ELIRA -2 Trial

Safety and Effectiveness of Transcutaneous Electrical Nerve Stimulation (TENS)-Assisted Weight Loss and/or Appetite Suppression

Protocol Number: CD-005

Original Date May 8, 2018

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ELIRA-2

SAFETY AND EFFECTIVENESS OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)-ASSISTED WEIGHT LOSS AND/OR APPETITE SUPPRESSION

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Protocol Number: CD-005

Study Device: The Elira wearable, patch system

Date of Protocol: Version 4.0; May 3, 2019

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations. The study will be monitored according to standard clinical monitoring procedures and in compliance with Title 21 CFR Part 812.

I have read and agree to abide by the requirements of this protocol.

_____

Principal Investigator Signature Date

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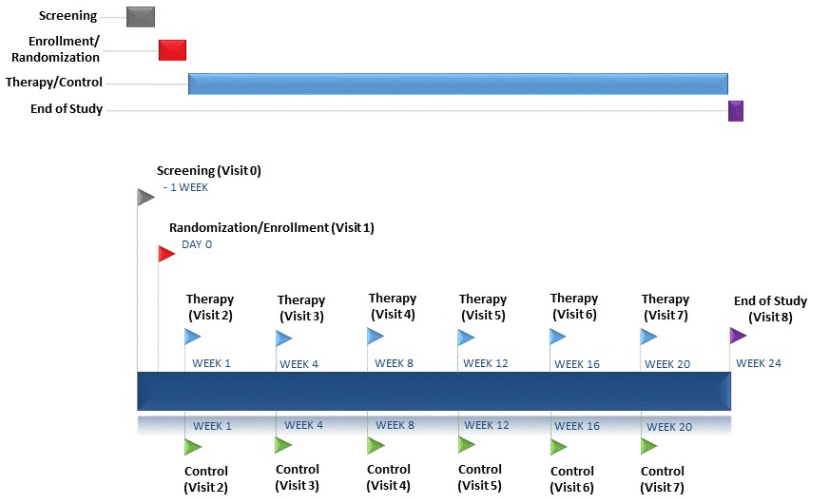
PROTOCOL SUMMARY

Study Title	ELIRA-2: Safety and Effectiveness of Transcutaneous Electrical Nerve Stimulation (TENS)-Assisted Weight Loss And/Or Appetite Suppression
Study Coordinating PIs	Shelby Sullivan, MD and Steven Edmundowicz, MD
Study Rationale	Previous studies have shown that TENS facilitates weight loss in overweight subjects. The therapy in these trials was delivered using an over the counter device not optimized for daily use. The present pivotal study will test the hypothesis that daily, wearable TENS is safe and effective for appetite suppression and weight loss therapy in overweight- to Type 1 obese-subjects (i.e. BMI of 25 -35 kg/m^2 inclusive). Ancillary endpoints include changes in hemoglobin A1c and blood lipids as secondary measures associated with weight loss.
Name of the Device(s) Used in Study	The Elira wearable patch system.
Description of Components	The Elira wearable patch system is an RF coupled, wearable transcutaneous electrical nerve stimulation (TENS) device controlled via Bluetooth by a smart phone unit running a custom application which directs therapy from the patch within safe limits set by a clinician and also includes a diary. Subjects will be supplied as well with paper diaries for appetite and symptoms along with an electronic scale.
Study Design	Randomized, adaptive parallel arm study. Subjects will be initially screened during a screening period (+/- 7 days). During this screening period, subjects will sign an Informed Consent Form (ICF), have their weight/height and blood pressure measured as part of a physical exam, take a pregnancy test (females of child bearing potential), get blood drawn for analysis (blood lipids, HbA1c), and complete the PHQ-9 and pre-study survey. Subjects will be asked to complete their first batch of diaries to set a baseline hunger value. At the end of the screening period, eligible subjects will be enrolled/randomized in the study and be randomized to either a treatment or control group. After enrolling, both control and treatment subjects will be instructed to follow a healthy diet and reduce calories as desired for the duration of the study and will receive training on the use of the electronic scale and completion of paper diaries. For the treatment group, subjects will be instructed on use of the Elira wearable patch system. Photographs will be taken at the enrollment visit. Following this, subjects will enter the Therapy Period for ~24-weeks. At the 12 week visit, subjects will be assessed for weight loss, blood pressure, blood lipids, HbA1c, patient preference questionnaire and their participation will continue through months 4-6 for the Safety phase of the Therapy Period. The Therapy Period will be considered complete (pending laboratory results, adverse events or serious adverse events). Patient (treatment) photographs will also be taken at the 12 week visit.

	The study utilizes an adaptive approach where cohorts of enrolled/randomized subjects (in groups of ~25 per arm) are assessed for dose response and progression to achievement of primary and secondary endpoints. Frequent interim endpoint assessment utilizing Markov-chain Monte Carlo (MCMC) methods coupled with Longitudinal analyses will be utilized to determine sample sizes for future cohorts (assessed primarily via Normal dynamic linear modeling [NDLM]). Long term safety of the device will be shown through 6 months of usage.
Subject Population / Sample Size	The primary endpoints are powered at a final enrollment of 75 subjects per group, for a total of 150 subjects, but interim analyses based on Bayesian posterior probability distributions with multiple imputation will be utilized to assess interim significance. In the event the interim analysis is not significant, up to 300 subjects may need to be enrolled in order to achieve final separation between groups for statistical significance. Thus, Elira may need to screen up to 500 subjects to account for exclusions prior to enrollment.
Study Duration and Sites	Minimum study duration for each patient will be 25 weeks. As it is expected that recruitment of 150 subjects will take up to 24 weeks, the overall study duration is anticipated to be a minimum of 37 weeks, assuming all cohorts are enrolled. The study will be conducted at up to 10 centers.
Inclusion Criteria	Subject is between 18 – 65 years of age inclusive. Subject has a BMI of 25-35 kg/ m^2 inclusive. Subject has signed the informed consent form and is able to comply with study protocol and adhere to study visit schedule. Subject is able to wear and use a wearable, patch TENS system. Subject is able to use a touch screen hand held smart phone. Subject is fluent in English and can complete patient questionnaires. Subject is male or non-pregnant, non-lactating female, who agrees to use effective contraceptive methods throughout the length of the trial based on PI approval. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at screening or enrollment visit, prior to placement of ELIRA device.
Exclusion Criteria	Subject has any known gastrointestinal disorder that in the opinion of the PI precludes enrollment into the trial. Subject has had a prior bariatric procedure or any previous procedure on the stomach. Subject has any significant multisystem disease in the opinion of the PI. Subject has > 6.5 HbA1c. Subject has significant cardiac arrhythmia, ectopy, or significant cardiovascular disease. Subject has an existing implanted electrical stimulator (e.g., pacemaker, AICD). Subject is a female of child-bearing potential who is pregnant or intends to become pregnant during the trial period. Subject has current and/or a history of cancer within the past 5 years (not including basal cell carcinoma or cervical carcinoma in situ).

	Subject has had a weight change of ± 5% of his/her Total Body Weight in the 3 months prior to screening. Subject has a moderate / severe psychiatric disorder. Subject has a diagnosed neurological disease. Subject has a diagnosed eating disorder. Subject has a skin disorder affecting the thoracic dermatomes Subject has active or **/**has ever had shingles in the **abdomen** area. Subject has abdominal surgery or other scars which may interfere with stimulation in the opinion of the PI. Subject is currently enrolled in other, potentially confounding research. Subject has known allergic reaction to materials in the electrodes and/or is otherwise unable to tolerate stimulation with the wearable TENS system. This includes known allergies to latex, nickel and/or hydrogels. Subject has a history of sensitive skin, including eczema, wheel-and-flare or other skin irritation, per PI discretion. Subject is actively participating or unwilling to discontinue participation in another weight loss program. Subjects may not enroll in paid or unpaid programs that involve in-person or online apps or coaching, beginning new fitness regimens or utilizing meal planning or paid nutritional coaching during the course of the ELIRA study. Subject is taking weight loss control medications including but not limited to OTC medications, Metformin, and Belviq. (See Appendix 8) Subject is planning any major medical treatments or surgeries that could cause weight loss. Subject is unable to take anti-nausea medications planned for the study. Inability to walk at least 0.8 kilometers per day (10 minutes of continuous walking). Current smoker or user of nicotine product or smoking cessation within 1 year of the screening date. History of treatment for or current abuse of drugs or alcohol. A score of ≥10 on the Patient Health Questionnaire 9 (PHQ-9), demonstrating moderate depression. Any subject that the investigator considers inappropriate for the study for medical reasons. Subject has a history of moderate/severe migraines or other severe headache disorders requiring the treatment of Topiramate. Subject is on drug therapy which may alter antral motility or appetite, per PI discretion (Appendix 8).
Study Outline	



Dosing Regime	Treatment subjects will be trained in rotation of the patch electrodes every 24h such that it is applied to varying locations on the T6/T7 dermatome. Each treatment subject will receive two treatments of up to 40 mA of sustained current stimulation for 30 minutes each delivered approximately 30 minutes prior to meal times (based on established times set in the smartphone application), not to exceed 75min daily without express consent of PI. Based on tolerance of the therapy, a subject may decrease his/her dose by dropping one of the therapy sessions after receiving approval from a clinical coordinator and/or PI. In addition, subjects who do not experience sufficient appetite suppression may also add up to three 5-minute "on-demand" sessions at 20mA between regular doses after receiving approval from a clinical coordinator and/or PI. The nominal stimulation dose per day for any subject will thus be 1200mA (60 minutes at 20 mA) while the maximum dose for any given subject will be 3000 mA (75 minutes at 40 mA).
Visit Schedule	**Screening/Baseline Visit 0 (-1 week; ±7 days) –** Obtain Informed Consent prior to any study procedures. Confirm subject has met all inclusion criteria and no exclusion criteria. History & Physical including height & weight, diet history, baseline clinical parameters, provide laboratory requisition, urine pregnancy test for women of childbearing potential (FOCBP), and questionnaires. Subjects will be given their first batch of paper diaries to complete to establish a baseline hunger. **Enrollment/Randomization Visit 1 (Day 0;**1; all durations are **± 7 days) –** Confirm subject continues to meet all inclusion criteria and no exclusion criteria. Assessment of T6/T7 dermatomes, clinical parameters, BP, weight, perform urine pregnancy test for FOCBP if not done at screening, administer TFEQ-R18V2 Questionnaire, assess for adverse events and changes to concomitant medications. Subjects will be randomized based on the blocked randomization algorithm.

	Treatment and Control subjects will be instructed to follow a healthy diet and reduce calories, if possible, throughout the study and given the Diet Resources sheet in Appendix 18.11. They will also receive an electronic scale with instructions on use will be provided, and 8 copies of a daily paper diary will be provided. Subjects will be instructed to return with their paper diary(ies) at the next scheduled visit. Only the treatment subjects will receive a handheld smartphone with the custom application and an Elira wearable patch system. It is recommended for treatment subjects to utilize an TENS Clean-Cote Skin Wipes and/or alcohol prep pad wipe to maintain a clean application area for the treatment. Treatment subjects will also receive Cetaphil Moisturizing Lotion to be used nightly after removing the ELIRA patch and applied throughout the abdomen area. Subject will be instructed to notify site immediately if any irritation occurs. Treatment subjects will stimulate under the supervision of the investigator or coordinator for 30 minutes prior to being discharged with the device. Treatment subjects will be assessed for toleration of the stimulation to further evaluate dose adjustment. Treatment subjects will be discharged with the Elira wearable patch system & Smartphone App and instructions on use. Treatment subjects will be instructed to return with the Elira wearable patch system and smartphone app at their next scheduled visit. Completion of patient questionnaires (All subjects). A below the neck photograph of the Treatment subjects will be taken at the enrollment visit, with the subjects dressed in biker shorts and sports bra (F) or athletic shorts (M). **Therapy Phase Visits 2, 3, 4, 5, 6, and 7 (week 1, 4, 8, 12, 16, and 20, respectively; ± 7 days) –** Treatment and Control subjects will be assessed for adverse events, changes to concomitant medications and commitment to exclusion criteria. Obtain BP and weight. Administer the TFEQ-R18V2 Questionnaire. Collect and review paper diaries, dispense new paper diaries and review instructions for weekly completion. All subjects will be encouraged to follow a healthy low-calorie diet throughout the study. At week 1, subjects will return their first week's worth of paper diaries. At week 4, subjects will be given a new set of 8 paper diaries and instructed to complete paper diaries for each week beginning the day after the visit. At week 8, they will return their "week 4 diaries" and be given the next set of 8 paper diaries to be completed each week,…,until the final week of using the device (week 23-24). Treatment subjects will be assessed for any adverse device effects (ADE), T6/T7 dermatome assessment, review and download of diary data, and stimulation adjustment (if needed). If skin irritation is present, PI will classify as Mild, Moderate or Severe and confirm system compliance (wipes, lotion, patch rotation, etc.). Mild irritation may require up to 3 days without stimulation. Moderate irritation may require up to 2 weeks without stimulation. Severe irritation may require medical attention and study termination. PI or designee will assess when irritation is present and review for resolution. Treatment subjects will be discharged with the smartphone application and the Elira wearable patch system and instructions on use. Treatment subjects will be instructed to return with the Elira wearable patch system and smartphone app at their next scheduled visit. Treatment subjects may be contacted by PI or clinical coordinator periodically through the trial to address any questions or concerns related to device function. **End of Study Visit 8 (week 24; ± 7 days) –** Treatment & Control subjects will be assessed for adverse events, changes to concomitant medications and commitment to exclusion criteria. Physical including weight, requisition for laboratory tests, blood

	pressure, labs, and urine pregnancy test for FOCBP, and completion of questionnaires (– PHQ9, TFEQ-R18V2, and Patient Preference Survey). Collect, and review paper diaries. This visit may be rescheduled if the paper diaries were not completed the week prior. Treatment Group Only- Complete End of Study Questionnaires- subjects will return the Elira wearable patch system and the smartphone application. Treatment subjects will be assessed for ADEs and have their T6/T7 dermatome area examined. Treatment subjects will be photographed (below the neck) in similar attire to their initial visit for weight loss reference.
Study Endpoints	Primary Safety/Tolerability Endpoint: Safety/Tolerability will be assessed by the non-inferiority of incidence of serious adverse events (SAEs), unanticipated SAESs(USAEs), device-related SAEs (DSAEs) and Unanticipated Device Related SAEs (UDAEs) that are associated with the TENS therapy throughout the stimulation and the follow-up period versus historical control (compared with other TENS systems). Safety variables will be tabulated and presented for all subjects including enrolled, but discontinued, subjects. Number of subjects undergoing active stimulation and any reasons for discontinuation of study treatment will be tabulated. Safety/Tolerability will be assessed through 6 months of therapy. Primary Effectiveness Endpoint: The primary efficacy endpoint is the percent reduction in appetite suppression as measured by percent change in appetite scores at the end of 3 months of the Therapy period compared to Baseline between Treatment and Control. A co-primary endpoint will be total body weight loss (%TBWL), measured as End Weight – Initial Weight divided by Initial Weight, multiplied by 100, at the end of 3 months of the Therapy period compared to Baseline between Treatment and Control. Secondary Effectiveness Endpoints: Number of subjects reporting >5% total body weight loss at the end of 3 months of the Therapy compared to Baseline between Treatment and Control Blood pressure, blood lipids, and HbA1c at the end of 3 months of the Therapy compared to Baseline between Treatment and Control groups. % changes in BMI at the end of Therapy compared to Baseline between Treatment and Control groups Ancillary Endpoints: Cross validation between smartphone app hunger scales and paper VAS diaries collected at the same times. Changes between the following values: Ease of use/prevalence of use errors associated with the patch unit and dietary application during initial training. Subject preference scores at the end of Therapy compared to Baseline between Treatment and Control groups.

Statistical Analysis	**Statistical Analysis Plan, 2019MAY31** ELIRA -2 Trial: Safety and Effectiveness of Transcutaneous Electrical Nerve Stimulation (TENS)-Assisted Weight Loss and/or Appetite Suppression Protocol Number: CD-005, Original Date:2018MAY08, V4.1, Revised Date:2018AUG14 **Signature Page** Author: Michelle Secic _____ Date _____ Approver: _____ Date _____ Approver: _____ Date _____ **STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN** **General Methods** Categorical variables will be summarized by number and percent. Continuous variables will be summarized by total number (N), mean, standard deviation (SD), median, minimum and maximum. Ninety-five percent, 2-sided confidence intervals will be reported, as appropriate. As this was a randomized trial, the groups are expected to be balanced on demographic and baseline characteristics. No formal testing for this is planned. Planned analyses and summaries for the primary safety endpoint, co-primary efficacy endpoints, secondary efficacy endpoints and exploratory efficacy endpoints are detailed below. **Analysis Populations** The intent to treat (ITT) analysis population is defined as all subjects who were enrolled. The modified intent to treat (mITT) analysis population is defined as all subjects who initiated therapy (i.e., initiated their first Treatment Period Visit) and had data through week 12. All safety and effectiveness analyses will be completed on the mITT analysis population. The per protocol (PP) analysis population is defined as all subjects who met all inclusion/exclusion criteria, completed all visits in the study without any major protocol deviations. All effectiveness analyses will be completed on the PP analysis population.

Safety Analyses

The primary safety endpoint is defined as the proportion of subjects free of TENS-related serious adverse events and adverse device effects through the therapy phase, safety success rate. The success rates will be compared between groups using chi-square test or Fisher's exact test, as appropriate.

Efficacy Analyses

Co-Primary Efficacy Analyses

The percent change from baseline in the co-primary endpoints, appetite suppression scores, at the end of 3 months will be analyzed with analysis of covariance (ANCOVA), with a factor for group treatment and a baseline covariate for the appetite score at baseline. Specifically, the appetite suppression scores include four individual components (satisfied, full, hungry, eat from Table 1 of the diaries), each ranging from 0 to 100:

- How satisfied do you feel? 0=I am not hungry at all, 100=I have never been more hungry
- How full do you feel? 0=I am completely empty, 100=I cannot eat another bite
- How hungry do you feel? 0=Not full at all, 100=Totally full
- How much do you think you can eat? 0=Nothing at all, 100=A lot

These scores are captured in a diary once a week with 8 time points. The weeks are captured as week 0 through week 24. The time points at each week include:

- 30 minutes before breakfast
- 30 minutes after breakfast
- 60 minutes after breakfast
- 90 minutes after breakfast
- Pre-lunch
- Midafternoon
- 30 minutes before dinner
- Bedtime

For each of the four appetite suppression variables, the 8 time points at week zero will be average at week 0 for the baseline score (baseline), and the 8 time points at week 12 will be averaged at week 12 for the 3-month score (3month). Then the primary endpoint of the percentage change at 3 months will be calculated as: 100% x (3month – Baseline)/Baseline

Next, the percent change from baseline in the co-primary endpoint, %TBWL, at the end of 3 months will be analyzed with analysis of covariance (ANCOVA), with a factor for group treatment and a baseline covariate for the %TBWL at baseline.

Note that the ANCOVA analyses with last observation carried forward (LOCF) imputation for missing data on the mITT population for the co-primary endpoints are the main analyses for the study and if either %TBWL or any of the 4 appetite suppression variables result in statistical significance, then the study will be deemed a success.

Secondary Efficacy Analyses

	Area under the curve (AUC) statistics will be provided by group on each of the appetite suppression scores to assess the impact of the device on appetite at three months. AUC will be calculated using the trapezoidal method for total AUC across 3 months. To further understand the time points and weekly diary entries on appetite suppression, all time points and weekly entries will be analyzed in a repeated measures analysis of variance (RMANOVA) for each of the four appetite suppression endpoints separately. The RMANOVA will not use percentage changes but will use the actual appetite suppression scores with a factor for group treatment, time (week and time point), as well as the interaction factor between time and treatment. The occurrence rate for subjects experiencing >5% TBWL at the end of 3 months will be compared between groups using chi-square test or Fisher's exact test, as appropriate. Blood pressure, blood lipids, and HbA1c at the end of 3 months of the Therapy compared to Baseline between groups using t-tests or Wilcoxon rank sum tests, as appropriate. The percent change from baseline in BMI at the end of 3 months of the Therapy compared to Baseline between groups using t-tests or Wilcoxon rank sum tests, as appropriate. ***Exploratory Efficacy Summaries*** Summary statistics will be provided by visit and by group for the other time points (besides the 3 month time point) for percent change from baseline in appetite suppression scores, %TBWL, occurrence rate for >5% TBWL, blood pressure, blood lipids, and HBA1c. In addition, summary statistics will be provided by visit and by group for ease of use, prevalence of use errors associated with patch unit and dietary application, and preference scores. **Justification of Sample Size** As per the protocol, the calculation sample size for the study is based on conservative imputation of results from other studies on weight loss including the use of TENS for weight loss. The degree of coaching/dietary support throughout the present study is moderate intensity lifestyle/weight coaching. The sample size modeling assumes an average of 3.5% TBWL in Control Subjects using diet and exercise alone. The estimated weight loss in Treatment Subjects is modeled from preliminary data on T6/T7 dermatomal TENS when used for weight loss: 6% TBWL. The variance of the responses in the study (i.e. Standard Deviation) was modeled at +/- 5% TBWL. This value was taken from previous dermatomal TENS weight loss study results. The model assumes a 30% drop out rate across groups and an 80% powered endpoint using an adaptive p spending model wherein interim posterior probability assessments are allowed after enrolling proscribe cohorts of not less than 67% of subjects. The alpha penalty will be minimized per interim by assessing the relationship between stimulation (i.e. dose) and weight loss using Normalized Linear Dynamic Modeling (NLDM) to determine overall sample size projected (i.e. futility) rather than assessing the primary hypothesis per se. Monotonicity will not be assumed in this analysis. This modeling provides an estimate of 80 subjects per group, for a total study size of 160 subjects. However, the protocol allows for enrollment of additional subjects should the interim model project under powering of the primary endpoint. **Handling of Missing Data** Every effort will be made to collect all data at each time point in the study. The PI and the Clinical Data Monitor will minimize the amount of missing data by appropriate management of

	the prospective clinical trial, proper screening of subjects, and training of clinicians. If a subject misses a dietary entry in to either the paper or electronic diary, a look back entry for that value is allowed provide for the week preceding the event. Outside this window, data will be considered missing. All partial data available for subjects who drop out during the course of the study will be included. Missing data will only be imputed for the co-primary endpoints. The LOCF method will be utilized at the 3 month time point for the two co-primary endpoints of percent change from baseline in appetite suppression scores and %TBWL. The ANCOVA analysis with LOCF on the mITT population for the co-primary endpoints were planned for the main analyses for the study to determine study success. Note, however, by definition, the mITT population may not need LOCF as only those with a week 12 visit will be included in the mITT population. A patient, however, may have had a week 12 visit but have missing data on some or all co-primary endpoints, in which case LOCF methods will be used. To assess the potential effect of missing data on the co-primary effectiveness endpoints, a tipping point analysis will be computed for each co-primary endpoint on the mITT population. If none of the 5 co-primary endpoints are missing at week 12, the tipping point analysis will be a moot point and will not be conducted. A tipping point analysis involves imputing each missing data point, one-at-a-time until the study conclusion is tipped in the other direction (i.e., from statistically significant to non-statistically significant or vice versa, from non-statistically significant to statistically significant).
Risk/Benefit Analysis	If shown to be safe and effective, the therapy could eventually provide overweight/ moderately obese subjects a low risk option for appetite suppression and weight loss beyond diet and lifestyle modification alone. The potential adverse events and adverse device effects and risks associated with this study and the use of the patch System are identical to those normally associated with standard TENS system used for pain control and similar indications.

CONTACT LIST

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Statistical Analysis	Ian Welsford, PhD
Data Safety Monitoring Board	Virender K. Sharma, MD

1. INTRODUCTION

1.1 BACKGROUND

According to the Centers for Disease Control (CDC) up to 35% of adults over the age of 20 are obese, meaning they have a body mass index (BMI) of over 30 kg/m^2 while up to 69% of similarly aged adults are overweight, meaning they have a BMI of 25-30 kg/ m^2 ([1]; Appendix 1). Individuals who are overweight or obese are at high risk for adverse impacts to quality of life (QOL) factors including general health ([2]), pain ([3]) and psychosocial status ([4]). However, losing weight via calorie restriction dieting is notoriously difficult for such individuals ([2]). Sustained loss of even 5-10% of weight is uncommon with most dieters ([2, 3]) with most regaining nearly half of the lost weight after one year ([4]). While the precise physiological, sociological and genetic factors associated with weight gain and weight loss remain an area of intense investigation, what is becoming clear is that sustained weight loss requires long term calorie intake reduction ([2]), which, in turn, appears to require, among other factors, appetite control ([2, 4]). The purpose of the present non-significant risk (NSR) study is to investigate the effect of transcutaneous electrical nerve stimulation (TENS) on weight loss in overweight-to moderately (i.e. Type 1) obese individuals (i.e. BMI of 25 to 35 kg/ m^2 inclusive [15,16]; Appendix 1) with a long-term goal of determining if such an approach may be of benefit in assisting such individuals in achieving their weight loss goals.

1.2 PENS AND TENS FOR WEIGHT LOSS

Transcutaneous electrical nerve stimulation (TENS) involving the delivery of electrical current to subcutaneous nerve branches via an electrode placed on the skin surface is a well-established treatment modality for muscle pain, muscle atrophy and spasms as well as for pain associated with a variety of conditions including diabetic neuropathy. More recently this modality has been shown to be effective in treating certain symptoms associated with migraine headaches by delivering electrical stimulation to branches of the trigeminal nerve ([8]). A related therapy, Percutaneous Electrical Nerve Stimulation (PENS), in which electrode is inserted into the epidermis, is now in general medical usage for the treatment of urinary incontinence, fecal incontinence, and back pain ([5-8]).

The clinical evidence for a PENS effect on appetite and weight loss is provided by Ruiz-Tovar's study which demonstrated significant weight loss for PENS stimulation of dermatome T6 (the area of skin supplied by cutaneous branches of a single cranial or spinal nerve) via appetite suppression in a European sham control study of 105 subjects ([9]). Similar preliminary clinical results utilizing TENS have been reported in appetite control and subsequent weight loss by Dr. John Faul, a Stanford University researcher, who was granted a method patent (Transcutaneous Electrical Nerve Stimulator for Appetite Control) for his invention that uses TENS to stimulate the thoracic spine area at T6–T10. Each of these studies utilized obese subjects and provided stimulation only during in-clinic supervised sessions. The present study is designed to extend these preliminary studies by utilizing TENS in overweight-to Type 1 obese-subjects (i.e. BMI of between 25 and 35 kg/ m^2 inclusive [15,16]) stimulating in an outpatient/at home setting using a wearable, patch TENS system.

1.3 THE HYPOTHESIZED MECHANISM OF T6/T7 STIMULATION FOR APPETITE SUPPRESSION AND WEIGHT LOSS

The effect of PENS, and presumably, TENS, has been widely demonstrated by posterior tibial nerve neuro-stimulation in treating urinary and fecal incontinence, creating a somato-autonomic reflex ([10,11]; Figure 1). The definition of a somato-autonomic reflex is a reflex elicited by stimulation of somatic tissue (strictly speaking, tissue of the musculoskeletal system and the dermis of the skin), and manifesting as an alteration of the autonomic nervous

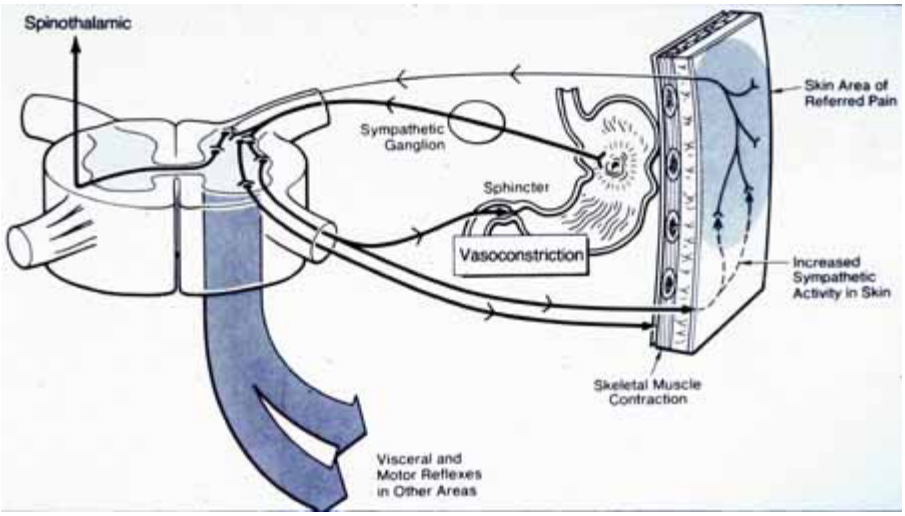


Figure 1: Somato-Autonomic Reflex Arc

system function (Figure 1). Altered autonomic nervous system functions may lead to changes in the function of dependent organs (like the stomach and other gastrointestinal organs), a situation sometimes referred to as a Somato-visceral reflex. To the PI's knowledge, the study cited by Ruiz-Tovar is the first to report using PENS of dermatome T6 to reduce appetite and, consequently, obtain a clinically-significant weight loss ([9]). It is likely that the effect is produced by the creation of a Somato-autonomic reflex in similar fashion to percutaneous electrical stimulation of the posterior tibial nerve in treating incontinence, but in this case suppressing appetite ([10]).

As supported by Dr. Faul's preliminary results ([9]), it is likely that similar results to PENS can be obtained using TENS to stimulate the same region, given the shallow 2 to 4 milimeter depth of sensory afferents throughout the target dermatome. Chen reported that electric gastric stimulation with a gastric pacemaker may affect the central nervous system by segregating hormones in the stomach and regulating satiety and/or appetite, with ghrelin being particularly involved in this mechanism ([11]). As shown by Ruiz-Tovar's study, the electric stimulation's main effect is appetite reduction. This study consisted of 105 subjects divided into 3 groups. Group 1 included 45 subjects who underwent dermatome T6 stimulation and maintained a 1,200 calorie diet and who were scheduled for bariatric surgery. These subjects had BMIs of greater than 40 or greater than 35 with co-morbidities. Group 2 included 45 subjects that maintained a 1,200 calorie diet only and who were scheduled for bariatric surgery. These subjects also had BMIs of greater than 40 or greater than 35 with co-morbidities. Group 3 included 15 subjects with a BMI greater than 30 who received sham stimulation (at the ankle) and who maintained a 1,200 calorie diet. Group 1, the treatment arm, evidenced dietary compliance in excess of 90% and achieved a significant weight loss success (equal to or greater than 5 kilograms (11 pounds) in 76.7% of subjects, as compared to Groups 2 and 3 where weight loss success was less than 6.7% and 0.0%, respectively. No complications were observed associated with the technique.

It thus appears likely that, through safely stimulating T6/T7 via TENS, a Somato-visceral reflex arc will be activated which will suppress appetite and support eventual weight loss in overweight and obese subjects.

2. STUDY RATIONALE

The purpose of the present study is to determine the safety and effectiveness of stimulation via a wearable patch TENS system of the T6/T7 dermatome on appetite suppression in adult (18 to

65 years of age inclusive), overweight/obese subjects (i.e. a BMI of 25 to 35 kg/m^2 inclusive[15, 16]; Appendix 1) who desire to lose weight. The study will seek thus to extend existing data on the use of dermatomal stimulation on obese and morbidly obese patient to subjects who are overweight/obese (i.e. a BMI of 25 to 35 kg/m^2 [15, 16]; Appendix 1).

2.1 JUSTIFICATION FOR STUDY GIVEN RISK/BENEFIT OUTCOME

Up to 35% of adults over the age of 20 in the United States are overweight. Being overweight places individuals at higher risk for a number of what are termed metabolic disorders including diabetes mellitus. This risk association is thought to be the reason for the high health care costs associated with overweight and obesity. While diet and exercise do show efficacy in a substantial subset of subjects, long term weight control is difficult to achieve for the vast majority of overweight individuals. The physiological and psycho-social reasons for this are not well characterized and likely highly complex, but a key component of this challenge is associated with appetite control. The present study seeks to determine if a method of appetite control utilizing T6/T7 dermatome stimulation in obese individuals can be utilized to the broader overweight population. The study utilizes non-invasive TENS stimulation within the range of the energy delivery well known to be safe for at-home use for nerve and muscle pain. Subjects will be informed of all potential side effects related to stimulation prior to enrollment and, throughout the study, subjects will be monitored and allowed to decrease or discontinue stimulus if any such side effects are deemed to be intolerable for participants.

In addition, since appetite and weight loss can be affected by a variety of physiological and psychosocial factors ([12,13, 15, 17]), the change in appetite will be measured weekly using a validated tool, the Visual Analog Scale (VAS[14]; See Appendix 3**)** and also assessed at baseline at the end of the study via administration of the Three Factor Eating Questionnaire R-18 V2 (TFEQ-R1V2[17, 18]). Please note that while the VAS was first developed for pain, it has been validated for weight loss/appetite applications ([14]) while the TFEQ-R18V2 has specifically been validated in weight loss applications ([17, 18]). The present study is not intended to be a formal validation of the assessment tool's applicability to the population targeted by the present study per se; it is intended simply as an assessment of potential changes in such parameters correlated with delivery of therapy during the study. Thus, the use of the tool as presented is considered scientifically valid.

Thus, the non-significant risk of the study is more than balanced by the potential societal benefit of the development of this novel, non-invasive appetite control method.

3. DEVICE DESCRIPTION

The TENS System consists of:

TENS Unit (Appendix 2)	ELIRA wearable Patch
Electronic Diary tool (Appendix 5)	Diary/dietary application running on and Android Smart-phone: 4.5" 720p HD TFT display Size (LWH): 2.6 inches, 0.46 inches, 5.1 inches Weight: 4.96 ounces
Device Accessories	Extra packs ELIRA electrodes Device/Phone Chargers Electronic Scale Plastic Phone Cover and System Pack

Other study accessories	TENS Clean-Cote Skin Wipes or **ALCOHOL** prep pads/wipes Cetaphil Moisturizing Lotion (16oz), and Paper diaries

4. STUDY OBJECTIVES

The objectives of this study are to demonstrate safety and effectiveness of a wearable patch TENS system (Appendix 2) in driving weight loss and appetite suppression when coupled with an integrated weight loss reduction strategy. The study is designed to demonstrate that TENS stimulation sufficient to drive weight loss and appetite suppression is safe and tolerable when compared to standard of care, and that adverse events/adverse device effects are similar to other TENS device use cases.

5. STUDY DESIGN

Randomized, adaptive parallel arm study. Subjects will be initially screened during a screening period (1 week, ±7 days; Figure 2). During this screening period, prior to study procedures being performed, subjects will sign an informed consent form. Then they will have their weight and blood pressure measured, FOCBP will have a pregnancy test, get blood drawn for analysis (blood lipids, HbA1c), and complete patient preference questionnaires. At the end of the screening/baseline period, eligible subjects will be offered the chance to enroll in the study. After enrolling, subjects will be randomized to treatment or control groups.

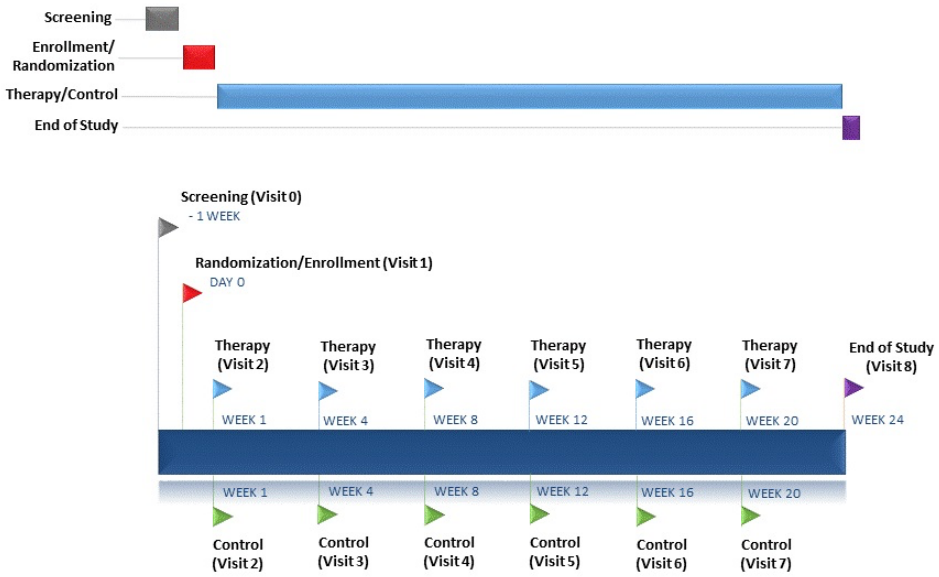
The Treatment group will be instructed to follow a healthy diet that they will follow for the duration of the study and will receive training on the use of the paper diaries, electronic scale, smartphone app and the Elira wearable patch system. All treatment subjects will be required to stimulate in the office for up to 30minutes to confirm sufficient system training and to acknowledge understanding stimulation settings. A below neck photograph will be taken of the treatment group in requested attire (i.e. biker shorts and sports bra for women, biker shorts for men). Following this, subjects will enter the Therapy Period, for a ~24-week duration. Treatment subjects may be contacted by PI or clinical coordinator to address any questions related to device functionality or compliance. Device usage will be monitored throughout therapy phase to ensure proper functionality and subject safety.

The Control group will be instructed to follow a healthy diet that they will follow for the duration of the study and will receive training on the use of the weekly paper diary and electronic scale. The Control group will not receive the electronic smartphone app or the Elira wearable patch system/components.

At the end of the 3 months of the Therapy Period, all subjects will be assessed for weight loss, blood pressure, blood lipids, HbA1c, and will continue to participate through months 4-6 to confirm the long term safety of the device prior to being terminated from the study. A below neck photograph will also be taken at the 12 week visit.

The Kaplan Meier estimator will be utilized to compare decrease in %Total Body Weight Loss (&TBWL) and appetite scores between treatment and control subjects. Maximum likelihood statistics will be utilized to correct for censoring. Z statistics will be calculated to ensure lack of skewness or curtosis and square root arc sine transformations will be undertaken on the data if required prior to analysis.

Figure 2: Study Outline



5.1 DOSING SCHEDULE

All Treatment Subjects will be trained in required rotation of the patch electrodes every 24h such that it is applied to varying locations on the T6/T7 dermatome. Each active therapy subject will receive up to 40 mA sustained current of stimulation for up to 30 minutes delivered within approximately 30min of meal time (pre-meal breakfast and dinner), not to exceed 75 min daily (including up to 3-5min rescue sessions). Based on tolerance of the therapy, a subject may decrease his or her dose by dropping one of the pre-meal sessions after receiving approval from a clinical coordinator and/or PI. Subjects who do not experience sufficient appetite suppression may also add up to 3 between meal 5min rescue sessions delivered after receiving approval from a clinical coordinator and/or PI. The nominal stimulation dose per day for any subject will thus be 1200 mA (60 minutes at 20 mA) while the maximum dose for any given subject will be 3900 mA (90 minutes at 40 mA and rescue sessions).

During the therapy period, Treatment Subjects will undergo initial assessments to ensure they are familiar with the device, the daily electronic diary, weekly paper diary, and diet options. All subjects (Treatment and Control) will be required to undergo follow-up assessments at least once per every 4 weeks during the study. Additional unscheduled visits per subject will be permitted during the study to address issues related to subject safety. PI and/or clinical coordinator will oversee any adjustments to treatment dosing or stimulation parameters and may contact treatment subjects to address any concerns regarding device functionality.

5.2 DATA COLLECTION:

All subjects will be asked to keep a VAS paper diary (hunger, appetite, weight and diet) in which they will record such values weekly. Subjects will record their diary variables. For treatment

subjects, any adjustments to stimulation session schedule will be recorded within the electronic diary and by clinical coordinators.

5.3 ASSIGNMENT & BLINDING

Subjects meeting the Inclusion and Exclusion criteria will be enrolled and randomized into either Treatment or Control groups. The randomization algorithm will be blocked to account for site bias and to ensure counterbalance across sites. As this is an open label study, there will be no consideration for blinding.

6. STUDY ENDPOINTS

6.1 PRIMARY ENDPOINTS

6.1.1 Primary Safety/ Tolerability Endpoints:

- Safety/Tolerability will be assessed by the non-inferiority of incidence of serious adverse events (SAEs), unanticipated SAES (USAEs), device-related SAEs (DSAEs) and Unanticipated Device Related SAEs (UDAEs) that are associated with the TENS therapy throughout the therapy/treatment period versus historical control.
- Safety variables will be tabulated and presented for all subjects including enrolled, but discontinued, subjects. Number of subjects undergoing TENS and any reasons for discontinuation of study treatment will be tabulated.
- Safety variables will be collected over a 6 month duration.

6.1.2 Primary Effectiveness Endpoint:

The primary efficacy endpoint is the percent reduction in appetite suppression as measured by percent change in appetite scores at the end of 3 months of the Therapy period compared to Baseline between Treatment and Control.

A co-primary endpoint will be total body weight loss (%TBWL), measured as End Weight – Initial Weight divided by Initial Weight, multiplied by 100, at the end of 3 months of the Therapy period compared to Baseline between Treatment and Control.

6.1.3 Secondary Effectiveness Endpoints:

- Number of subjects reporting >5% total body weight loss at the end of 3 months of the Therapy period as compared to Baseline between Treatment and Control
- Blood pressure, blood lipids, and HbA1c at the end of 3 months of the Therapy Period as compared to Baseline between Treatment and Control groups.
- % changes in BMI at the end of 3 months of the Therapy Period compared to Baseline between Treatment and Control groups.

6.1.4 Ancillary Endpoints:

- Cross validation between smartphone app hunger scales and paper VAS diaries collected at the same times.

Changes between the following values:

- Ease of use/prevalence of use errors associated with the patch unit and dietary application during initial training.
- Subject preference scores at the end of Therapy Period compared to Baseline between Treatment and Control groups.

6.2 ENDPOINT DEFINITIONS & RECORDING METHODS

Endpoint data in hunger, appetite, and dietary compliance are obtained from subject reported assessments (Appendix 4, 5). That is, the measurement of success is based on the subject's report of the parameter using validated tools where available.

Primary source data will be paper based, with each subject receiving diary worksheets to record responses. Treatment subjects will also be assigned an Android Smart Phone onto which has been loaded a copy of custom dietary application (Appendix 5). Subjects will be trained on the use of these tools and assessed for accurate use prior to taking them home. To ensure data privacy, the network interface card (i.e. SIM card) for the phone will be removed such that data can only be downloaded *via* a direct USB link.

7. STUDY POPULATION

7.1 INCLUSION CRITERIA

7.1.1 Subject is between 18 – 65 years of age inclusive.

7.1.2 Subject has a BMI of 25-35 kg/ m^2 inclusive.

7.1.3 Subject has signed the informed consent form and is able to comply with study protocol and adhere to study visit schedule.

7.1.4 Subject is able to wear and use a wearable, patch TENS system.

7.1.5 Subject is able to use a touch screen hand held smart phone.

7.1.6 Subject is fluent in English and can complete questionnaires.

7.1.7 Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at screening or enrollment visit, prior to placement of ELIRA device.

7.1.8 Subject is male or non-pregnant, non-lactating female, who agrees to use effective contraceptive methods throughout the length of the trial based on PI approval.

7.2 EXCLUSION CRITERIA

7.2.1 Subject has any known gastrointestinal disorder that in the opinion of the PI precludes enrollment into the trial.

7.2.2 Subject has had a prior bariatric procedure or any previous procedure on the stomach.

7.2.3 Subject has any significant multisystem disease in the opinion of the PI.

7.2.4 Subject has > 6.5 HbA1c.

7.2.5 Subject has significant cardiac arrhythmia, ectopy, or significant cardiovascular disease.

7.2.6 Subject has an existing implanted electrical stimulator (e.g., pacemaker, AICD).

7.2.7 Subject is a female of child-bearing potential who is pregnant or intends to become pregnant during the trial period.

7.2.8 Subject has current and/or a history of cancer within the past 5 years (not including basal cell carcinoma or cervical carcinoma in situ).

7.2.9 Subject has had a weight change of $\pm$ 5% of his/her Total Body Weight in the 3 months prior to screening.

7.2.10 Subject has a moderate / severe psychiatric disorder.

7.2.11 Subject has a diagnosed neurological disease.

7.2.12 Subject has a diagnosed eating disorder.

7.2.13 Subject has a skin disorder affecting the thoracic dermatomes.

7.2.14 Subject has active or /has ever had shingles in the abdominal area.

7.2.15 Subject has abdominal surgery or other scars which may interfere with TENS stimulation in the opinion of the PI.

7.2.16 Subject is currently enrolled in other potentially confounding research.

7.2.17 Subject has known allergic reaction to materials in the TENS electrodes and/or is otherwise unable to tolerate stimulation with the wearable TENS system. This includes known allergies to latex, nickel and/or hydrogels.

7.2.18 Subject has a history of sensitive skin, including eczema wheel-and-flare or other skin irritation, per PI discretion.

7.2.19 Subject is actively participating or unwilling to discontinue participation in another weight loss program. Subjects may not enroll in paid or unpaid programs that involve in-person or online apps or coaching, beginning new fitness regimens or utilizing meal planning or paid nutritional coaching during the course of the ELIRA study

7.2.20 Subject is taking weight loss control medications including but not limited to OTC medications, Metformin, and Belviq. (See Appendix 8)

7.2.21 Subject is planning any major medical treatments or surgeries that could cause weight loss.

7.2.22 Subject is unable to take anti-nausea medications planned for the study.

7.2.23 Inability to walk at least 0.8 kilometers per day (10 minutes of continuous walking).

7.2.24 Current smoker or user of nicotine product or smoking cessation within 1 year of the screening date.

7.2.25 History of treatment for or current abuse of drug or alcohol.

7.2.26 A score of ≥10 on the Patient Health Questionnaire 9 (PHQ-9), demonstrating moderate depression.

7.2.27 Any subject that the investigator considers inappropriate for the study for medical reasons.

7.2.28 Subject has a history of moderate/severe migraines or other severe headache disorders requiring the treatment of Topiramate.

7.2.29 Subject is on drug therapy which may alter antral motility or appetite, per PI discretion. (Appendix 8).).

7.3 SELECTION AND ENROLLMENT OF SUBJECTS

Prospective study subjects will be screened for study eligibility. A subject is considered enrolled after:

1. Written Informed Consent is obtained.
2. Meeting all inclusion and exclusion criteria and randomized into the study.
3. This study will utilize unique subject numbers for the purpose of trial data collection. Subjects signing an Informed Consent but not meeting all criteria will not be considered enrolled in the study, but the signed Informed Consents will be maintained by the PI for seven (7) years.

Following enrollment, subjects should remain in the study until completion of the required Therapy Phase.

A subject's participation may be discontinued for the following reasons:

- Subject Withdrawal: As subject participation in a clinical trial is voluntary, the subject may choose to discontinue participation at any time without penalty or loss of benefits.

- Investigator Termination: The Investigator may terminate the subject's participation without regard to the subject's consent if the Investigator believes termination is medically necessary.
- Lost-to-Follow-up: A subject is lost-to-follow up if he/she does not complete required follow-up, but has not "officially" withdrawn consent. In order to consider a subject lost to follow-up, site personnel should make all reasonable efforts to locate and communicate with the subject. A minimum of three (3) attempts to contact the subject should be recorded in the source documentation including date, time and name of site personnel attempting to make contact.

8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Statistical Analysis Plan, 2019MAY31

ELIRA -2 Trial: Safety and Effectiveness of Transcutaneous Electrical Nerve Stimulation (TENS)-Assisted Weight Loss and/or Appetite Suppression

Protocol Number: CD-005, Original Date:2018MAY08, V4.1, Revised Date:2018AUG14

Signature Page

Author: Michelle Secic _____ Date _____

Approver: _____ Date _____

Approver: _____ Date _____

8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

8.1.1 General Methods

Categorical variables will be summarized by number and percent. Continuous variables will be summarized by total number (N), mean, standard deviation (SD), median, minimum and maximum. Ninety-five percent, 2-sided confidence intervals will be reported, as appropriate.

As this was a randomized trial, the groups are expected to be balanced on demographic and baseline characteristics. No formal testing for this is planned.

Planned analyses and summaries for the primary safety endpoint, co-primary efficacy endpoints, secondary efficacy endpoints and exploratory efficacy endpoints are detailed below.

8.1.2 Analysis Populations

The intent to treat (ITT) analysis population is defined as all subjects who were enrolled.

The modified intent to treat (mITT) analysis population is defined as all subjects who initiated therapy (i.e., initiated their first Treatment Period Visit) and had data through week 12. All safety and effectiveness analyses will be completed on the mITT analysis population.

The per protocol (PP) analysis population is defined as all subjects who met all inclusion/exclusion criteria, completed all visits in the study without any major protocol deviations. All effectiveness analyses will be completed on the PP analysis population.

8.1.3 Safety Analyses

The primary safety endpoint is defined as the proportion of subjects free of TENS-related serious adverse events and adverse device effects through the therapy phase, safety success rate. The success rates will be compared between groups using chi-square test or Fisher's exact test, as appropriate.

8.1.4 Efficacy Analyses

Co-Primary Efficacy Analyses

The percent change from baseline in the co-primary endpoints, appetite suppression scores, at the end of 3 months will be analyzed with analysis of covariance (ANCOVA), with a factor for group treatment and a baseline covariate for the appetite score at baseline. Specifically, the appetite suppression scores include four individual components (satisfied, full, hungry, eat from Table 1 of the diaries), each ranging from 0 to 100:

- How satisfied do you feel? 0=I am not hungry at all, 100=I have never been more hungry
- How full do you feel? 0=I am completely empty, 100=I cannot eat another bite
- How hungry do you feel? 0=Not full at all, 100=Totally full
- How much do you think you can eat? 0=Nothing at all, 100=A lot

These scores are captured in a diary once a week with 8 time points. The weeks are captured as week 0 through week 24. The time points at each week include:

- 30 minutes before breakfast
- 30 minutes after breakfast
- 60 minutes after breakfast
- 90 minutes after breakfast
- Pre-lunch

- Midafternoon
- 30 minutes before dinner
- Bedtime

For each of the four appetite suppression variables, the 8 time points at week zero will be average at week 0 for the baseline score (baseline), and the 8 time points at week 12 will be averaged at week 12 for the 3-month score (3month). Then the primary endpoint of the percentage change at 3 months will be calculated as:

100% x (3month – Baseline)/Baseline

Next, the percent change from baseline in the co-primary endpoint, %TBWL, at the end of 3 months will be analyzed with analysis of covariance (ANCOVA), with a factor for group treatment and a baseline covariate for the %TBWL at baseline.

Note that the ANCOVA analyses with last observation carried forward (LOCF) imputation for missing data on the mITT population for the co-primary endpoints are the main analyses for the study and if either %TBWL or any of the 4 appetite suppression variables result in statistical significance, then the study will be deemed a success.

Secondary Efficacy Analyses

Area under the curve (AUC) statistics will be provided by group on each of the appetite suppression scores to assess the impact of the device on appetite at three months. AUC will be calculated using the trapezoidal method for total AUC across 3 months.

To further understand the time points and weekly diary entries on appetite suppression, all time points and weekly entries will be analyzed in a repeated measures analysis of variance (RMANOVA) for each of the four appetite suppression endpoints separately. The RMANOVA will not use percentage changes but will use the actual appetite suppression scores with a factor for group treatment, time (week and time point), as well as the interaction factor between time and treatment.

The occurrence rate for subjects experiencing >5% TBWL at the end of 3 months will be compared between groups using chi-square test or Fisher's exact test, as appropriate.

Blood pressure, blood lipids, and HbA1c at the end of 3 months of the Therapy compared to Baseline between groups using t-tests or Wilcoxon rank sum tests, as appropriate.

The percent change from baseline in BMI at the end of 3 months of the Therapy compared to Baseline between groups using t-tests or Wilcoxon rank sum tests, as appropriate.

Exploratory Efficacy Summaries

Summary statistics will be provided by visit and by group for the other time points (besides the 3 month time point) for percent change from baseline in appetite suppression scores, %TBWL, occurrence rate for >5% TBWL, blood pressure, blood lipids, and HBA1c. In addition, summary statistics will be provided by visit and by group for ease of use, prevalence of use errors associated with patch unit and dietary application, and preference scores.

8.2 Justification of Sample Size

As per the protocol, the calculation sample size for the study is based on conservative imputation of results from other studies on weight loss including the use of TENS for weight loss. The degree of coaching/dietary support throughout the present study is moderate intensity lifestyle/weight coaching. The sample size modeling assumes an average of 3.5% TBWL in Control Subjects using diet and exercise alone. The estimated weight loss in Treatment Subjects is modeled from preliminary data on T6/T7 dermatomal TENS when used for

weight loss: 6% TBWL. The variance of the responses in the study (i.e. Standard Deviation) was modeled at +/- 5% TBWL. This value was taken from previous dermatomal TENS weight loss study results. The model assumes a 30% drop out rate across groups and an 80% powered endpoint using an adaptive p spending model wherein interim posterior probability assessments are allowed after enrolling proscribe cohorts of not less than 67% of subjects. The alpha penalty will be minimized per interim by assessing the relationship between stimulation (i.e. dose) and weight loss using Normalized Linear Dynamic Modeling (NLDM) to determine overall sample size projected (i.e. futility) rather than assessing the primary hypothesis per se. Monotonicity will not be assumed in this analysis. This modeling provides an estimate of 80 subjects per group, for a total study size of 160 subjects. However, the protocol allows for enrollment of additional subjects should the interim model project under powering of the primary endpoint.

8.3 Handling of Missing Data

Every effort will be made to collect all data at each time point in the study. The PI and the Clinical Data Monitor will minimize the amount of missing data by appropriate management of the prospective clinical trial, proper screening of subjects, and training of clinicians. If a subject misses a dietary entry in to either the paper or electronic diary, a look back entry for that value is allowed provide for the week preceding the event. Outside this window, data will be considered missing. All partial data available for subjects who drop out during the course of the study will be included.

Missing data will only be imputed for the co-primary endpoints. The LOCF method will be utilized at the 3 month time point for the two co-primary endpoints of percent change from baseline in appetite suppression scores and %TBWL. The ANCOVA analysis with LOCF on the mITT population for the co-primary endpoints were planned for the main analyses for the study to determine study success. Note, however, by definition, the mITT population may not need LOCF as only those with a week 12 visit will be included in the mITT population. A patient, however, may have had a week 12 visit but have missing data on some or all co-primary endpoints, in which case LOCF methods will be used.

To assess the potential effect of missing data on the co-primary effectiveness endpoints, a tipping point analysis will be computed for each co-primary endpoint on the mITT population. If none of the 5 co-primary endpoints are missing at week 12, the tipping point analysis will be a moot point and will not be conducted. A tipping point analysis involves imputing each missing data point, one-at-a-time until the study conclusion is tipped in the other direction (i.e., from statistically significant to non-statistically significant or vice versa, from non-statistically significant to statistically significant).8.4 Subject Population for Safety and Effectiveness Analysis

Safety analyses will be conducted an Intent to Treat (ITT) basis (i.e. all subjects who were enrolled). Primary and Secondary effectiveness analyses will be performed on a modified intent-to-treat basis (MITT; i.e. all subjects who initiated therapy, defined as subjects who initiated their first Treatment Period Visit) as will all per subject effectiveness analyses (e.g. responder analyses). Primary and Secondary endpoints (e.g. weight loss, appetite) will also be conducted on a completer, or per protocol basis (defined as those subjects that completed all visits in the study).

8.5 Deviations from the statistical analysis plan

Any deviations in the analysis of the final data set from the statistical analysis plan will be documented and justified in the final report.

9. STUDY PROCEDURES

The study is divided into four phases as defined below (See Appendix 66 for Schedule of Visits):

Study Phase	Definition
Screening Visit	Obtain Informed Consent. Completion of Pre-Study Survey. Determination of Inclusion and Exclusion criteria (including PHQ-9 questionnaire; Appendix 3), Medical History and Physical, Obtain Concomitant Medications, Weight Loss History, Blood Pressure, Height and Weight, Blood Tests (including a lipid panel, HbA1c, and Urine Pregnancy Test for FOCBP. Dispense and Instruct on completion of Weekly Diary.
Randomization / Enrollment Visit	Confirm Inclusion/Exclusion criteria has been met, Weight, blood pressure, and AEs/Concomitant Medications assessed. Completion of baseline TFEQ-R18V2 (Appendix 4). Assessment of T6/T7 Dermatomes, UPT for FOCBP (if not done at screening). Completion of pre-enrollment photographs. Randomization of subject. For both groups (control and treatment) train and dispense paper diaries and electronic scale, encourage low-calorie diet for duration of study, provide Diet Resources sheet (Appendix 18.11) In Addition, For Treatment Group only, training) and assessment of use of smart phone app and Elira wearable patch system (Appendix 2); Initiation of therapy and dose adjustment. Provide TENS Clean-Cote Skin Wipes and/or Alcohol Prep Pads and Cetaphil Moisturizing Lotion with instructions on use, following a healthy low-calorie diet, as needed, dispense smart phone app and Elira wearable patch system. ELIRA Device training (Treatment Group). Paper VAS sheets
Therapy Period	For Control and Treatment Groups: Confirm Inclusion/Exclusion criteria continues to be met, collect blood pressure, AEs, and review Adverse Device Events, paper diary (dispense additional diaries), weight, blood pressure, assess for AE's/concomitant medications, completion of hunger and Completion of TFEQ-R18V2, encourage continuation of low-calorie diet at each scheduled visit. Blood Tests taken at 12 weeks for lipids and HbA1c. Photographs will be taken at 12 weeks . In Addition, For Treatment Group only: assess for Adverse Device Effects at each visit. Collect Elira wearable patch system and smart phone and download data, assess subjects use of electronic diary, completion paper sheets and stimulation sessions at each visit. Dispense smart phone app and Elira wearable patch system at each visit.
End of Study Visit	For Control and Treatment Groups: Collect the weekly paper diary (if subject has not completed the weekly paper diary, he/she will reschedule the end of study visit for one week later to allow time for completion), Physical, weight, blood pressure, assess for AE's/concomitant medications, UPT for FOCBP, blood pressure, completion of PHQ9, TFEQ-R18V2, End of Study Survey, Blood Tests (including a lipid panel and HbA1c) and photography.

	In Addition, Treatment Group only: assess for Adverse Device Effects, collect Elira Wearable patch system and smart phone and download data, assess subjects use of electronic diary completion and stimulation sessions. Assess T6/T7 dermatomes. Complete End of Study Questionnaire.

9.1 INFORMED CONSENT

Prior to subject participation in this study, the PI or designee must obtain written Institutional Review Board (IRB) approval for the protocol and the Informed Consent Form.

Once the subject's eligibility has been determined, the Investigator or person designated by the Investigator who has been trained to the Protocol, will explain the nature and scope of the study, discuss potential risks and benefits of participation, answer all questions from the subject and ask the subject to participate in the study. The study will be explained to the study subject in lay terms. If the subject agrees to participate, the Informed Consent must be personally signed and dated by the subject and the Investigator or person designated by the Investigator. Any additional persons required to sign the Informed Consent by the IRB will also do so. A copy of the signed and dated Informed Consent must be provided to the study subject. Study subjects will be assured that they may withdraw from the study at any time and for any reason.

Failure to obtain a signed Informed Consent prior to the procedure constitutes a major Protocol deviation.

9.2 SCREENING PROCEDURES

All candidates must be screened for eligibility. A member of the research team assigned to the study should review the subject's medical history to screen for eligibility.

The following tests and procedures must be performed prior to TENS therapy:

- Physical examination, medication history, height, weight and BMI.
- Relevant medical history including subject demographic information and weight loss history.
- Patient Preference Survey and PHQ-9.
- Urine Pregnancy Test (UPT) for FOCBP; blood lipid panel, HbA1c.

9.3 PHYSICAL EXAMINATIONS

A general physical examination will be performed as well as an examination of organ systems (central nervous system [CNS], cardiac, peripheral vascular, pulmonary, musculoskeletal, abdominal, dermatologic and lymphatic). The dermatologic exam will focus on Dermatome T6-T7 site for any active disease, scars, tattoos, or other problems that would make the site unacceptable for the TENS Unit. Depilation by waxing, shaving, chemical depilatories or any other method in the selected application site is not allowed during the study.

9.4 BODY MASS INDEX

Height and weight without shoes will be used to determine body mass index (BMI) in accordance with the BMI Chart ([15,16]; Appendix 1) and confirmed by NIH BMI Calculator. Subjects will be encouraged to wear the same or similar clothing at each visit for more consistent weight measurements.

9.5 MEDICAL HISTORY AND DEMOGRAPHICS

A complete medical history evaluation, including surgical history and demographic data (age, gender, race, ethnicity, and highest level of education) and weight loss history will be obtained for each subject.

9.6 VITAL SIGNS

Blood Pressure (sitting position after 3 minutes rest) will be measured.

9.7 MEDICATIONS

All medications must be reported on the appropriate case report form (CRF) through the end of study. Medications must remain stable from Screening/Baseline through the Therapy Phase of the study. The only exception is medications may be changed for subject health or safety reasons (but not specifically to attempt to reduce weight loss or appetite).

9.8 QUESTIONNAIRES

All subjects will be required to complete the Pre-Study Survey and PHQ-9 at screening/baseline visit. All subjects will be required to complete a VAS diary for hunger and fullness according the following schedule: 1 day with 8 entries following enrollment (approximately week 0-1), 1 day with 8 entries following the 4, 8, 12, 16 and 20-week visit (approximately week 4) and 1 day with 8 entries in the last week of the study (approximately week 24). All subjects will be required to complete the TFEQ-R18V2 at enrollment and at each Therapy Visit (Appendix 3). All subjects will be required to complete PHQ9-, TFEQ-R18V2 and End of Study Questionnaire at the last study visit (Visit 8 or early termination visit).

9.9 URINE PREGNANCY TESTS (UPT)

A urine pregnancy test will be done in the clinic for all females of child-bearing potential (FOCBP) prior to enrollment in the study. The results will be recorded. This can be completed either at Screening Visit (Visit 0) or Randomization/Enrollment Visit (Visit 1) and at the end of study visit.

9.10 DIET

Subjects will be encouraged to maintain a healthy lowcalorie diet throughout the study. The study doctor and/or research coordinator will provide guidance to assist the subjects on maintaining the diet.

9.11 ELECTRONIC DAILY DIARY DEVICE

For Treatment Group Subjects only, an Android Smart Phone running a semi-custom daily diary application to capture hunger, calories, and weight will be provided. Subjects will be instructed on use by PI or designee.

9.12 STIMULATION

Refer to the Programming Manual provided with the TENS System for full details on the use of the System (Appendix 2). The subject should be instructed to bring their diary (Appendix 5) to the Investigator's office for all office visits to allow for proper downloading of data.

9.12.1 General information on Stimulation:

The TENS unit utilizes low intensity electrical stimulation to activate nerve endings under the skin. While response to TENS varies typically subjects report a mild tingling or burning sensation during and immediately after stimulation session. In addition, mild numbness, termed paresthesia, may be experienced.

9.12.2 Starting the Therapy Phase

During the Therapy Phase, the subject's TENS is programmed to the following settings:

Parameter	Suggested Initial Setting
Frequency	20 Hz (up to 120Hz)
Pulse-Width	200μs
Amplitude	20mA (Up to 40 mA)

It is also important that the subject complete the diary during this period. If subject does not feel sensation, subject is to notify PI or Coordinator because it may indicate improper device function. The TENS unit will be replaced if dropped or becomes defective and non-functioning. It is recommended that subjects confirm response to stimulation during the office visits.

10. RISK ANALYSIS

A detailed description of the potential risks associated with specific aspects of the TENS System and diary use are detailed below:

10.1 RISKS

10.1.1 Application and post application risks

While the TENS unit utilized in the present study delivers therapy in a comparable manner to standard commercially available TENS units, there are some risks associated with the device. These include skin irritation at the site of electrode application, numbness and tingling, pain and burning sensations at the site of stimulation. Skin irritation may be mild, moderate or severe based on skin sensitivity. Study design and PI/staff training has been implemented to maintain subject safety. In addition, there is some chance that subjects may feel some gastrointestinal (GI) symptoms including nausea or other GI discomfort (heartburn, dyspepsia, cramping). Dropping the unit may cause damage to the TENS unit. Subjects are instructed to avoid use of the device if it has been damaged in any way and not to use the device while it or any portion of the subject are immersed in water. Subjects are instructed to contact PI or designee, if therapeutic sensation is not present. Any discomfort associated with TENS should be immediately reported to the PI or designee.

10.1.2 Risks associated with appetite loss

While appetite loss is beneficial to weight loss, severe appetite suppression may place the subject at risk for hypoglycemia and dehydration which may entail risks to alertness and other conditions. Prolonged appetite suppression can cause alterations in mood and mental acuity and impact activities of daily living (ADL).

Adverse Events: The adverse events listed below are anticipated to occur at low frequency, and the subject needs to be aware that they may occur.

<u>From TENS:</u>
Paresthesia
Burning sensation
Pain
Skin irritation (urticaria) at or near the electrode application site

Redness at site of stimulation
Mild swelling at site of electrode stimulation
Nausea
GI discomfort
Dyspepsia
Heartburn
Cramping
Gastroparesis

From appetite loss:
Mild hypoglycemia
Dehydration
Alterations in mood
Mild trouble sleeping
Alterations in mental acuity
Anorexia

From potential use of anti-nausea medication (PI Discretion):
Drowsiness
Dizziness
Constipation
Stomach upset
Blurred vision
Dry mouth/nose/throat may occur
Mental/mood changes (such as restlessness, confusion)
Difficulty urinating
Fast/irregular heartbeat

From potential use of Cetaphil Moisturizing Lotion
Irritation
Swelling

10.2 MINIMIZATION OF RISKS

Although all of the risks associated with the application and use of the TENS System and their respective frequencies may not be fully known at this time, the preceding risks have been identified through an extensive literature search and represent the most up to date understanding of risks associated with such a study and have been subjected to verification and validation testing to ensure that risks have been mitigated to the extent possible. All efforts will be made throughout the course of the trial to minimize these risks by:

1. Selecting an Investigator who is experienced and skilled in weight loss and TENS use;
2. Using clearly defined Inclusion/Exclusion criteria to ensure that only appropriate subjects are enrolled;
3. Ensuring that the treatment and follow-up procedures are consistent with current medical practices. Each subject will receive more extensive clinical follow-up than would typically be the case for standard care. These additional clinical follow-ups should increase the likelihood of early detection of any adverse events;

4. Utilizing a TENS designed so that it can be easily be applied and removed if necessary. Device monitoring will be conducted throughout the Therapy Phase to ensure subject safety.

11. ADVERSE EVENTS: DEFINITIONS & REQUIREMENTS

At each evaluation, the Investigator will determine whether any adverse events (AEs) have occurred. For the purpose of this Protocol, an AE is any undesirable clinical occurrence in a subject whether or not related to the investigational treatment. Any pre-existing condition that exhibits a change in nature, severity or degree of incidence during the clinical study is an AE. This definition does not depend on a causal relationship with the device or the Protocol requirements. AEs will be tracked and categorized as outlined within the present protocol.

Subjects are encouraged to report AEs with or without questioning (e.g., How has your health been since the last visit?). If it is determined that an AE has occurred, the Investigator will obtain all the information required to complete the AE Case Report Form.

In addition, subjects will be instructed to contact the Investigator and/or designee if any significant AEs occur between study evaluation visits. Serious AEs and unanticipated adverse device effects will be collected throughout the entire course of the study.

The Investigator will use the following definitions to assess the relationship of the AE to the use of the TENS system and/or daily electronic diary:

Not Related	▪ Not associated with device application ▪ Due to an underlying or concurrent illness or effect of another device or drug
Unlikely	▪ Little or no temporal relationship to the study device **and/or** ▪ A more likely alternative etiology exists
Possible	▪ Temporal sequence between device application and event is such that the relationship is not unlikely **or** ▪ Subject's condition or concomitant therapy could have caused the AE
Probable	▪ Temporal sequence is relevant **or** ▪ Event abates upon device application completion/removal **or** ▪ Event cannot be reasonably explained by the subject's condition
Highly Probably	▪ Temporal sequence is relevant **and** ▪ Event abates upon device application completion/removal **or** event recurs on repeated device application

11.1 SERIOUS ADVERSE EVENTS

All Serious Adverse Events (SAEs) must be reported to the PI (or designee) and sponsor within 24 hours after any clinical staff member becomes aware of the incident.

An Adverse Event is considered **serious** if the event:

- Led to a death
- Led to a serious deterioration in the health of the subject that:
  - Resulted in a life-threatening illness or injury;
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required in-subject hospitalization or prolongation of existing hospitalization;
  - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function;

All SAEs need to be followed until the event is resolved (with or without sequelae). The PI or designee will decide if more follow-up information is needed in case the event is not resolved at study completion. In case of death, all possible information that is available (e.g., autopsy or other post-mortem findings), including the possible relationship to the TENS System and/or daily electronic diary should be provided.

11.2 UNANTICIPATED ADVERSE DEVICE EFFECTS

An unanticipated adverse device effect is defined as any 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 the Protocol or Supplementary Protocol.

The Investigator must also report the unanticipated adverse device effect to the Institutional Review Board (IRB) within their pre-specified timeline.

12. SPONSOR RESPONSIBILITIES, RECORDS, AND REPORTS

12.1 GENERAL RESPONSIBILITIES

The Principal Investigator (PI) maintains the overall responsibility for this study including ensuring that the study is conducted according to the regulatory requirements of the United States Food and Drug Administration (FDA) (Code of Federal Regulations Title 21), Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements, the Protocol, and any conditions of approval imposed by the Institutional Review Board (IRB) and the relevant Competent Authorities. The PI will adhere to general duties as outlined by 21 CFR and GCP.

12.2 SELECTION OF CLINICAL INVESTIGATORS SITE

The PI and the site are qualified according to these criteria:

- Adequate subject population available to meet the requirements of the study
- Adequate time to be personally involved in the study
- Adequate research staff and resources to support the study
- Willingness to take the primary responsibility for the accuracy, legibility, and security of all study data
- Willingness to observe confidentiality at all times
- Associated with an IRB which satisfies all regulatory authority requirements and conducts meetings on a regular basis
- Access to appropriate emergency medical facilities if needed
- Other requirements as previously noted in Protocol

12.3 TRAINING OF INVESTIGATOR AND SITE PERSONNEL

The training of the Investigator and appropriate clinical site personnel will be the responsibility of the PI, or designee, and may be conducted during a site initiation visit or other appropriate meetings.

12.4 MONITORING

A Monitor will be assigned to perform source document review to be performed against entries on the Case Report Form for the data related to safety and performance outcomes, and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations.

All data entered by the subject onto the electronic diary will be uploaded onto a secure, central database. The data in the database are considered source documentation and are protected by

auditable change logs. The data and change logs may be monitored by the Clinical Data Monitor to confirm data integrity. Further efforts to ensure data privacy and integrity include the removal of the network interface (a.k.a. SIM) card from the handheld Smart Phones used in the study to ensure that only controlled data download/upload conducted by study coordinators can occur.

At the completion of the study, the assigned monitor will perform a close-out visit to ensure that all clinical trial materials and subject data are properly documented.

If a member of the research team becomes aware that any individual associated with the study is not complying with the signed Investigator Agreement, the Protocol, the Declaration of Helsinki, or other applicable regulatory requirements, or any conditions of approval imposed by the IRB or Regulatory Authorities, the PI will either secure compliance or, failing to secure compliance, will discontinue the individual's participation in the investigation.

12.5 REPORTS

The sponsor will submit appropriate reports to the Regulatory Authorities or the investigational site as identified by local regulations. These include unanticipated adverse device effects, withdrawal of IRB approval or Regulatory Authority approval, annual progress reports, recall information, final reports and device use without Informed Consent.

12.6 RECORD MAINTENANCE

The clinical site will maintain study records for at least seven (7) years after the study is terminated or according to site and country specific requirements.

12.7 REGULATORY AUDITS

Domestic regulatory authorities, the IRB, and an auditor authorized by the sponsor may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

The Investigator and/or designee must be available to respond to reasonable requests and audit queries made by authorized regulatory representatives during the audit process.

12.8 CONFIDENTIALITY

All data and information collected during this study will be considered confidential. All data used in the analysis and summary of this study will be anonymous, and without reference to specific study subject names. Access to study subject files will be limited to authorized personnel or designees of Investigator, and research staff. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. National regulations regarding confidentiality will be followed as appropriate.

13. INVESTIGATOR RESPONSIBILITIES, RECORDS, AND REPORTS

13.1 GENERAL RESPONSIBILITIES

Principal Investigator at the site must:

- Assure compliance of all staff to the protocol
- Ensure all staff are trained to the protocol, TENS system and electronic diary
- Obtain and maintain a copy of the Institutional Review Board (IRB) approved Informed Consent form;

- Documentation of IRB approval of the final protocol (and amendments if applicable) providing evidence of the following:
  - A statement of IRB approval for the proposed study at the institution
  - Clear identification of the reviewed documents (may be done by attaching review packet to approval letter)
  - The date the study was approved
  - A statement that the Informed Consent document (revision date referenced) has been approved (may be a separate documented letter)
  - A listing of any conditions attached to the approval
  - Identification of the approved Principal Investigator at the site
  - The signature of the IRB chairperson

Until the study is completed, the Investigator will advise the IRB of the study progress at least annually. Written approval from the IRB must be obtained yearly to continue the study. Any amendments to the protocol, as well as associated consent form changes, will be submitted to the IRB and written approval obtained prior to implementation. Serious adverse event reports will be submitted as requested by the IRB.

13.2 INFORMED CONSENT

A copy of the Informed Consent must be forwarded to the IRB. All study subjects must provide written informed consent using an IRB-approved Informed Consent. The study must be explained to the study subjects in English. The Principal Investigator at the site, or designated representative, must be available to answer all of the study subject's study-related questions. Study subjects will be assured that they may withdraw from the study at any time for any reason and receive alternative conventional therapy as indicated.

13.3 PROTOCOL DEVIATIONS

A Protocol Deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the Protocol.

Investigators must approve any major deviations from the Protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control; however, the event is still considered a deviation and must be reported on the appropriate Case Report Form (CRF).

Deviations must be reported to the PI regardless of whether medically justifiable, pre-approved or performed to protect the subject in an emergency. Subject-specific deviations will be reported on a Protocol Deviation CRF.

Regulations require that the PI and site maintain accurate, complete and current records, including documents showing the dates of and reasons for each Protocol Deviation. For reporting purposes, Protocol Deviations are defined as major and minor as follows:

Major Deviation:	Any deviation from subject Inclusion and Exclusion criteria, subject Informed Consent procedures or authorized device use.
Minor Deviation:	Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc.

Minor Deviations that continue to occur may be classified as Major Deviations if corrective action is not taken to secure future compliance to the Protocol.

13.4 REPORTING REQUIREMENTS

As required by the IRB, the Investigator is responsible for reporting study progress to the IRB at least annually. The Investigator/Sponsor, as required by the local regulations, should notify the IRB in writing after completion, termination, or discontinuation of the study at the site. If the study is discontinued due to safety concerns, the Investigator will notify the IRB immediately. Timelines for notification are dependent on IRB requirements.

13.5 SOURCE DOCUMENTS

Source documents are defined as original documents, data and records. These may include hospital records, clinic and office charts, laboratory data/information, and recorded data from automated instruments, subject-reported data collected from the diary and transmitted to the secure database, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

The Investigator shall maintain all source documents as required by the Protocol, including laboratory results (e.g., pregnancy tests), subject report forms, supporting medical records, and Informed Consent forms for at least seven (7) years after the study is terminated or according to site and country specific requirements.

13.6 ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/institution will permit direct access to source data/documents in order for IRB review and regulatory inspections to be performed. These data may be shared with regulatory agencies.

13.7 DATA COLLECTION

Required data for this study will be captured on standardized CRFs. CRFs will be completed and stored for data analysis. Any deficiencies identified on the CRF will be communicated to the PI by the Clinical Data Monitor as appropriate.

13.8 ON-SITE AUDITS

The Investigator and/or designee must be available to respond to reasonable requests and audit queries made by authorized regulatory representatives during the audit process.

14. SITE MONITORING PROCEDURES

A Clinical Data Monitor will be responsible for the monitoring of this study. Responsibilities may be shared with Investigator or designee and include:

1. Conducting site initiation visits (training to product and protocol) after Institutional Review Board (IRB) approval and before first subject enrollment.
2. Maintaining regular contact with the site through telephone contact, email and on-site visits.
3. Assuring that the Protocol is followed; verifying that complete, timely and accurate data are submitted.
4. Monitoring subject data, including: reviewing Case Report Forms (CRFs) for completeness, verifying data to source documentation including operator worksheets retained with CRF documentation and hospital charts, and addressing problems with inconsistent, illegible and/or incomplete data.
5. Assuring that the Investigator's study file is maintained and that the site facilities continue to be adequate.

6. Conducting a close-out visit after completion of all CRFs.

During the study, the study site will be visited periodically by the Clinical Data Monitor. The Clinical Data Monitor will ensure Protocol compliance, accurate recording of results, reporting of adverse events, and record keeping. The Clinical Data Monitor will evaluate and summarize the results of each site visit in written reports, identifying any repeated data problems with any Investigator and specifying recommendations for resolution of noted deficiencies.

15. DATA QUALITY ASSURANCE

Standard Case Report Forms (CRFs) will be provided for use at all investigational sites. The Investigator is responsible for completion and timely submission of the forms for data entry and analysis. For subject reported outcome information recorded by the subject in the smartphone app diary, an audit trail will ensure any changes made to the data are properly attributed and have been reviewed and approved by the Investigator.

Subject data obtained from the CRFs and diary data from the handheld diary will be maintained by the PI, the management of these data will be compliant with the relevant parts of United States (US)CRF data regulations, including CFR Part 11.

Data entry will be performed by the Clinical Data Manager or designee.

Quality assurance procedures are designed to ensure that complete, accurate and timely data are submitted, that Protocol requirements are followed, and that complications, Adverse Events (AEs) and adverse device effects (ADE) are correctly reported.

Incoming data are reviewed to identify inconsistent or missing data and AEs/ADEs. Any data issues will be addressed with the Principal Investigator at the site. All hard copy forms and data files will be secured to ensure confidentiality.

16. ETHICAL REQUIREMENTS

16.1 DECLARATION OF HELSINKI

The study will be performed in accordance with ISO/EN 14155, parts 1 and 2, recommendations guiding physicians in biomedical research involving humans adopted by the 18th World Medical Assembly, Helsinki, Finland (1964 and later revisions), United States Food and Drug Administration (FDA) regulations, and International Congress on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

It is the responsibility of the Principal Investigator at the site to obtain approval of the study protocol from the competent Institutional Review Board (IRB) and to keep them informed of any Serious Adverse Events (SAEs), serious adverse device effects, and Protocol amendments. All correspondence with the IRB should be filed by the Investigator

16.2 SUBJECT INFORMATION AND CONSENT

It is the responsibility of the Investigator to give each subject full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved, and to obtain signed Informed Consent from all subjects prior to inclusion in the study.

The original, signed Informed Consent is filed with the subject study records, and a copy is provided to the subject.

16.3 SUBJECT DATA PROTECTION

The subjects will be identified in the Case Report Forms (CRFs) with a unique subject number and initials.

Per applicable regulations, the subject must be informed that the data will be stored and analyzed by computer, that national regulations for handling of computerized data will be followed, and that only the Investigator and designated research staff will have access to individual subject data. Furthermore, the subjects should be informed about the possibility of inspection of relevant parts of the hospital records by Health Authorities.

16.4 REPORTING AND COMMUNICATION OF RESULTS

All information and data generated in association with this study will be held in strict confidence and remains the sole property of PI.

16.5 CLINICAL TRIAL TERMINATION

A subject's participation in the clinical trial will be terminated if the Investigator believes it is in the subject's best medical interest or if the subject no longer complies with the clinical trial requirements. The subject may also decide to withdraw from the clinical trial at any time and terminate participation. The IRB and/or other Regulatory Authorities may decide to interrupt this clinical trial if either believes that this is necessary.

16.6 PROTOCOL MODIFICATIONS AND DEVIATIONS

The PI will submit Protocol modifications to the IRB as necessary.

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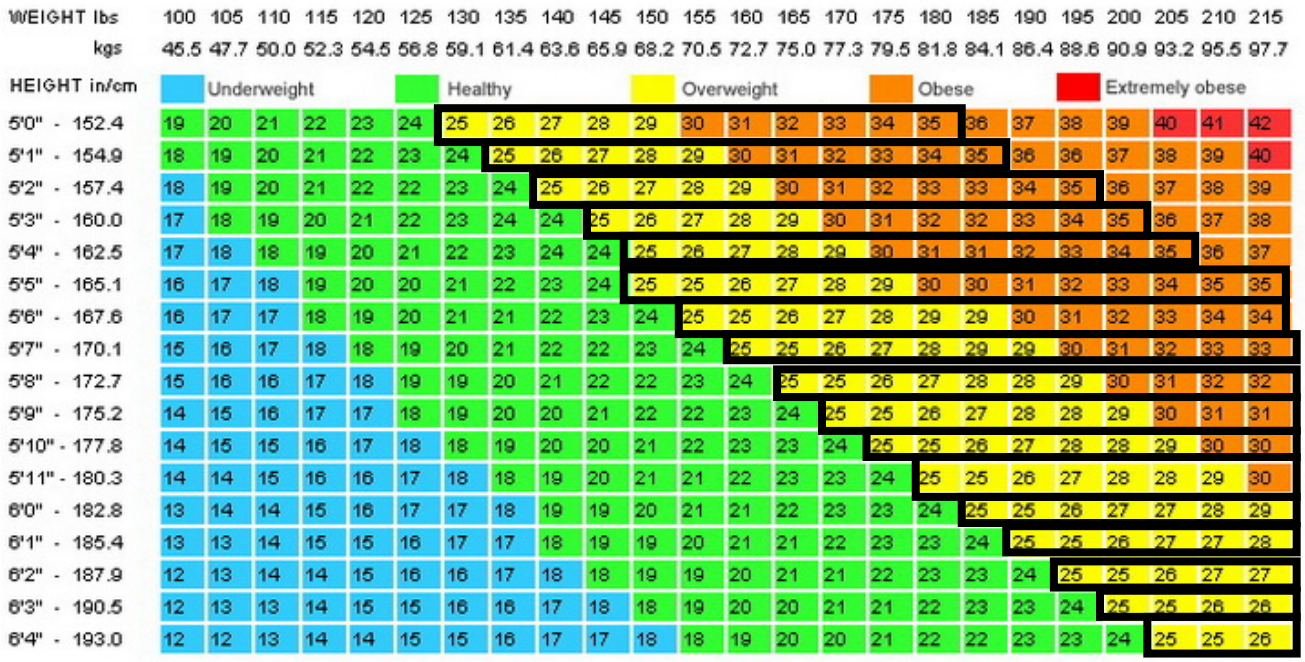
18. APPENDICES

18.1 APPENDIX 1: BMI RANGES TARGETED FOR MEN AND WOMEN ENROLLED IN STUDY (AN EXAMPLE OR NIH ONLINE SOURCE) [15,16]

Males (target BMI indicated by Black Bars):

WEIGHT lbs	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215
kgs	45.5	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7
HEIGHT in/cm	Underweight					Healthy						Overweight				Obese				Extremely obese				
5'0" - 152.4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
5'1" - 154.9	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37	38	39	40
5'2" - 157.4	18	19	20	21	22	22	23	24	25	26	27	28	29	30	31	32	33	33	34	35	36	37	38	39
5'3" - 160.0	17	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	32	32	33	34	35	36	37	38
5'4" - 162.5	17	18	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	31	32	33	34	35	36	37
5'5" - 165.1	16	17	18	19	20	20	21	22	23	24	25	25	26	27	28	29	30	30	31	32	33	34	35	35
5'6" - 167.6	16	17	17	18	19	20	21	21	22	23	24	25	25	26	27	28	29	29	30	31	32	33	34	34
5'7" - 170.1	15	16	17	18	18	19	20	21	22	22	23	24	25	25	26	27	28	29	29	30	31	32	33	33
5'8" - 172.7	15	16	16	17	18	19	19	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	32	32
5'9" - 175.2	14	15	16	17	17	18	19	20	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	31
5'10" - 177.8	14	15	15	16	17	18	18	19	20	20	21	22	23	23	24	25	25	26	27	28	28	29	30	30
5'11" - 180.3	14	14	15	16	16	17	18	18	19	20	21	21	22	23	23	24	25	25	26	27	28	28	29	30
6'0" - 182.8	13	14	14	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28	29
6'1" - 185.4	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28
6'2" - 187.9	12	13	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27
6'3" - 190.5	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	25	25	26	26
6'4" - 193.0	12	12	13	14	14	15	15	16	17	17	18	18	19	20	20	21	22	22	23	23	24	25	25	26

Females (target BMI indicated by Black Bars):



WEIGHT lbs	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215
kgs	45.5	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7
HEIGHT in/cm	Underweight						Healthy					Overweight					Obese							
5'0" - 152.4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
5'1" - 154.9	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37	38	39	40
5'2" - 157.4	18	19	20	21	22	22	23	24	25	26	27	28	29	30	31	32	33	33	34	35	36	37	38	39
5'3" - 160.0	17	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	32	32	33	34	35	36	37	38
5'4" - 162.5	17	18	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	31	32	33	34	35	36	37
5'5" - 165.1	16	17	18	19	20	20	21	22	23	24	25	25	26	27	28	29	30	30	31	32	33	34	35	35
5'6" - 167.6	16	17	17	18	19	20	21	21	22	23	24	25	25	26	27	28	29	29	30	31	32	33	34	34
5'7" - 170.1	15	16	17	18	18	19	20	21	22	22	23	24	25	25	26	27	28	29	29	30	31	32	33	33
5'8" - 172.7	15	16	16	17	18	19	19	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	32	32
5'9" - 175.2	14	15	16	17	17	18	19	20	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	31
5'10" - 177.8	14	15	15	16	17	18	18	19	20	20	21	22	23	23	24	25	25	26	27	28	28	29	30	30
5'11" - 180.3	14	14	15	16	16	17	18	18	19	20	21	21	22	23	23	24	25	25	26	27	28	28	29	30
6'0" - 182.8	13	14	14	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28	29
6'1" - 185.4	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28
6'2" - 187.9	12	13	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27
6'3" - 190.5	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	25	25	26	26
6'4" - 193.0	12	12	13	14	14	15	15	16	17	17	18	18	19	20	20	21	22	22	23	23	24	25	25	26

18.2 APPENDIX 2: TENS UNIT USER MANUALS (ADDITIONAL FILE SUBMITTED SEPARATELY)

ELIRA

EDP ON-BODY DEVICE

PATIENT INSTRUCTIONS FOR USE

CAUTION - Investigational device. *Limited by Federal (or United States) law to investigational use.*

A: INITIAL SETUP with CLINICIAN

1 Snap on Electrode Patch

Snap the electrode patch to the EDP.

DO NOT remove the protective liner from the electrode patch.

2 Register Account

Start the Elira app on the phone provided. Proceed with registration steps.

3 Turn on EDP

Turn the EDP on by pressing and holding the button 10 seconds and releasing it.

4 Turn on EDP

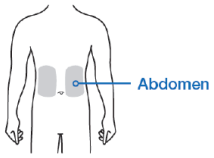
Follow the on-boarding process required by the app.

5 Remove Liner

Remove the electrode patch protective liner.

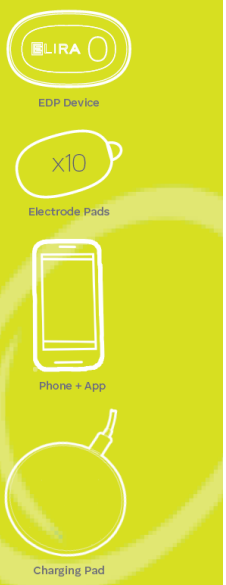
6 Place EDP

Place the EDP at T6 dermatome location.



WARNINGS

SYSTEM COMPONENTS



ELIRA

Elira Therapuetics
anNdsakfal
kNADkoasdf, ha 23443

C: DAILY USE

1 Snap on the Patch

Upon waking remove EDP from charging pad.

DO NOT remove the protective liner from the electrode patch.

2 Turn on EDP

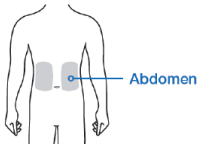
Turn the EDP on by pressing and holding the button 10 seconds and releasing it.

3 Remove Liner

Remove the electrode patch protective liner.

4 Place EDP

Place the EDP at T6 dermatome location.



5 Treatment cycle

Follow prescribed treatment cycle.

6 Remove EDP

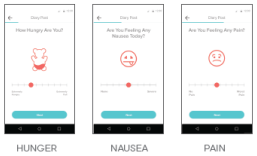
Remove EDP before bed, apply the protective liner to the electrode patch for overnight storage

7 Charge EDP Overnight

Place EDP on charger. Disconnect Bluetooth connection

8 Log Dairy Post

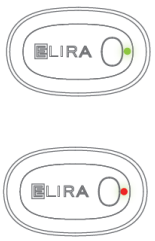
Complete diary entry for the day.



D: PATCH LIFE

The electrode patch life will vary, depending on care and skin type, but should be replaced when it no longer adheres well to the skin. If your skin type is oily or has residue on it, you may need to replace the electrode pad more frequently.

E: SYSTEM STATUS



THERAPY LIGHT

The Status LED blinks **GREEN** once ever 10 seconds while the device is in Therapy mode.

ERROR LIGHT

Low Battery - The Status LED blinks **RED** in high frequency.

Error Events:
Impedance out of range
Temperature out of range
Max Session Count Reached
Device Mode Error
The Status LED blinks **RED** in low frequency.

CAUTION - **Investigational device.** *Limited by Federal (or United States) law to investigational use.*

ELIRA

18.3 APPENDIX 3: PHQ-9 QUESTIONNAIRE

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Subject Initials:_____

Date:_____

18.4 APPENDIX 4: TFEQ-R18V2 [17]

The Three-Factor Eating Questionnaire

Please read each statement and select from the multiple-choice options the answer that indicates the frequency with which you find yourself feeling or experiencing what is being described in the statements below.

1. When I smell a delicious food, I find it very difficult to keep from eating, even if I have just finished a meal.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

2. I deliberately take small helpings as a means of controlling my weight.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

3. When I feel anxious, I find myself eating.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

4. Sometimes when I start eating, I just can't seem to stop.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

5. Being with someone who is eating often makes me hungry enough to eat also.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

6. When I feel blue, I often overeat.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

7. When I see a real delicacy, I often get so hungry that I have to eat right away.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

8. I get so hungry that my stomach often seems like a bottomless pit.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

9. I am always hungry so it is hard for me to stop eating before I finish the food on my plate.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

10. When I feel lonely, I console myself by eating.

    Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

11. I consciously hold back at meals in order not to weight gain.

    Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

12. I do not eat some foods because they make me fat.

Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

13. I am always hungry enough to eat at any time.

Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

14. How often do you feel hungry?

Only at meal times (1) / sometimes between meals (2) / often between meals (3) / almost always (4)

15. How frequently do you avoid "stocking up" on tempting foods?

Almost never (1) / seldom (2) / moderately likely (3) / almost always (4)

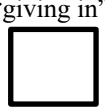
16. How likely are you to consciously eat less than you want?

Unlikely (1) / slightly likely (2) / moderately likely (3) / very likely (4)

17. Do you go on eating binges though you are not hungry?

Never (1) / rarely (2) / sometimes (3) / at least once a week (4)

18. On a scale of 1to 8, where 1 means no restraint in eating (eating whatever you want, whenever you want it) and 8 means total restraint (constantly limiting food intake and never "giving in"), what number would you give yourself?



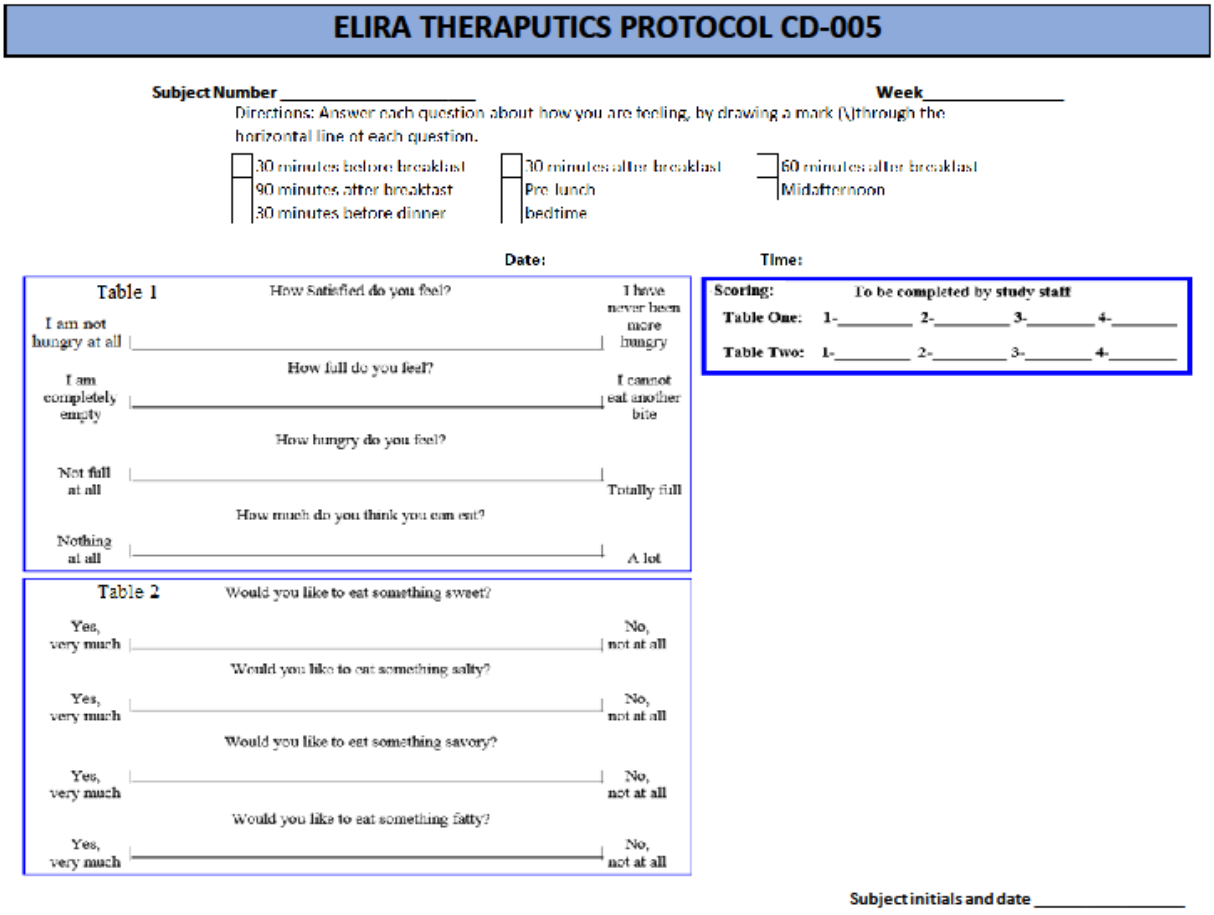
Revised 18-Item (Karlsson et. Al. 2000)

18.5 APPENDIX 5: VAS AND DAILY DIARY APPLICATION

Recommended primary scales for self-reported appetite in healthy adults[a]

Scale	Question	Anchors	
		Low	High
Hunger	How hungry are you?	I am not hungry at all	Extremely I have never been more hungry
Fullness	How full are you?	I am completely empty	I cannot eat another bite

[a]Line scales 100-150 mm (paper) or appropriate length for electronic capture systems are to be used for each of these questions.



ELIRA THERAPUTICS PROTOCOL CD-005

Subject Number _____ **Week**_____

Directions: Answer each question about how you are feeling, by drawing a mark (\)through the horizontal line of each question.

☐ 30 minutes before breakfast ☐ 30 minutes after breakfast ☐ 60 minutes after breakfast
☐ 90 minutes after breakfast ☐ Pre-lunch ☐ Midafternoon
☐ 30 minutes before dinner ☐ bedtime

Date: **Time:**

Table 1 How Satisfied do you feel?

I am not hungry at all — I have never been more hungry

How full do you feel?

I am completely empty — I cannot eat another bite

How hungry do you feel?

Not full at all — Totally full

How much do you think you can eat?

Nothing at all — A lot

Scoring: To be completed by study staff

Table One: 1-_____ 2-_____ 3-_____ 4-_____

Table Two: 1-_____ 2-_____ 3-_____ 4-_____

Table 2 Would you like to eat something sweet?

Yes, very much — No, not at all

Would you like to eat something salty?

Yes, very much — No, not at all

Would you like to eat something savory?

Yes, very much — No, not at all

Would you like to eat something fatty?

Yes, very much — No, not at all

Subject initials and date _____

18.6 APPENDIX 6: SCHEDULE OF EVENTS

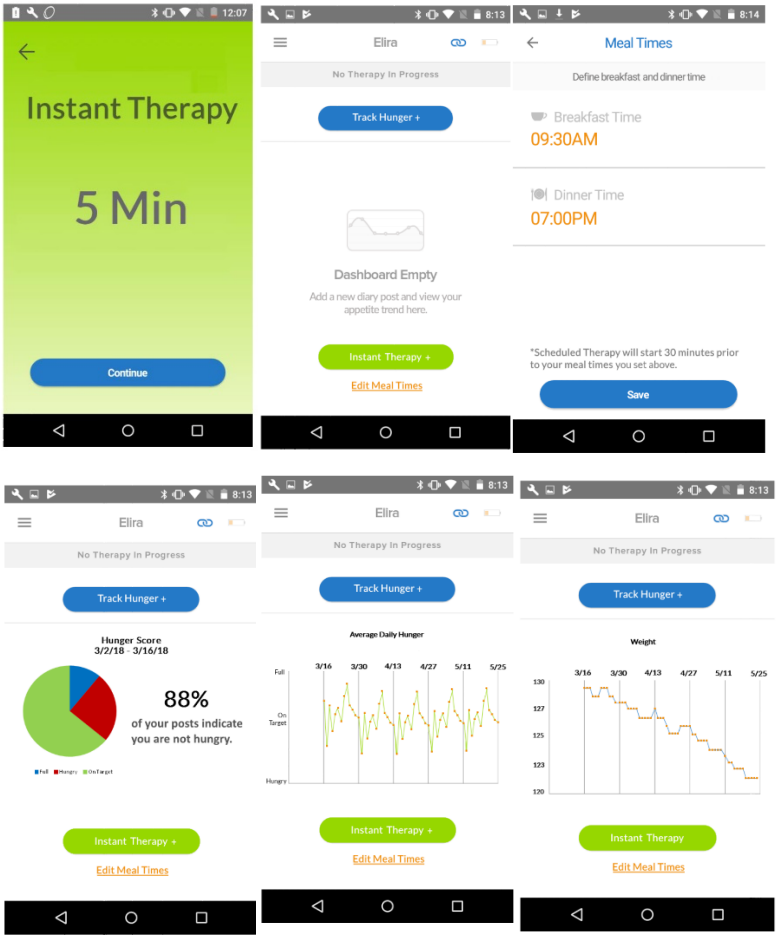
APPENDIX 6: SCHEDULE OF VISITS

STUDY PERIOD	SCREENING	ENROLLMENT	THERAPY/CONTROL						END OF STUDY[7]
VISIT #	VISIT 0	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT8
WEEK #	WEEK -1	WEEK 0	WEEK 1	WEEK 4	WEEK 8	WEEK 12	WEEK 16	WEEK 20	WEEK 24
VISIT WINDOW[1]	±7 DAYS	±7 DAYS	±7 DAYS	±7 DAYS	+/- 7 DAYS	+/- 7 DAYS	+/- 7 DAYS	±7 DAYS	± 7 DAYS
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X	X	X	X	X	X	X	X
Medical History	X								
Diet History	X								
Physical Exam	X								X
T6/T7 dermatome assessment	X[3]	X[3]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Blood Pressure	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Laboratory Requisition - Blood Tests[2]	X					X			X
Urine Pregnancy Test (FOCBP)	X	X[6]							X
Administration of PHQ-9	X								X

Administration of TFEQ-R18V2		X	X	X	X	X	X	X	X
Administration of Pre-Study Survey	X								
Administration of Post-Study Survey									X
Provide/Train on Paper Diaries[3]	X	X		X	X	X	X	X	
Collect and Review Paper Diaries[3]			X	X	X	X	X	X	X
Randomization[5]		X							
Provide/Train on Electronic Scale		X							
Provide and Train on Electronic Diary Application[4]		X	X	X	X	X	X	X	
Collect and Review Electronic Diary[4]			X	X	X	X	X	X	X
Provide and Train on TENS Unit and Patches[4]		X	X	X	X	X	X	X	
Collect and Examine TENS Unit and Patches[4]			X	X	X	X	X	X	X
Training on Electrode Placement[4]		X	X	X	X	X	X	X	
Adjust TENS Unit, if applicable[4]		X	X	X	X	X	X	X	
Provide/instruct (as needed) on TENS Clean-Cote Skin Wipes an/or Alcohol Prep Pads[4]		X	X	X	X	X	X	X	
Provide/Instruct (as needed) on Cetaphil Lotion[4]		X	X	X	X	X	X	X	
Concomitant Medication Review[3]	X	X	X	X	X	X	X	X	X
Assessment of Adverse Events[3]	X	X	X	X	X	X	X	X	X
Assessment of Adverse Device Effects[4]		X	X	X	X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	X	X	
Photographs taken		X				X			X
Study Exit									X

1 – all visits are ± 1 week
2 – Blood tests include HbA1c, lipid panel,
3 – to be completed for control and treatment group
4 – to be completed for treatment group only
5 – randomization into control or treatment group
6- Either Screening or Randomization Visit, Not Needed at Both.

18.7 APPENDIX 77: ELECTRONIC DIARY APPLICATION (SEE SAMPLES SCREEN SHOTS)



18.8 APPENDIX 8: LIST OF POTENTIAL DRUG INTERACTIONS

	Weight *positive* medications (cause weight gain)	Weight *negative* medications (cause no gain* or weight loss)
DIABETES	Glipizide Glyburide Insulin Pioglitazone Rosiglitazone	Acarbose* Exanatide Glimepiride* Liraglutide Metformin Sitagliptan*
HYPERTENSION	Atenolol Clonidine Hydralazine Labetalol Prazosin Terazosin Valsartan	Amlodipine Captopril* Carvedilol* Enalapril* Furosemide Hydrochlorathiazide* Lisinopril Losartan* Metoprolol* Olmesartan
PSYCHIATRIC	Citalopram Clozapine Lithium MAO-I Mirtazapine Olanzapine Paroxetine Phenothiazines Risperdone TCA	Amphetamines Buproprion Escitalopram* Fluoxetine Sertraline
CHRONIC PAIN	Amitriptyline Celecoxib Gabapentin Methadone Pregabalin	Acetaminophen* Baclofen* Carisoprodol* Cyclobenzaprine* Diclofenac* Fentanyl Hydromorphone Ibuprofen* Morphine Naproxen* Tramadol

FIGURE 1: Commonly prescribed weight positive, negative, and neutral* medications.

*List of drugs includesdrugs includes some pharmaceuticals that may impact study participation. May not be complete and is up to PI discretion.

18.9 APPENDIX 9: END OF STUDY SURVEY

Name or Subject Identifier: _____

ELIRA End of Study Survey

Thank you for completing the weight loss study. Please circle your response to each question below.

1. My experience wearing the device and using the associated app can be described as (enter text below):

   _____

   _____

2. What I liked MOST about this product (circle all that apply):
   - Non-invasive / non-surgical
   - Helps control appetite
   - Easy to use
   - Technology / app component
   - Convenience / automatic nature
   - No medications or pills
   - Wearable
   - Low side effects
   - Discreet
   - FDA cleared
   - Other (please specify):_____

3. What I liked LEAST about this product (circle all that apply):
   - Safety
   - Side effects
   - Efficacy (Effectiveness)
   - Sensation while wearing it
   - Skin patch / wearable
   - Having to connect to a smartphone
   - Not natural or healthy way to lose weight
   - Other (please specify):_____

4. Overall, this product helped suppress my appetite (circle one):
   - Always
   - Most of the time
   - Occasionally
   - Never

5. I found that the instant sessions helped suppress my appetite (check one):
   - Always
   - Most of the time
   - Occasionally
   - Never

6. Please indicate your level of agreement with the following statements (check one box for each statement):

	Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree
The product easily fits my daily lifestyle.					
Wearing this product was comfortable					
I got used to using this product quickly.					
The app was easy to use					
The device seems safe.					
My appetite was lower than normal while using this product.					
The product helped me lose more weight than I could have on my own.					
I am happier with how I look and feel after wearing this product.					
I wish I could continue wearing this product.					
I believe this product would work for most people.					
I would recommend this product to my friends.					

7. Where would you expect that patients could purchase the Elira device? Circle all that apply.

   - From my aesthetic physician (dermatologist, plastic surgeon, medspa)
   - From my general practioner or internal medicine physician
   - From my OB/GYN
   - From a weight lost cinic
   - Other (please specify): _____

7. What barriers to your normal lifestyle did using this product create:

_____

_____

8. I wish the following additions/changes could be made to the device:

_____

_____

9. I wish the following additions/changes could be made to the Smartphone application:

   _____

   _____

10. I would pay this much money out-of-pocket for this device: _____

11. I am willing to be contacted by Elira for more details on my experience after this trial to help improve the product design:
    - YES
    - NO

12. I am willing to allow Elira to use this information as a user testimonial (using my first name only):
    - YES
    - NO

18.10 APPENDIX 10: PRE-STUDY SURVEY

Name or Subject Identifier: _____

ELIRA Pre-Study Survey

Thank you for your interest in the weight loss study. Please circle your response to each question below.

1. How much weight do you think you need to lose?
    a. None
    b. Less than 5 lbs
    c. 5 – 10 lbs
    d. 11 – 15 lbs
    e. 16 – 20 lbs
    f. More than 20 lbs
    g. Not sure

2. A number of weight loss programs offer the potential to lose 1-2 lbs per week. Do you consider this a reasonable amount of weight for you to lose per week in a weight loss program?
    a. Yes
    b. No, I would expect to lose <u>less than 1 pound</u> per week
    c. No, I would expect to lose <u>more than 2 pounds</u> per week

3. Which, if any, of the following have you attempted in order to lose weight in the past? Select all that apply.
    a. Dieting on your own (not through a specific program)
    b. Dieting with free online coaching or support (like MyFitnessPal)
    c. Exercise or increasing amount of exercise
    d. Paid weight loss program (Jenny Craig / Weight Watchers, etc.)
    e. Gym membership
    f. Medical weight loss through a physician
    g. Prescription diet pills or other prescription medications
    h. Over-the-counter diet pills or appetite suppressants
    i. Surgical or other invasive procedures, e.g. gastric balloons or LAP-band
    j. Body sculpting targeting specific areas, e.g. Cool Sculpting
    k. Other (please specify)
    l. I haven't tried to lose weight in the past

4. How would you describe your level of success with prior weight loss methods?
    a. I was able to lose weight and keep all or most of the weight off
    b. I was able to lose weight but regained some or most of the weight back
    c. I was not able to lose weight

5. What is the <u>primary reason</u> you want to lose weight? Please circle one.
    a. Better health
    b. Improved appearance
    c. Lifestyle (e.g. being more acrive)
    d. Recommended by my Company's wellness program
    e. Special event (wedding, reunion, party, etc.)

f. Other (please specify) _____

6. Is it easy or difficult for you to lose weight?
   a. Very easy
   b. Somewhat easy
   c. Sometimes easy, sometimes difficult
   d. Somewhat difficult
   e. Very difficult
   f. I've never tried to lose weight before

7. What are your primary barriers to weight loss? Select all that apply.
   a. Time
   b. Cost
   c. Willpower
   d. Appetite control
   e. Fear of failure
   f. Concerns about side effects of medication or surgery
   g. Other (please specify)

8. Please indicate your level of agreement with the following statements

	Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree
I always try to look and feel my best					
I try to keep up with the latest trends					
How you look on the outside says a lot about you					
I enjoy shopping for new clothes					
I would be more confident if I lost weight					
I feel like I'm hungry more often than other people					
Hunger is my biggest barrier to losing weight when dieting.					
I have talked to a friend or family member about trying to lose weight					
I have been frustrated by my weight for a long time					
I wish I could control how much I eat					
I wish I could lose weight without exercising					
Losing weight is a very difficult process					
Posiitve messages motivate me to stay on track with my goals.					

18.11 APPENDIX 11: DIET GUIDELINES

The Centers for Disease Control and Prevention has information available online that you may want to reference. Some helpful information and links are below:

"Whether you need to lose weight, maintain your ideal weight, or gain weight, the main message is – calories count! Weight management is all about balancing the number of calories you take in with the number your body uses or "burns off."

If you need to lose weight, you'll need to reduce your daily calorie consumption in line with your goal. An adult can lose 1 to 2 pounds per week by eating 500-1,000 fewer calories per day. During this study, try to reduce your calorie intake as much as possible."

Links to specific pages on the CDC website are below:

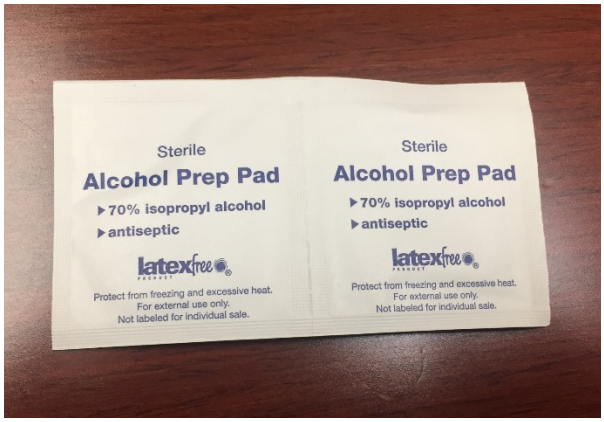
Losing Weight: https://www.cdc.gov/healthyweight/losing_weight/index.html

Healthy Eating: https://www.cdc.gov/healthyweight/healthy_eating/index.html

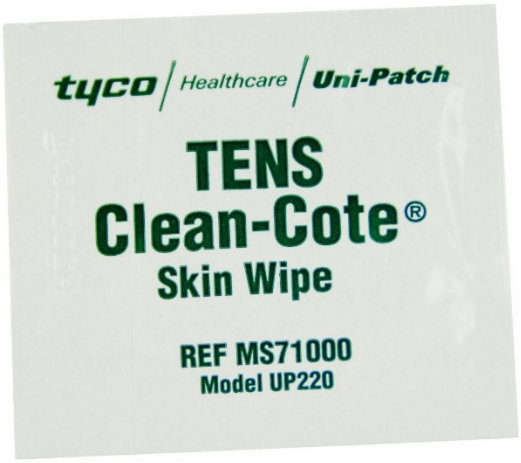
Cutting Calories: https://www.cdc.gov/healthyweight/healthy_eating/cutting_calories.html

Meal Ideas: *https://www.cdc.gov/healthyweight/healthy_eating/cutting_calories.html*

18.12 TRIAL COMPONENTS


Sterile
Alcohol Prep Pad
▸70% isopropyl alcohol
▸antiseptic
latexfree
Protect from freezing and excessive heat.
For external use only.
Not labeled for individual sale.
Sterile
Alcohol Prep Pad
▸70% isopropyl alcohol
▸antiseptic
latexfree
Protect from freezing and excessive heat.
For external use only.
Not labeled for individual sale.


Directions:
Apply topically as needed
to cleanse intended area.
See box for complete
Drug Facts information.
Discard after single use.
Flammable, keep away
from fire or flame.
RK12YMS
LOT 67017030014
Directions:
Apply topically as needed
to cleanse intended area.
See box for complete
Drug Facts information.
Discard after single use.
Flammable, keep away
from fire or flame.
RK12YMS
LOT 67017030014


tyco / Healthcare / Uni-Patch
TENS
Clean-Cote®
Skin Wipe
REF MS71000
Model UP220


TAYLOR
AMERICA'S LEADING BATH SCALE™
DIGITAL SCALE
ACCURACY & STYLE
• Extra large 4.2" x 2.3" readout with blue blacklight
• Unique textured mat design with stainless steel finish
• 11.8" x 11.8" platform
126.4
TAYLOR
7413
4516
V0341
TAYLOR
Distributed by Taylor Precision Products, Inc.
Seattle, WA 98134 USA
Questions about your scale?
1-866-843-3905 or visit our website:
www.shoptaylorusa.com
Made in China.
Model #7413
≤400 lb (≤180 kg)
.2 lb increments (.1 kg)
"STEP-ON" Instant Read
2 AAA Batteries (Included)