STUDY NAME: CLINICAL EVALUATION OF SAFETY AND EFFICACY OF RADIO-FREQUENCY ASSISTED LIPOLYSIS (RFAL) OF BREAST ENVELOPE AND NIPPLE-AREOLAR COMPLEX (NAC) POSITION

Date: August 2018

Identifiers: NCT03863834 Unique Protocol ID: D0607738

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Date:	August 2018
Protocol No:	**D0607738**
Revision No.:	**B**
Sponsor:	InMode MD Ltd.

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INMODE aesthetic solutions	*Clinical Evaluation of Safety and Efficacy of Radio-Frequency Assisted Lipolysis (RFAL) of Breast Envelope and Nipple-Areolar Complex (NAC) Position*	
	Protocol No: DO607738A *SIRB ID: 6254*	*Rev. Date: August, 2018*

APPROVALS:

	Name	Title	Signature	Date
Written by:	MARIA SHUSTERMAN, RN	CLINICAL MANAGER		
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Approved by:				

Revision Log:

Revision #	Date	Modification
A		First Release
B	8.8.18	

PROTOCOL SYNOPSIS

Study Title	CLINICAL EVALUATION OF SAFETY AND EFFICACY OF RADIO-FREQUENCY ASSISTED LIPOLYSIS (RFAL) OF BREAST ENVELOPE AND NIPPLE-AREOLAR COMPLEX (NAC) POSTION
Study Number	D0607738A
Principal Investigators	Dr. Jacob Unger
Study Design	This is a single center clinical study to determine the safety and efficacy of using Radiofrequency (RF) energy for minimally invasive breast lift procedure. Treatment areas will include breast area.
Study Sites / Country	Dr. Jacob Unger Maxwell Aesthetics 2020 21st Ave, South, Nashville, TN, 37212, USA
Planned Study Duration	Study duration including recruitment will be up to 18 months.
Investigational Product	The InMode RF™ platform has been cleared by the United States Food and Drug Administration (FDA) (K151793) for use in dermatological and general surgical procedures for electrocoagulation and hemostasis.
Planned Sample Size	Up to 10 adult subjects
Subject Selection	Investigator will determine patient's eligibility to participate in the study according to inclusion/exclusion criteria.

INMODE aesthetic solutions	*Clinical Evaluation of Safety and Efficacy of Radio-Frequency Assisted Lipolysis (RFAL) of Breast Envelope and Nipple-Areolar Complex (NAC) Position*	
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Study Objectives	The purpose of this study is to evaluate the safety and efficacy of RFAL for the Breast Envelope and Nipple-Areolar Complex (NAC) Position as measured by the Vectra 3D circumferential imaging system (Canfield, NJ).
Main Eligibility Criteria	Inclusion Criteria • Informed consent agreement signed by the subject. • Healthy females 21 to 60 years of age. • Presence of grade I-III Breast Ptosis, mastopexy with history of breast augmentation, correction of asymmetry, mastopexy alone, mastopexy following implant removal and modest breast reduction in combination with or without lipoaspiration. • Post-menopausal or surgically sterilized or using a medically acceptable form of birth control at least 3 months prior to enrolment and during the entire course of the study (i.e., oral contraceptives, IUD, contraceptive implant, barrier methods with spermicide, or abstinence). • Willingness to follow the treatment and follow-up schedule and the post-treatment care. • All participants must have a recorded mammogram before the beginning of the study. Exclusion Criteria • Pacemaker or internal defibrillator, or any other active electrical implant anywhere in the body.

- Permanent implant in the treated area such as metal plates and screws, silicone implants or an injected chemical substance.
- Current or history of skin cancer (remission of 5 years), or current condition of any other type of cancer, or pre-malignant moles.
- Severe concurrent conditions, such as cardiac disorders, epilepsy, uncontrolled hypertension, and liver or kidney diseases.
- History of bleeding coagulopathies or use of anticoagulants in the last 2 weeks.
- Impaired immune system due to immunosuppressive diseases such as AIDS and HIV or use of immunosuppressive medications.
- Poorly controlled endocrine disorders, such as diabetes or thyroid dysfunction.
- Any active condition in the treatment area, such as sores, psoriasis, eczema, and rash.
- History of skin disorders, keloids, abnormal wound healing, as well as very dry and fragile skin.
- Use of Isotretinoin (Accutane®) within 6 months prior to treatment.
- Significant systemic illness or occult systemic illness.
- Illness, infection or skin diseases localized in area of treatment.
- Other therapies or medication which may interfere with treatment.
- Breastfeeding, pregnant, or planning to become pregnant during the study.
- Allergy to lidocaine or other anaesthesia.

	• Recent surgery in treatment area within the past 6 months. • Participation in a study of another device or drug within 3 months prior to enrolment or during this study. • As per the Investigator's discretion, any physical or mental condition which might make it unsafe for the patient to participate in this study. • As per the practitioner's discretion, refrain from treating any condition that might make it unsafe for the patient.
Risk to the Subject	Risks involved with study participation, include: 1. Pain 2. Excessive swelling (Edema) 3. Excessive skin redness (Erythema) 4. Bleeding 5. Bruising 6. Burn 7. Blistering 8. Crusting 9. Scarring 10. Skin pigmentation, textural, and/or contour alterations 11. Infection 12. Asymmetry 13. Temporary injury to nerves (neuropraxia) where nerve branches are superficial

Scope and Duration of the Study

The clinical study will include up to 10 subjects at one site. Eligible subjects will receive single treatment according to the study protocol and will be followed up for a period of up to 1 year to document treatment safety and efficacy.

DEVICE DESCRIPTION

The system is a bipolar RF device where the first RF electrode is the treatment cannula delivering the RF energy to the adipose tissue, vessels, subcutaneous matrix and the subdermal space and the second RF electrode is connected rigidly to the first electrode via a hand piece and is applied to the skin surface above the first electrode. The second electrode creates a transcutaneous pathway for the radiofrequency energy, localizing the electrical energy between the electrodes and eliminating the need to ground the patient. The second electrode is also able to monitor, in real time, the skin surface temperature, allowing for a greater degree of safety while heating the subdermal and subcutaneous tissues.

Sagging, deflated breasts are a complaint of women worldwide following childbirth, weight loss or aging. This problem can be corrected in some women with implant placement, but not all women want larger breasts. Even fewer want the scars associated with traditional mastopexy, especially those women with darker skin types. With 9 out of 10 patients choosing nonsurgical options for aesthetic treatment, a procedure where skin is not excised is deemed preferable by the majority of patients seeking correction of droopy breasts.

Recent studies showing tissue tightening with subsequent skin surface area reduction following treatment with radiofrequency assisted devices indicated a minimally invasive pathway towards treating breast ptosis. Questions regarding this type of treatment include longevity of correction, changes within the breast parenchyma over time and the degree of improvement possible with this minimally invasive technique.[1]

The proposed method of RFAL and tissue tightening is based on controlled heating of the fibrous bands attached to the under-surface of the skin as well as the external skin surface and blood and tissue coagulation, leading to skin contraction in treated area. The potential advantages of the RF current treatment are:

- Coagulation of blood vessels which provides for an opportunity for less ecchymosis following the procedure
- Less mechanical damage
- Higher efficacy in fibrous and difficult to treat body contour areas
- Skin tightening

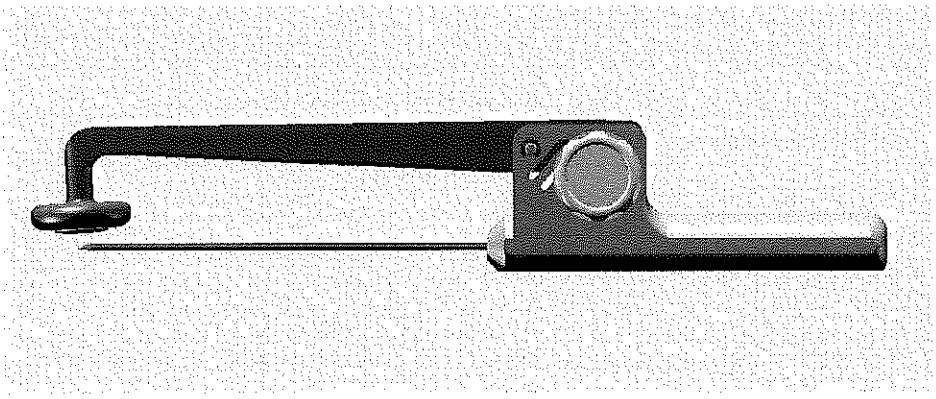
The InModeRF is a Radio-Frequency device comprising of the following main modules:

- AC/DC power supply isolating system modules from AC voltage
- RF generator providing output of RF power to the hand piece
- Microcontroller controlling RF output, monitoring tissue electrical parameters, skin surface temperature and proper functioning of electronic modules.

InModeRF DEVICE

Hand piece delivers RF power to the subject and has the following main elements

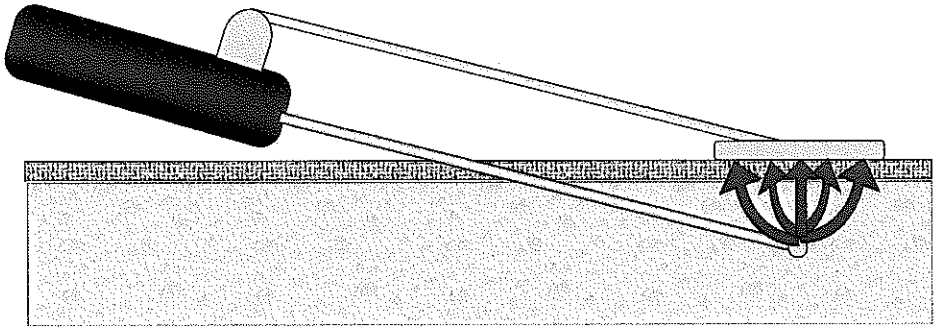
- Internal electrode insulated with Teflon with a treatment tip at the distal end
- External electrode with temperature sensor
- Mechanism adjusting distance between electrodes



HAND PIECE

Principles of operation

Operation of InModeRF device is based on the concept of a minimally invasive procedure. The hand piece is comprised of two electrodes where an internal electrode is inserted into subcutaneous fat layer and its size is designed for thermal destruction of adipose tissue with RF energy. A second external electrode is applied to the skin surface. Both electrodes have a rigid connection with an adjustable distance between them. RF power and tip size of the internal electrode are designed to liquefy fat in the vicinity of the electrode tip. The external electrode has a much larger area that creates much lower power density on the skin of the patient. The RF current flows from the internal electrode to the external electrode. The hand piece can monitor both tissue impedance and temperature in real time. The outer temperature measurement acts as safety mechanism that stops the RF current in the case the skin temperature is reaches the desire temperature set by the doctor. The figure below shows RF energy distribution in tissue between electrodes.



RF energy distribution between electrodes

STUDY DESIGN

Prospective, self-controlled, open label, single arm clinical study

CLINICAL PROCEDURE

At the first visit, the Investigator will discuss with the subject the various treatment alternatives for a Breast Ptosis, both non-surgical and surgical, including the minimally invasive RF and other treatment modalities.

VISIT 1:

SCREENING

During the first visit, the investigator or a representative on his behalf will obtain an Informed Consent Form (ICF) from the subject, clearly indicating his/her understanding of the requirements and risks involved with study participation.

Possible adverse effects include but not limited to bleeding, infection, scarring, skin contour irregularities, thermal trauma to the skin, asymmetry, scarring, surgical shock, pulmonary complications, skin loss, seroma, allergic reaction, and anesthesia related complications can occur and should be discussed and understood. The subject must understand the importance of pre-treatment and

post-treatment instructions and that failure to comply with these instructions may increase the probability of complications.

The Investigator will obtain a focused subject medical history including exclusion criteria specified herein and the front, back and both sides of the treatment area using a high resolution digital camera, as well as additional information that is specified in the case report form.

The follow-up visits should be scheduled 1 week, 6 weeks, 3 months, 6 months and optional 12 months after the treatment.

Photographs should be taken prior to the baseline treatment and at each of the follow-up visits, as well as Vectra 3D Imaging and static measurements. Participants must have a recorded mammogram prior to the first treatment. All measurements will be recorded on the case report form (CRF).

VISIT 2:

TREATMENT

The treatment will be performed once. The treatment procedure should be conducted according to the following guidelines:

Treatment Parameters

Treatment area	Treatment depth	Hand Piece	External Cut-off Temperature	Internal Cut-off Temperature	Treatment time
Small Speciality areas (Knees, Arms ...)	5-10mm	FaceTite HP101306A	35-38°C	50-60°C	15-60sec
Large Speciality areas	10-15mm	20W-40W BodyTite HP172246A	35-40°C	55-70°C	15-60sec
Thin body area <20mm	10-15mm	20W BodyTite HP172206A	35-38°C	55-70°C	30-120sec

TREATMENT RECOMMENDATIONS:

- Take sterile hand piece from the package and connect to the system.
- Set treatment parameters.
- Open the distance between electrodes to electrodes to the desired depth of treatment.
- Subject will receive sedative and local anesthesia preparation. Tumescence anesthesia may also be used during treatment.
- **Local Anesthesia:** 1% Lidocaine with epinephrine injections are administered intradermally in the proposed treatment area of the RAF and aspiration ports, usually in inconspicuous intertriginous areas adjacent to the areas to be treated.

- After administrating the anesthesia, create 3mm incision for the access port and introduction of the internal electrode. Tumescent anesthesia may be also used during the treatment.

Tumescent anesthesia: 50cc of 1% Lidocaine + 2cc of 1:1,000 Adrenaline in 1000cc of Ringers lactate solution (the Hunstad formula) is infused into the treated area through the incision. The volume of infusion should be approximately equal to amount of fat to be removed. The tumescent fluid can be preheated to approximately 36^0C prior to infusion.

- Apply sterile water-based gel to the skin surface of the treatment site.
- Introduce internal electrode through the incision.
- If skin tightening is required, set the minimal distance between electrodes (5mm).
- Hold hand piece handle with one hand and press with other hand the tip of external electrode to the skin surface.
- Press the footswitch to deliver RF energy.
- Move distal end of the electrodes evenly over the treated area. Ensure good contact between external electrode and skin. This can be achieved by putting your non-dominant hand on the hand grip provided on the external electrode.
- One or two fingers on the external electrode hand can be placed along the skin as you are moving and you can feel the internal electrode with these fingers to reassure yourself of its depth.
- Mark out the loose skin to be treated into two separate, large zones using a surgical marking pen. Move the internal subdermal electrode and external electrode smoothly back and forth within each large zone until the desired temperature has been reached, and then continue to treat that zone at the desired temperature for 5 minutes.
- After the Sound Indicator emits the audible indicator that the desired temperature is reached, continue heating your treatment zone for 5 minutes to optimize subdermal stimulation. Once heated for 5 minutes at the desired temperature, move to the next large thermal grid until all

grids have been treated and the subdermal skin has had the temperature elevated to the desired end temperature.

- When desired amount of energy is delivered switch device to the Standby mode and remove internal electrode from the body.
- Introduce a small to medium suction with connected syringe or mechanical aspiration system through the same incision to the treated layer of fat.
- It is recommended that a gentle aspiration be performed by employing blunt, bullet tipped, vented cannulas and turning the wall aspiration pressure down.
- Apply vacuum to the syringe or aspiration system to remove the excessive fluids from the body.
- Assess the desired contour endpoint by visual inspection of the nipple areola complex.
- Close incisions with sutures. If your customary practice is to leave your liposuction access ports non-sutured, you may do so.
- Following the procedure, use standard post operation pressure dressing including lipoplasty compression garments. If the skin laxity on the breasts is significant, consideration for a closed drainage system may be made.

VISIT 3:

FOLLOW UP

Follow-up session 1-week post treatment. Photographs will be taken. Any adverse events and their persistence will be recorded. [Patient and physician satisfaction forms to be completed on 5-point scale at each post op visit]

VISIT 4:

FOLLOW UP

Follow-up session 6-weeks post treatment. Photographs will be taken. Any adverse events and their persistence will be recorded. Patient and PI will fill in the questionnaires.

VISIT 5:

FOLLOW UP

Follow-up session 3 months post treatment. Photographs will be taken. Any adverse events and their persistence will be recorded. Patient and PI will fill in the questionnaires.

VISIT 6:

FOLLOW UP

Follow-up session 6 months post treatment. Photographs will be taken. Any adverse events and their persistence will be recorded. Patient will undergo mammogram and results will be recorded in CRF. Patient and PI will fill in the questionnaires.

VISIT 7 (If Applicable):

FOLLOW UP

Follow-up session 12 months post treatment. Photographs will be taken. Any adverse events and their persistence will be recorded. Patient and PI will fill in the questionnaires.

TREATMENT PARAMETERS STUDY

The investigator may decide to have different parameters on the same patient. For example, the right side may be treated in lower power for longer time, and on the left side higher power for shorter duration. The total energy (kJ) deposited into the tissue may vary.

POST-TREATMENT CARE

- The incision's area should be covered with medical dressing and with firm pressure dressing or compression garment if required. Compression may be needed per the physician's order. The subject should be instructed that there may be drainage from incision area and that it should be consistently cleaned and disinfected.
- In case of side effects; burns, blistered or ulcerated skin can be treated with a prescribed antibiotic ointment, burn treatment cream or other prescribed medication.
- Bed rest may be helpful after the treatment.
- Discomfort, if any, may be relieved by placing a cool (not frozen) pack on treated area.
- During the first 1-2 weeks following treatment, care should be taken to prevent trauma to the treated site: avoid hot baths, excessive physical activities, etc.
- A prophylactic antibiotic regimen may be prescribed for subjects starting one day before treatment until one-week post-treatment according to physician discretion. Prophylactic antibiotics should be administered on the day of treatment and continued for a minimum of 2 doses following the RAL procedure.
- Discomfort can be reduced by cool compresses or standard post-operative analgesic.
- Compression garments may be used for up to 6 weeks.
- Appropriate vigorous exercise restrictions should be instituted.
- Subject is to contact physician if there is any indication of infection, fever, excessive swelling, redness, undue pain, shortness of breath, swelling of the ankles, chest pain, irregular heart beat or any other unusual or untoward symptom.

SAFETY AND RESULT MEASUREMENTS

Photography

At each of the specified time points (before the treatment and at the follow-up visits), photos of the body should be taken, including a frontal photo, back photo and two side images of the body from knee up to breast line as it is shown in the picture on the next page. Hands of the subject should be at the side of the body in the position that does not block and does not shade the treated area.

The photos should be taken under controlled conditions, including the colour of the background material, distance from the camera, angle and lighting, including flash, in order to achieve consistent, high-quality before & after pictures. Each picture should be accompanied with the date, visit number, subject ID, subject initials.

Vectra 3D Photography

3D photography of the breast region will be taken in all patients during the routine preoperative work-up using a commercial 3D scanner, VECTRA XR scanner (Canfield Scientific). Patients will be asked to stand with their arms in varying positions and each scanning takes approximately 1–2 seconds. Photographs will be created in both standard format and pixelated format to highlight surface contour.

Weight

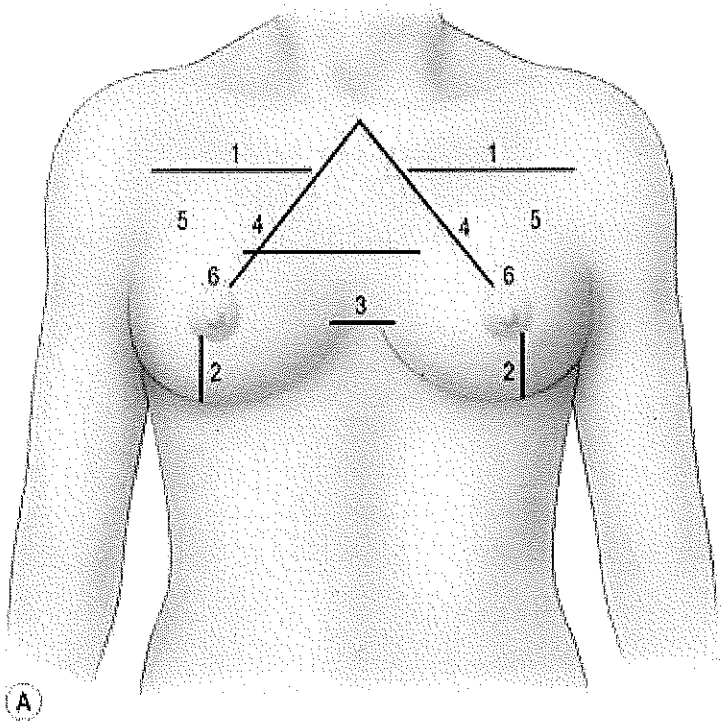
Subject weight measurements should be taken before the treatment and at each follow-up visit.

Static Measurements

Additional evaluation of changes in breast shape, including upper pole fullness, breast projection, and bottoming out will be assets by static measurements:

- Sternal Notch to Nipple
- Nipple to IMF
- Base Width (at point of breast take off from chest wall)

- Nipple to nipple.



1. Base width (BW)
2. Nipple to inframammary fold distance (N-IMF)
3. Intermammary distance
4. Sternal notch to nipple distance (SN-N)
5. Soft tissue pinch test (PT)
6. Maximum skin stretch (MSS)

EVALUATION

Three independent plastic surgeons will evaluate photographs of the preoperative and postoperative photographs at 3-, 6- and if applicable, 12-month results.

DISCONTINUATION

Subjects enrolled in the study will be free to discontinue their participation in the study at any time. A decision to discontinue participation will not prejudice their medical care. In those instances, Investigators will attempt to obtain clinical results and side effect evaluation concerning the subject prior to his/ her withdrawal.

DATA ANALYSIS

Statistical analysis of all major body factors will be performed to determine quantitatively the treatment efficacy.

The data will be analysed by the Sponsor using basic descriptive statistics, as well as comparison tests, where applicable. Treatment-related complications will be monitored and reported; if applicable, their incidence rate will be calculated and analysed for any relationship to treatment parameters and/or skin type.

RISK/BENEFIT ANALYSIS

RISKS

The risks in this surgical procedure are derived from the physical impact of the surgical treatment on the tissue, the anesthesia used and the biopsy procedure (if applicable and patient's agreement is obtained). The possible risks include pain, excessive skin redness (erythema), damage to natural skin texture (scratching, crusting, blister, burn), bleeding, bruising, infection, scarring, skin contour irregularities and/or asymmetry and pulmonary complications. Certain people may be sensitive to the anesthesia used and therefore require longer time for recovery. Some of the risks of the anesthesia are difficult breathing, redness, itching, and/or swelling at the site of the application or injection. If any of the symptoms occur, tell the study doctor immediately. The biopsy procedure carries the risks of infection and/or scarring.

Should a risk related to the treatment become evident, the physician shall provide the appropriate treatment for this event. Nevertheless, should any sort of damage occur or if the treated areas or the patient in general feel uncomfortable following treatment, the subject should inform the study center for the attention of the study physician.

Subjects will not have to pay for treatment cost that is intended to resolve study complications.

BENEFITS

Potential benefits may include measurable nipple-areolar lift, as well as improvement in the elongated, tubular appearance in those patients with severe ptosis.

ALTERNATIVES

Besides the traditional surgery for breast tightening, other options include non-invasive skin tightening procedures using lasers, bipolar or monopolar devices as well as ultrasound.

ADVERSE EVENTS

The Physician must document on the Adverse Events form, in standard medical terminology, all adverse signs and symptoms regardless of severity or frequency that are either volunteered by subjects or observed during the course of the study. Included in the description will be the nature of the sign or symptom, the date of onset, whether the event was serious, the severity, the relationship to study treatment or device, the action taken, the date of resolution, and the outcome.

- Possible serious adverse event is any event that:
  - Results in death;
  - Is immediately life-threatening (injury or illness);
  - Results in hospitalization, or prolongs an existing hospitalization;
  - Results in permanent impairment of body structure or function, or in persistent or significant disability/incapacity;
  - Results in an injury that requires medical intervention to prevent permanent impairment of body structure or function;
  - Is a device malfunction or deterioration in the characteristics and/or performance of the device that results in death or serious deterioration in health;

- Is a device malfunction or deterioration in the characteristics and/or performance of the device that, if it were to occur again, could result in death or serious deterioration in health;
- Is a congenital anomaly/birth defect;
- Is a malignancy (cancer);
- Is any medically significant injury, event or experience that requires medical/surgical intervention to prevent one of the outcomes listed above;
- Results in end-organ toxicity, including hematologic, renal, cardiovascular, hepatic, gastrointestinal, and central nervous system events;
- Results in unreliable test results leading to inappropriate diagnosis or therapy.

All serious adverse events, whether or not deemed expected or device-related, must be reported to the clinical monitor immediately or within 24 hours by telephone.

Anticipated adverse events in this study include: pain, excessive skin redness (erythema), damage to natural skin texture (scratching, crusting, blister and burn), bleeding, bruising, infection, scarring, skin contour irregularities and/or asymmetry, pulmonary complications, complications following reaction to surgery and/or to anesthesia. There are also specific anticipated adverse events that may occur due to the punch biopsy procedure: complications following reaction to the anesthesia, infection and scarring. If an *un*anticipated adverse event occurs at any time during or after the use of the InModeRF system, the Physician must report it to the Sponsor. If the unanticipated adverse event, in the opinion of the Sponsor or the Physician, is likely to affect the safety of the subjects or the conduct of the study, the IRB will be notified of the effect within 10 working days after the Sponsor first receives notice of it.

COST TO PARTICIPANTS

There is no cost to subject for participation.

COMPENSATION TO PARTICIPANTS

Patients will be compensated $100.00 for study completion (Last 12M FU).

COMPENSATION FOR RESEARCH RELATED INJURY

In the event of a research-related injury, the sponsor of the study will pay for reasonable costs of medical treatment, except for the costs covered by the patient's medical insurance. The Sponsor will not provide any other form of compensation.

RECORDS AND REPORTS

Data from the pre/post-treatment evaluations, the treatment sessions, complications, if any, and all follow-up evaluations will be recorded on the CRFs prepared for this clinical study.

Should a subject drop from the study prematurely, the Physician will attempt to obtain clinical results and side effects evaluation concerning the subject prior to his/her withdrawal. All specified records and reports concerning this study will be forwarded to the Sponsor within a reasonable period of time.

The participating Physicians shall retain all study-related documentation for a period of two years following the date on which the clinical investigation is terminated or discontinued.

CONFIDENTIALITY

This clinical study is confidential. To ensure appropriate protection of subject privacy, in addition to the informed consent, a HIPAA authorization will be required for investigational sites located in the United States. It is intended that the results of this study may be published as marketing material or in the scientific literature. This should be done without disclosing the identity of the participants in the written data or photos, as will be mentioned clearly in the Informed Consent.

APPENDIX I

STUDY SCHEMATICS

	Visit 1 Pre Tx 1	Visit 2 Tx 1	Visit 3 1 W FU	Visit 4 6 W FU	Visit 5 3 M FU	Visit 6 6 M FU	Visit 7 12 M FU
Informed consent process	X						
Eligibility & medical history	X						
Final enrollment	X						
Mammogram	X						
CRF measurements: Weight, static measurements		X	X	X	X	X	X
Photography		X	X	X	X	X	X
3D Image		X	X	X	X	X	X
Treatment [1]		X					
Removal of stitches			X				
Physician assessment of results			X	X	X	X	X
Subject satisfaction			X	X	X	X	X
End of study							X

[1] It is important to document what kind of anesthesia was used during the treatment and if tumescent fluid was used as well which may influence the subject's sensation.

References

1. Diane I. Duncan M.D., Pilot Study Using RF Assisted Tissue Tightening for Nonexcisional Breast Lifting. Prime Journal vol.7 Issue 5, September October 2017, pp. 18-20