. Other Serious (Important Medical Events)
   The event does not fit the other outcomes, but the event may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event.

8.1.3 Definition of Unanticipated Adverse Device Effects (Events)

An unanticipated adverse device effect 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 application (including supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

8.2 Classification of an Event

8.2.1 Severity of Event

Each adverse event should be assessed for its severity, or the intensity of an event experienced by the subject, using the following classifications:

- **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 events are usually relieved by simple therapeutic measures.
- **Severe:** prevents normal, everyday activities. These events may require systemic drug therapy or other medical treatment.

8.2.2 Relationship to the Investigational Device

The investigators should differentiate between device and procedure related AEs by classifying events directly attributable to the device itself as "device related" and events that occur from the procedure, irrespective of the device, as "procedure related". Since the study device delivers helium-based plasma energy to the tissue, events directly attributable to the application of energy to the tissue (i.e. burns) or the use of helium (i.e. gas buildup) should be classified as device related. Events that are known to occur in subdermal procedures utilizing tumescent anesthesia and/or undermining of soft tissue (i.e. edema[17,18], hematoma[18,19], nerve injury[19], pain/tenderness[17]) without the use of the study device should be classified as procedure related.

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 and/or study procedure, 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 study procedure, is not clearly due to another condition and the involvement of the study device is unknown.

The investigator should assess the relationship of the adverse event to the investigational device. The relationship should be assessed using the categories presented in **Table 6**.

TABLE 6. RELATIONSHIP BETWEEN ADVERSE EVENTS AND INVESTIGATIONAL DEVICE

Definite	Definite relationship exists between the device/procedure and an adverse event
Probably Related	A reasonable causal relationship between the device/procedure and an adverse event is more likely than not.

Possibly Related	A reasonable relationship exists between the device/procedure and an adverse event, but the causal relationship is unclear or lacking.
Not Likely Related	A temporal relationship exists between the device/procedure and an adverse event, but there is no reasonable causal relationship. For example, the adverse event occurs in a time frame, which makes a causal relationship to device treatment improbable.
Unrelated	No relationship between treatment with the device/procedure and the adverse event exists.

8.3 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during a study visit or upon review by a study monitor. All ETEs and AEs will be captured on the appropriate CRF. Information to be collected includes event description, date of onset, clinician's assessment of seriousness and severity, relationship to study device/treatment (assessed only by those with the training and authority to make a determination), actions taken, and date of event resolution. All AEs occurring while on study must be documented appropriately regardless of relationship.

A pre-existing condition should not be reported as an adverse event unless there has been a substantial increase in severity or frequency of the problem that has not been attributed to natural history. Changes in the severity of an event will be documented to allow for a determination if the event should be re-categorized from an ETE to AE.

Safety evaluations for this study include an interview with the study subject at each follow-up visit by the Investigator or delegated study staff to elicit information about any medical occurrence that meets the definition of Adverse Event. This information will be documented in CRF without regard for cause or relation to device and/or procedure.

In addition, study subjects will be instructed in the Informed Consent Form, post-procedure take-home instructions, and verbally by study staff to report all complications experienced post study procedure to the site personnel as soon as they occur/are observed. Study staff will ensure that monitoring and management of all adverse events is prioritized.

Study investigators are provided liberty to mitigate adverse events as deemed necessary per IHC GCP Guidelines E6(R2)4.3.2 which states "During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events related to the trial".

Adverse event resolution dates will be determined by investigator using either in-person or remote (phone, video call, text, email, etc.) examinations or communication with the subject. To ensure the most accurate reporting of adverse event durations, investigators are instructed not to wait until scheduled office follow-up visits to assess resolution.

It is the Investigator's responsibility to determine seriousness, severity, and relatedness of the Adverse Event to the device and procedure using the definitions in this protocol.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of ETEs/AEs/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

All Adverse Events (AEs) and Expected Treatment Effects (ETEs) 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, ETE, 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 in the ICF, post-treatment take home instructions, and verbally by study staff to report all AEs to the clinical study staff. AE information will be collected throughout the duration of the study and recorded on CRFs.

Any new medical problem, or an exacerbation of an existing condition, reported from the time the informed consent form is signed must be followed until the last study visit after the last study treatment or until event resolution.

8.4.2 Serious Adverse Event Reporting

Serious adverse events must be reported to the Sponsor as soon as possible, preferably within 24 hours but in no event later than 72 hours. Any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included in **Definition of Serious Adverse Event** must be documented on an SAE CRF.

The Sponsor will conduct an investigation. If the Sponsor determines that the investigation presents an unreasonable risk to subjects, all investigations or parts of the investigation presenting that risk will be terminated as soon as possible. The investigator must report serious adverse events to the reviewing IRB according to the IRB regulations.

8.4.3 Unanticipated Adverse Device Effect Reporting

If an unanticipated adverse device effect occurs, the study investigator shall complete the appropriate study-specific CRF and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in **Apyx Medical Study Contact List**. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.4.5 Reporting of Deaths

The investigator must notify the Sponsor as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of a subject's death, regardless of whether the death is related or unrelated to the investigational device. The investigator should attempt to determine, as conclusively as possible, whether the death is related to the device. The cause of death and the investigator's discussion regarding whether or not the death was device-related should be described in a written report. The investigator mush report death to the reviewing IRB according to the IRB regulations at the study site.

8.5 Study Halting Rules

This clinical trial will be halted if subjects' safety is questioned based on a reporting of severe, device-related AEs at an excessive frequency. 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 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. The study sponsor will notify all investigators to immediately halt any

continuing enrollment activities and not enroll any additional study participants. The study sponsor will inform the IRB/FDA of the temporary halt and the disposition of the study.

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 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. Enrollment and treatment would be suspended during root cause investigation to determine the cause of the respective AE.

9. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

10. STATISTICAL METHODOLOGY

10.1 Statistical and Analytical Plans

For the purposes of this pilot study, descriptive statistics will be performed.

10.2 Sample Size

This study will include up to 10 treated subjects from up to 3 US sites.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/ DOCUMENTS

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, study specific CRFs, progress notes, electronic data, computer printouts, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons.

12. QUALITY ASSURANCE AND QUALITY CONTROL

Quality Assurance and Quality Control procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution via data queries.

Following written SOPs, the clinical study monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

This clinical study will be conducted in accordance with the Protection of Human Subjects Regulations, including Subpart B Informed Consent of Human Subjects (21 CFR Part 50); the Institutional Review Board Regulations (21 CFR Part 56); the Financial Disclosure by Clinical Investigators Regulations (21 CFR Part 54); and the Investigational Device Exemptions Regulations (21 CRF Part 812), and the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

Prior to initiation of any study procedures, the protocol, informed consent, and recruitment materials, and all participant materials will be submitted to a duly constituted IRB for view and approval. In addition, any amendments to the protocol or Informed Consent Form will be reviewed and approved by the IRB. The Sponsor must receive a letter documenting IRB approval at the clinical site prior to the initiation of the study.

The investigator is responsible for providing the appropriate reports to its reviewing IRB during the course of the clinical study. These reports will include:

- Informing the IRB of the study progress periodically as required, but at least annually.
- Reporting any unanticipated adverse device effects within 10 working days of first learning of the event.
- Reporting any deviations from the clinical protocol to protect the life or well-being of a subject in the case of an emergency within five working days after the emergency occurred.
- Reporting the use of the device without obtaining informed consent from a subject within five working days of the event.
- Providing any other reports requested by the IRB.

The IRB must be notified of study completion within 30 days of the final visit of the last subject and should be provided with a summary of the results of the study by the investigator.

13.3 PARTICIPANT AND DATA CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without prior written permission from the Sponsor. Authorized regulatory officials and Sponsor personnel (or its representatives) will be allowed full access to inspect the records. Data disclosed outside the study team will be de-identified or will only include general group demographic information. Protected Health Information and/or identifiable study data will not be shared with anyone outside the study team or Health System, with the exception of the study sponsor, and federal regulators/ institutional officials for the purposes of auditing.

All investigational devices and/or other materials collected will be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Subjects should be identified only by initials and unique subject numbers on study specific CRFs. If necessary, their full names may be made known to a regulatory agency or other authorized officials. Information to be stored on the computer will be identified by subject ID and will be password protected.

14. DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

During each subject's visit to the clinic, study data will be documented by study personnel on study-specific Case Report Forms (CRFs) prior to entry into an Electronic Data Capture (EDC) system. Subject demographic information, procedural data, adverse events, device observations, and study required assessments will be documented on the CRFs by delegated site personnel. In addition, study personnel will record progress notes to document all significant observations, and any contact with a subject by telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. In this clinical trial, study specific CRFs may serve as source documents.

For transmission to the Sponsor, information from the study progress notes and other source documents will be promptly transcribed to study specific CRF to the EDC with the CRF attached for remote monitoring of the data. Transcription of study data onto study specific CRFs and entry into the EDC should be completed within 3 days of the study visit.

Copies of the electronic CRF (eCRF) serving as source documents must be maintained for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Any changes to information in the study progress notes, other source documents, and CRFs will be initialed and dated in ink on the day the change is made by a site study staff member authorized to make the change. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator and/or delegated staff.

Data management and oversight is the responsibility of the Sponsor. Responsibilities include, but are not limited to, the following:

- Clinical strategy and oversight.
- Clinical study operations.
- File management and study documentation.
- Site initiation visits and study close-out visits.
- Clinical quality assurance.
- Statistical support and programming.
- Data management, including database development and programming and electronic data capture (EDC) programming, training, and management.
- Management and oversight of photographic imaging.

Responsibilities may be delegated to applicable vendors.

14.2 Investigator Records and Reports

14.2.1 Investigator Records

Prior to participation in the investigation, the investigator must provide the following documentation to the Sponsor:

- Investigator Agreement, signed by the investigator, which lists any physicians who will be involved in conducting the investigation under the direction of the primary investigator.
- A copy of the principal investigator's, sub-investigator's, other delegated study clinicians' curriculum vitae.
- A letter signed by the chairperson of the IRB overseeing the conduct of this study indicating that the IRB has reviewed and approved this investigational plan.

- A copy of the IRB-approved Informed Consent Form.

During the study, investigators are required to maintain on file the following accurate, complete, and current records relating to this study. A summary of these records is listed below:

- Executed Clinical Trial Agreement.
- All correspondence and required reports, which pertain to the study, including IRB approvals and correspondence.
- Signed and dated consent forms.
- Relevant observations, including records concerning adverse events, condition of each subject upon entering and results of diagnostic tests.
- Study-specific CRFs and corrections to the forms.
- Protocol and amendments with signed Statement of Compliance.
- IRB-approved subject recruiting materials.
- Investigator curriculum vitae and medical license.
- Monitoring reports and correspondence.
- Study logs including: Site Training Log, Site Visit Log, Site Delegation Log, and Subject Enrollment Log.

14.2.2 Investigator Reports

Investigators are required to prepare and submit to the Sponsor the following complete, accurate, and timely reports on this investigation when are required. These reports, which are listed below, additional reports may be requested by the Sponsor:

- The investigator will notify the Sponsor of a subject death occurring during the investigation, as soon as possible, preferably within 24 hours of learning of the subject's death, but in no event later than 48 hours. The investigator will notify the reviewing IRB of a subject death as specified by the IRB.
- The investigator will notify the Sponsor of any unanticipated adverse device effects within 48 hours after learning of the effect. The investigator will notify its reviewing IRB of any unanticipated adverse device effects, as soon as possible, but no later than 10 working days after learning of the effect.
- The investigator will notify the Sponsor of the withdrawal of IRB approval, as soon as possible, but no later than five working days after learning of the withdrawal.
- The investigator will provide current progress reports to the Sponsor and reviewing IRB at regular intervals and at least on an annual basis.
- The investigator will notify the Sponsor and reviewing IRB of any deviation from the investigational plan to protect the life and physical well-being of a subject in an emergency, as soon as possible, but no later than five working days after the emergency occurred.
- The investigator will notify the Sponsor and reviewing IRB that an informed consent was not obtained from a subject, as soon as possible, but no later than five working days after such an occurrence.
- The investigator will provide a final summary report to the Sponsor and reviewing IRB within three months after termination or completion of the study.
- The investigator will provide any other information upon the request of an IRB, FDA, or the Sponsor.

14.3 Study Records Retention

The investigator is responsible for retaining the necessary records, including a copy of the protocol, device labeling, study-specific CRFs, medical records, original reports of test results, all study-related correspondence, a record of written informed consent, and any other documents pertaining to the conduct of this study.

All investigators participating in this study will maintain detailed clinical records during the investigation and for a period of at least two years after the latter of the following two dates:

1. The date on which the investigation is terminated or complete; or
2. The date the records are no longer required for purposes of supporting a premarket approval application.

The investigator must not dispose of any records relevant to this study without either:

1. Obtaining written permission from the Sponsor; or
2. Providing an opportunity for the Sponsor to collect such records.

The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor and the FDA.

14.4 Protocol Deviations

A protocol deviation is an event in which the investigator or site personnel did not conduct the study in accordance with the protocol or the Clinical Trial Agreement. This study should be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of a subject requires a protocol deviation, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). If the deviation from the protocol is necessary to protect the physical well-being of a subject in an emergency, such protocol deviations must be reported to the Sponsor and the reviewing IRB as soon as possible, but no later than five working days after the emergency occurred.

In the event of a significant deviation from the protocol due to an accident or mistake, the investigator or designee must contact the Sponsor at the earliest possible time to discuss the deviation and its impact on the study and subject continuation in the study. All protocol deviations and justification for the deviation will be documented on the applicable Case Report Form.

14.5 Publication and Data Sharing Policy

The data produced by this Apyx Medical-sponsored study is the sole property of Apyx Medical. Thereby, abstracts, publications and presentations of this data must be pre-approved by Apyx in writing (e-mail approval is acceptable). The Sponsor must also be provided with the opportunity to review all investigator-prepared abstracts, publications, or presentations. A period of thirty (30) days for presentational materials and abstracts and forty-five (45) days for manuscripts will be required for review and comment by Sponsor's Clinical and Medical Affairs Department. These requirements acknowledge Sponsor's responsibility to evaluate such publications for their accuracy, to ascertain whether Confidential Information is being inappropriately released, to provide the Principal Investigator with information which may not yet have been available to him/her, and to provide input from co-authors regarding content and conclusions of the publication or presentation. If requested in writing by the Sponsor, the Institution will withhold publication to protect the potential patentability of any invention described therein and/or made available to fulfill regulatory requirements.

Notwithstanding the foregoing, Institution agrees that if the Study is part of a multi-center study, the first publication of the results of the Study shall be made in conjunction with the results from the investigators at the other study centers as a multi-center publication.

The sponsor ensures that the study is registered, and study results are disclosed in at least one public clinical study registry, in accordance with national/international regulations and other requirements. Study registration may include a list of the study sites, as applicable.

15. STUDY ADMINISTRATION

15.1 STUDY INVESTIGATORS

Participating Investigators will be qualified based on professionals experienced in treatment of gynecomastia and skin laxity, such as plastic or cosmetic 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 applicable regulations.

15.2 AMENDMENT POLICY

The investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB, except if the deviation from the protocol is necessary to protect the life and physical well-being of a subject in an emergency. Such protocol deviations must be reported to the Sponsor and the reviewing IRB as soon as possible, but no later than five working days after the emergency occurred.

Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed by the investigator(s) and the Sponsor. If agreement is reached regarding the need for an amendment, the Sponsor will write it. The written amendment must be submitted to the chairman of the IRB identified with this responsibility. Except for "administrative amendments", investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; the scientific soundness of the investigational plan or protocol; and the right, safety or welfare of the human subjects involved in the investigation. When, in judgment of the chairman of the IRB, the investigators and/or the Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written Informed Consent Form will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before continued participation.

16. CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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ATTACHMENTS: OUTCOME MEASURES

ATTACHMENT A: PATIENT SATISFACTION QUESTIONNAIRE

Please have the subject complete this assessment while referring to their image in the mirror and current post-treatment photos compared to baseline photos. Provide the subject with a mirror.

Using a mirror and reviewing your post-treatment photos, compare how your treatment area currently looks compared to your pre-treatment photos.

1. On you **RIGHT** side, which, if any, changes do you see in the area treated?
   - ☐ Less sagging skin
   - ☐ Smoother skin texture
   - ☐ Skin Feels Better
   - ☐ Skin Feels Tighter
   - ☐ Skin Appears Tighter
   - ☐ Skin Looks more Radiant
   - ☐ Skin Seems more Youthful
   - ☐ Other: _____
   - ☐ None
2. On you **LEFT** side, which, if any, changes do you see in the area treated?
   - ☐ Less sagging skin
   - ☐ Smoother skin texture
   - ☐ Skin Feels Better
   - ☐ Skin Feels Tighter
   - ☐ Skin Appears Tighter
   - ☐ Skin Looks more Radiant
   - ☐ Skin Seems more Youthful
   - ☐ Other: _____
   - ☐ None

3. How would you characterize your satisfaction with the treatment on your **RIGHT** side?
   - ☐ Very Satisfied
   - ☐ Satisfied
   - ☐ Slightly Satisfied
   - ☐ Neither Satisfied or Dissatisfied
   - ☐ Slightly Dissatisfied
   - ☐ Dissatisfied
   - ☐ Very Dissatisfied

4. How would you characterize your satisfaction with the treatment on your **LEFT** side?
   - ☐ Very Satisfied
   - ☐ Satisfied
   - ☐ Slightly Satisfied
   - ☐ Neither Satisfied or Dissatisfied
   - ☐ Slightly Dissatisfied
   - ☐ Dissatisfied
   - ☐ Very Dissatisfied

5. Do you feel that one side of your chest looks better than the other *(check one)*?
   ☐ YES ☐ NO

   a. If Yes, which side do you like better?
      ☐ RIGHT ☐ LEFT

6. Do you feel that the skin on one side of your chest feels tighter than the other *(check one)*?
   ☐ YES ☐ NO

   a. If Yes, which side does the skin feel tighter?
      ☐ RIGHT ☐ LEFT

7. Do you feel the skin quality on one side of your chest is better than the other *(check one)*?
   ☐ YES ☐ NO

   a. If Yes, which side has better skin quality?
      ☐ RIGHT ☐ LEFT

Thank you for completing this questionnaire.

Subject Initials: _____ Date: _____ (DD/MON/YYYY)

APPENDIX PROTOCOL REVISIONS LOG

VERSION	DATE	SIGNIFICANT REVISIONS