TITLE: VESTIBULAR STIMULATION TO TRIGGER ADIPOSE LOSS (VESTAL) CLINICAL TRIAL

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

Vestibular Stimulation to Trigger Adipose Loss (VeSTAL) Clinical Trial

2. PRINCIPAL INVESTIGATOR

V.S. Ramachandran MD PhD, Center for Brain and Cognition, UCSD.

3. FACILITIES

All study visits will be carried out at the Altman Clinical and Translational Research Institute (ACTRI) building which is part of the La Jolla campus of UCSD. The DXA scanner is also located at the ACTRI. Subjects will also be provided with devices to take away with them for home usage. Dr Ramachandran's own offices are in Mandler Hall in the La Jolla campus of UCSD but study subjects will not be seen there.

4. ESTIMATED DURATION OF THE STUDY

Two years

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

There is an ongoing and worsening problem with obesity in the developed, and much of the developing world. Although it has long been realized that Western diets that are rich in sugar and fat play an important role in this, it has only recently been realized that exposure to these diets, particularly in childhood, can damage the part of the brain that determines how much fat there is in the body. The result of this damage is that the so-called "set-point" for fat in this part of the brain is pushed upwards. There is a lot of evidence from animals that activating the brain's balance (vestibular) system pushes this set-point for fat downwards to cause fat loss, probably because this tricks the brain into thinking that the animal is more physically active. The aim of this study is to see whether the same effect can be triggered in humans by non-invasively stimulating the vestibular system with a small electrical current through the skin behind their ears.

6. SPECIFIC AIMS

The purpose of this investigational device study is to collect data to support regulatory submissions, primarily in the United States of America, but it may also be used to support submissions in other regions.

The aim of this study is to better evaluate the efficacy of non-invasive electrical vestibular nerve stimulation (VeNS), together with a lifestyle modification program, as a method of reducing excess body weight, as compared to a sham control and lifestyle modification program.

Primary Objective: Establish the clinical performance of the Vestal device in patients who are overweight.

Secondary Objective: To evaluate the safety of the Vestal device relative to control group, in terms of the occurrence of adverse events, changes from baseline in vital signs (blood pressure and heart rate), and laboratory results in patients who are overweight.

7. BACKGROUND AND SIGNIFICANCE

This protocol describes the overall device investigation; governs the activities at the site of the device investigation and describes the study details, interactions and records to be generated throughout the study. This document serves as the lead document and supersedes all other documents. e.g. Instructions for Use (IFU).

This protocol will be applied at the following sites:

1. Altman Clinical and Translational Research Institute (ACTRI) building which is part of the La Jolla campus of UCSD
2. A second smaller site is being added to support the subject numbers detailed within this study protocol, the second site procedures will be identical to those described in this protocol. This second site will likely be at the City Hospital, Queen's University, Belfast in the U.K.

There is a growing realization that obesity can, in many ways, be viewed as a neurological disease triggered by lifestyle factors. There is clear evidence that the arcuate nucleus in the hypothalamus regulates a "set-point" for how much fat the body should have. It does so by altering appetite and metabolic rate so that deviations too far in either direction are strongly resisted. This set-point is determined by genetic, epigenetic and lifestyle factors. Thus, excessive exposure to dietary monosaccharides, such as glucose, and saturated fats, especially in childhood and adolescence, can damage the neurons of the arcuate nucleus and push the set-point up. This then can condemn sufferers to a lifetime of obesity.

Establishing a method of tuning down the set-point for body fat thus has to be a goal if we are to successfully combat the current obesity pandemic. A significant amount of animal work suggests that stimulating the vestibular system in the inner ear, by means of chronic centrifugation, actually does just that and causes a reduction in body fat. This is likely because the chronic vestibular activation is taken by the brain to represent a state of increased physical activity, and in order to optimize homeostasis it would be appropriate for the body to have a leaner physique, by reducing unnecessary energy expenditure from carrying excess fat.

It is possible to stimulate the vestibular nerve in humans by applying a small electrical current to the skin behind the ears. This is an established technology that is believed to be safe, but only previously used for research purposes. We found in a pilot study (110538) that recurrent stimulation of this kind for two or three hours a week over four months led to a statistically significant reduction in truncal fat in the active group as opposed to the control group who underwent sham stimulation.

Given the current, and increasing levels of global obesity, it is important to determine whether non-invasive electrical vestibular nerve stimulation (VeNS), otherwise known as galvanic vestibular stimulation, is a viable treatment option, since if it were this would be of significant scientific importance. The only way to answer this question is to use human subjects.

In writing this Research Plan we have consulted the following document from the FDA, which although aimed at weight loss medications, does contain pertinent advice.
http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071612.pdf

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R Fitzpatrick, B Day (2004) Probing the human vestibular system with galvanic stimulation. J Appl Physiol 96, 2301-16.

P Fuller, T Jones, S Jones, C Fuller (2004) Evidence for macular gravity receptor modulation of hypothalamic, limbic and autonomic nuclei. Neuroscience 129, 461-71.

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8, 561-65.

L Parton et al. (2007) Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity. Nature 448, 228-32.

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8. PROGRESS REPORT

The study was approved on 03/23/2017. Recruitment began in May 2017. The study conducted a Site Initiation Visit at UCSD-CTRI on 10/11/2017. The first person enrolled began on 11/07/2017. The study has enrolled 24 subjects to date, with two withdrawals. All subjects have been and continue to be closely monitored for any symptoms, adverse events or other issues, as well as to ensure that they are conforming with the study protocol requirements for usage of the VeNS device and Food Log app. Subjects are being scheduled to come in for the specified visits at UCSD. No major protocol deviations to date. See #9. Adverse Event section of Progress Summary submitted to the IRB in February 2018 for summary on adverse events to date. This summary also provides details on withdrawals from the study. Two internal monitoring visits have been performed thus far, on 11/21/2017 and on 01/19/2018.

9. RESEARCH DESIGN AND METHODS

Official Title A randomized, double blind sham controlled clinical trial to evaluate the efficacy of vestibular nerve stimulation (VeNS) (see Appendix 1), combined with a lifestyle modification program (see Appendix 2), compared to a sham control (see Appendix 1) and a lifestyle modification program as a means of reducing excess body weight.

Study Design

- Allocation: Randomized
- Endpoint classification: Efficacy Study
- Intervention Model: Parallel Assignment in 2:1 active to control allocation (Aim to recruit a total of 106 participants overall in the study across two sites, with a dropout allowance of 15% to generate a minimum of 60 active treatment and 30 control subjects). (In order to do this we estimate that we may have to screen up to 150 subjects). The UCSD site will aim to recruit a total of 60 subjects.
- Masking: Double Blind (Subject and all study staff including research dietician, nursing and Outcomes Assessor)

Pre-screening of Subjects

In order to prevent subjects traveling in needlessly to the study site it is proposed that the study staff allow prospective subjects to pre-screen themselves over the phone. This will involve the study coordinator reading out the inclusion and exclusion criteria to prospective subjects during an initial phone call. The screening questionnaire will not be completed at this stage. Rather the purpose is to make prospective subjects aware as to what the inclusion and exclusion criteria are, since there is no point in them wasting their time and coming in if they are obviously ineligible.

This will also allow study coordinators to provide prospective subjects with a verbal description of the study to the subjects. The text that the coordinator will follow is included for review with this submission.

Overview of Clinical Study

Subject enrollments will be completed during Site Visit 1 (Baseline visit). The ACTRI site can

accommodate up to 3 enrollments per day. All subjects will be part of the study consisting of: Site Visit 1 (~5 hours, 0 months for enrollment); Site Visit 2 (~3.5 hours, 3-month time point); Site Visit 3 (~3.5 hours, 6 months); Site Visit 4 (final visit ~3.5 hours, 12 months); and Home Use Period (12 months).

Site visit 1: the potential study participants will be introduced to the study and the study requirements, those wishing to participate in the study will be asked to complete required documentation (Informed Consent Form and HIPAA release document to allow the study personnel to access the results of blood results taken during the study and analyzed at UC San Diego Health) and receive investigational devices to be used in the home use period.

Participants will be asked to return for an interim visits at 3 and 6 months, and a final assessment/study end visit at 12 months.

Study participants will be asked to use the Vestal device on a daily basis for 1 hour, at least five times a week and, if they wish, every day.

Note: This protocol refers to 'study staff' throughout. The study staff role may be filled by clinical trial coordinators, assistants or clinical trial site staff who are trained technicians, nursing or dieticians qualified to perform the study participant enrollment and testing requirements throughout the study.

Summary of Site Visit 1 (0 months)

- Study staff provides potential subjects with a description of the study, including requirements for participation, specific study activities, and procedures, these procedures should focus on the home use of the device and operation of the device.
- Each potential subject reads and signs the Informed Consent Form/s, and receives a signed copy.
- Each potential subject receives a copy of the California Experimental Subject's Bill of Rights
- Study staff then enroll the subject and record/ screen demographic and medical history information to ensure compliance with inclusion/ exclusion criteria.
- Study staff provide training via the reading of the instructions for use for the vestal device, including connection to the application and operation of the device.
- Study staff will organize and arrange HealthWatch 360 app access for all study participants and show subjects how to input dietary intake and physical activities. Goal of app will be set to weight loss and subjects will also be told how to access exercise suggestions.
- Study staff will download Moves, and/or Fitbit app onto subject's smart device. This integrates in to the HealthWatch 360 app to provide information on the activity of the subject.
- Study participants will be given the relevant materials including the vestal device to return home and begin the home use period.
- Study participants will be instructed to return home and begin using the device.
- Dietary Counseling from research dietician including review of diet and discussion of Healthwatch 360 app use – 30 minutes.

Summary of the Testing Procedures Visit 1 (0 months)

- Urine pregnancy test (if applicable – i.e. a female of child bearing potential)
- Glucose finger prick (Diabetes screening)
- Check skin behind ears (visual inspection to ensure appears healthy)
- Weight and height to calculate BMI
- Hip and waist measurements
- Fasting Insulin level

- High Sensitivity C-Reactive Protein
- Lipid Panel
- Oral Glucose Tolerance Test (OGTT)
- Pulse rate and blood pressure
- Quality of life survey (Duke University IWQOL – http://www.qualityoflifeconsulting.com/iwqol-lite.html)
- DXA Scan (whole body scan)
- Audiogram test including otoscope examination of the ear canals.

Summary of the Testing Procedures Visit 2 (3 months)

- Urine pregnancy test (if applicable – i.e. a female of child bearing potential)
- Weight and BMI calculation
- Check skin behind ears (visual inspection to ensure appears healthy)
- Waist and hip measurements
- Fasting Insulin level
- High Sensitivity C-Reactive Protein
- Lipid Panel
- Oral Glucose Tolerance Test (OGTT)
- Pulse rate and blood pressure
- Quality of life survey (Duke University IWQOL – http://www.qualityoflifeconsulting.com/iwqol-lite.html)
- DXA Scan (whole body scan)
- Coordinator asks participant to complete adverse event monitoring questionnaire.
- Audiogram test including otoscope examination of the ear canals.

Other activities at Visit 2 (3 months):

- Dietary Counseling from research dietician including review of diet reports from Healthwatch 360 app – 15 minutes

Summary of the Testing Procedures Visit 3 (6 months)

- Urine pregnancy test (if applicable – i.e. a female of child bearing potential)
- Weight and BMI calculation
- Check skin behind ears (visual inspection to ensure appears healthy)
- Waist and hip measurements
- Fasting Insulin level
- High Sensitivity C-Reactive Protein
- Lipid Panel
- Oral Glucose Tolerance Test (OGTT)
- Pulse rate and blood pressure
- Quality of life survey (Duke University IWQOL – http://www.qualityoflifeconsulting.com/iwqol-lite.html)
- DXA Scan (whole body scan)
- Coordinator asks participant to complete adverse event monitoring questionnaire.
- Audiogram test including otoscope examination of the ear canals.

Other activities at Visit 3 (6 months):

- Dietary Counseling from research dietician including review of diet reports from Healthwatch 360 app – 15 minutes

Summary of Final Site Visit 4 (Final Site Visit) (12 months)

- Urine pregnancy test (if applicable – i.e. a female of child bearing potential)
- Weight and BMI calculation
- Check skin behind ears (visual inspection to ensure appears healthy)
- Waist and hip measurements
- Fasting Insulin level
- High Sensitivity C-Reactive Protein
- Lipid Panel
- Oral Glucose Tolerance Test (OGTT)
- Pulse rate and blood pressure
- Quality of life survey (Duke University IWQOL – http://www.qualityoflifeconsulting.com/iwqol-lite.html)
- DXA Scan (whole body scan)
- Coordinator asks participant to complete adverse event monitoring questionnaire.
- Audiogram test including otoscope examination of the ear canals.

Other activities at Visit 4 (12 months):

- The study participant will return the investigational device.

Frequency of Follow-Up Appointments

Visits in person at: enrollment (0 months); 3 months; 6 months; and 1 year. Telephone follow up at: weeks 2; months 1 & 9; and as required on an ad hoc basis. There will also be the facility to bring subjects in for review should concerns be raised after the telephone review – e.g. concern re skin irritation behind the ear. Study participants are also free to contact (call or email) study personnel at any time with any issues or inquiries.

Primary Outcome Measures (At 12 months)

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% total body weight lost (TBWL), and the difference is statistically significant.
- The proportion of participants who lose 5% or more of baseline body weight in the active-product group is at least 35% and is approximately double the proportion in the placebo-treated group; the difference between groups is statistically significant.

Secondary Outcome Measures (At 12 months)

- The difference in mean percent loss of baseline total body fat in the active versus placebo treated groups. (As measured by means of a whole body DXA scan– see Appendix 4).
- The proportion of subjects who lose at least 5% of baseline total body fat in the active versus placebo treated groups. (As measured by a whole body DXA scan).
- The difference in mean percent loss of baseline truncal body fat in the active versus placebo treated groups. (As measured by a whole body DXA scan).
- The proportion of subjects who lose at least 5% of baseline truncal body fat in the active versus placebo treated groups. (As measured by a whole body DXA scan).
- The difference in mean percent loss of baseline visceral adipose tissue in the active versus placebo treated groups. (As measured by a whole body DXA scan).
- The proportion of subjects who lose at least 5% of baseline visceral adipose tissue in the active versus placebo treated groups. (As measured by a whole body DXA scan).

- Difference in lean muscle mass in the active versus placebo treated group. (As also automatically measured by the whole body DXA scan).
- Difference in bone mineral content in the active versus placebo treated group. (As also automatically measured by the whole body DXA scan).
- Blood pressure
- Heart rate
- Lipid profile (Assess total non-HDL cholesterol, and HDL to total cholesterol ratio)
- High-sensitivity C-reactive protein
- Oral glucose tolerance test (See Appendix 5)
- Fasting insulin level
- Waist and hip circumferences
- Body Mass Index (BMI)
- Adjustment of concomitant medication – both reduction and new medications
- Quality of life – IWQOL-Lite questionnaire. This validated instrument, developed by Duke University, has been used by a variety of researchers to assess various obesity treatment options and their impact on individual patients. The questionnaire is available in a number of languages including Spanish. A detailed description is available on this website: https://olv.duke.edu/iwqol. As can be seen on this website this instrument has been used extensively in studies relating to weight loss and obesity: http://www.qualityoflifeconsulting.com/iwqol-litepublications.html.
- Dose response analysis: it is likely that some subjects will not utilize their device for the mandated 5 hours per week. Usage data will be available from the devices as they can distinguish when they are genuinely being used as opposed to just being turned on with air between the electrodes. Data from such subjects will be analyzed in the main study but if possible a dose response analysis will also be carried out. Analysis will be in an intention to treat manner – see Statistical Considerations.

Safety Endpoints and Adverse Event Monitoring

Based on the survey of adverse events devised by Utz et al. (2011) occurrence of the following adverse events will be specifically enquired about by the study coordinators during contact with the participants: headache; pain behind the ears; vertigo/ dizziness; blurred vision; nausea; fatigue/ tiredness; seizures; tinnitus; and other symptoms. The coordinators will ask and record whether these symptoms occur: never; almost never; sometimes; almost every time; or every time. And they will ascertain whether they occur while wearing the device, after wearing it, or both. Also, the coordinator will additionally ask whether the participants ever notice skin irritation after wearing the device.

We will monitor each instance of an adverse event causing a dropout from the study. The dropouts, together with causes, will be recorded and reviewed at the end of the study. This guidance from the FDA will be followed: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf. If it becomes evident that the proportion of subjects who drop out due to safety concerns/ adverse events convincingly exceeds 30%, the study will be halted.

Hearing Test and Ear Examination

The FDA provided feedback that some study participants should undergo a hearing test and otoscope examination of the ear canal. The FDA were aware that the study had started at this point and as discussed with the FDA there is no suggestion from any of the literature looking at the safety of GVS that hearing or the ear canal are adversely affected (Krystal et al., 2010; Marshall et al., 2010). And that a study specifically looking at the impact of GVS on cochlear function showed no effect (Cevette et al., 2012). Nonetheless, although there is no suggestion that hearing is adversely affected the FDA are requesting that such tests be carried out before agreeing to approve the device.

It is thus proposed that an audiogram (hearing) test be conducted on study participants at baseline and 3, 6 and 12 months. Participants who were enrolled in the study prior to the introduction of these hearing tests will be asked to undergo them at subsequent follow-up visits. Prior to the audiogram, the outer canals of the study participant's ears will be examined with an otoscope to make sure they are free of wax, that the tympanic membrane is intact, and that there is no infection. An audiologist will then place a pair of insert headphones (Etymotic, ER-3A) into the subject's ears and ask them to raise a hand or press a button when they hear a soft pure-tone. Bone conduction and air conduction thresholds (dB HL) will be measured at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz bilaterally. This is a standard hearing test to determine if hearing loss is present, and if so how much and of what type. A plot of frequency versus amplitude sensitivity threshold for each ear will be generated. The speech recognition threshold and word recognition score will also be obtained. All testing will be completed in a sound-treated booth in order to avoid extraneous noise. Tympanometry will also be carried out. This involves placing a small probe in the outer canal of the ear to generate a sound. Some of this sound is reflected back from the eardrum, which is picked up by a microphone allowing an assessment of the health of the eardrum and middle ear.

The testing will be performed by a member of the UCSD Audiology Team. The team is composed of: Genevieve Harris, MA; Meghan Spriggs, Au.D.; Deborah Wian, MA; and Erika Zettner, Ph.D. The test will be performed in the Audiology Department, which is in the Perlman Medical Offices, which is in Lowe Level Suite A adjacent to Jacobs Medical Center, and will take about an hour.

Data from the Belfast Site

In response to a suggestion from the FDA that a second site be opened for the study, the sponsor is looking to open this second site at Queen's University Belfast. The proposal is that the second site for the study will be located at the Northern Ireland Clinical Trials Unit, 1st Floor Elliott Dynes Building, Royal Hospitals, Grosvenor Road, Belfast, BT12 6BA, U.K. (http://www.research.hscni.net/northern-ireland-clinical-trials-unit). UCSD will serve as the principal site for the study and the data from the Belfast site will be sent to UCSD for a final pooled analysis by the UCSD bio-statistics team at the CTRI.

The UCSD OCGA have been asked to establish an unfunded collaboration agreement with Queen's University. Part of this agreement will mandate that the Belfast ICF states explicitly that data collected will be shared with UCSD for analysis. In terms of this arrangement, the bio-statistics team at UCSD will be responsible for carrying out the final analysis of all the data. The study at the second site will be executed in accordance with GCP guidance and study monitoring will be in place throughout. The Research Plan as executed at UCSD will also be executed at the second site. Data for each of the primary, secondary and safety endpoints for each of the participants at the second site will be transferred electronically (with PHI removed) to James Proudfoot in bio-statistics at UCSD.

Data will be transferred in an encrypted PDF format. Trial staff will be given direction on how to share the trial data and given access to one specific section of a controlled cloud service which is controlled via role based access. Once they have authenticated with the service and the service verifies that they have the correct role to access the system they will be directed to a single webpage within the application where they will be able to upload the encrypted PDF. This PDF is generated on the fly and is therefore not stored in another location that could become compromised. Generating the PDF on the fly means that the source data is extracted from the database, processed and delivered in the context of a single request. This is an important factor as this means that after the request finishes the data in the PDF will not be held in application memory once the request is finished and the data relating to the request is freed. After the PDF is generated it is delivered to the assigned statistician using TLS 1.2 (a strong protocol), ECDHE_ECDSA with X25519 (a strong key exchange), and AES_128_GCM (a strong cipher). These data will be transferred for each subject when they complete participation in the study. If they complete the study protocol this will be at the one-year mark, however, if they drop out early then data accrued up until that point will be sent.

References

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Krystal AD, Zammit GK, Wyatt JK, Quan SF, Edinger JD, White DP, Chiacchierini RP, Malhotra A. The effect of vestibular stimulation in a four-hour sleep phase advance model of transient insomnia. J Clin Sleep Med 2010; 15: 315-321.

Marshall MJ, Jasko JG, Zhang H. Therapeutic effectiveness and patient acceptance of a vestibular nerve activation intervention in chronic insomnia. Medicamundi 2010; 54: 89-93.

STATISTICAL CONSIDERATIONS

These statistical considerations were constructed in conjunction with James Proudfoot of the bio-statistics unit at the ACTRI.

Randomization

Treatment assignments will be generated via a randomized block procedure, with block sizes randomly chosen in the set {2, 4, 6, 8, 10, 12}. Subjects will be assigned 2:1 between treatment and control groups. Stratification will be performed by gender and center.

Methods: Primary Aims

For total body weight loss (TBWL) as a continuous measure, we will use a two-sample t-test to examine the differences between the control and active treatment groups at each time period. We will also build one-sided confidence intervals to test whether the difference between groups exceeds a superiority margin of 5%. As a secondary analysis, we will also use a linear regression with TBWL as the dependent variable and group and other covariates of interest (gender, age, etc.) as independent variables. To assess any longitudinal effects, we will use a linear mixed effects model for weight over time, with fixed covariates for baseline weight, time, group, and a time / group interaction, and a random intercept to account for within-subject correlation. We will use a one-sided exact binomial test to determine if the response rate in the treatment group significantly exceeds 35%, with response defined by a loss of at least 5% of their body weight at the 12-month follow-up. We will also use Fisher's exact test to compare the response rates in each group, and, as a secondary analysis, will consider the use of a logistic regression to control for any other covariates of interest. To investigate possible longitudinal trends, we will fit a logistic mixed effects model, similar to the linear mixed effects model described above.

Methods: Secondary Aims

For each continuous and categorical variable at each time point, we will use a two-sample t-test and Fisher's exact test, respectively. Summary statistics (mean, standard deviation, quantiles, counts, and percentages) and plots will be produced for all demographic and study outcomes. We will investigate the effectiveness of the device by usage by including usage time as a continuous covariate in a linear model for TBWL. CTRI Biostatistics Core personnel will conduct all analyses using the latest version of R (R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/). No alpha spending function is applied to adjust for multiple comparisons across the secondary aims, and no claims will be made based on any of the secondary endpoints, which are instead viewed as hypothesis generating endpoints.

Missing Data

The primary hypotheses will be tested on the intent-to-treat population. A sensitivity analysis will be

performed with the binary weight loss endpoint. This analysis will include a best-case scenario (assuming subjects with missing values have all lost over 5% body weight), a worst-case scenario (assuming no subjects with missing values have lost over 5% body weight), and a tipping point analysis (as described in Yan[1]). We will check the assumption that the data is missing completely at random, and use multiple imputation techniques to reduce bias in the estimation of the treatment effect. Missing data will be clearly reported and included in tables.

Power Calculation

The primary outcomes are TBWL from the start of treatment until the 12-month mark and the number of subjects who lose at least 5% of their baseline total body weight. We will power both of these tests at the 0.025 significance level (a Bonferonni correction to maintain a family-wise error rate of 0.05 in our primary analysis). For TBWL, we will test the following null and alternative hypothesis:

$$H_0: \mu_t - \mu_c \leq 5\%$$
$$H_1: \mu_t - \mu_c > 5\%$$

where μ_t and μ_c are the treatment and control mean TBWL in the ITT population. We will use a one-sided two-sample t-test to determine if there is a statistically significant difference in TBWL between our control and treatment arms beyond a superiority margin of 5%. With a total sample size of 90 subjects (30 sham and 60 active treatment), this t-test will have 80% power at the $\alpha = 0.025$ significance level to detect an effect size of $d = 0.63$. Assuming a similar standard deviation of TBWL as the ReShape trial (7.5%), this translates to a detectable difference in TBWL between the treatment and control groups of 4.75%. Assuming this same standard deviation, a two-sample superiority test will have 80% power assuming that the true difference between groups is 6.33%.

For the proportion of treatment subjects who lose at least 5% of their baseline total body weight, we will test the following null and alternative hypothesis:

$$H_0: P_t \leq 35\%$$
$$H_1: P_t > 35\%$$

where P_t is the proportion of treatment subjects who lose at least 5% of their body weight by the twelve month follow-up. With a total sample size of $n = 60$ active treatment subjects, an exact binomial test will have 80% power at the 0.025 significance level to detect an effect size of $h = 0.321$. This effect size is equivalent to observing a response rate of 50.8% in the treatment group, similar to that seen in the ReShape study. We note that our pilot data indicated that all subjects reached this endpoint, but the sample size was too small to reliably estimate an effect size for the use of powering this study (Kramer 2006).

Anticipating a drop out rate of 15%, we will plan to recruit $n = 106$ total subjects overall in the study across both sites.

Interim Analysis

No interim analysis will be performed.

Representativeness Analysis

As per the guidance from the FDA relating to the representativeness of the study population (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UC

M507278.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery) the following analyses will be conducted:
For each demographic characteristic an appropriate statistical test will be conducted to flag any differences between the two respective subgroups (active and sham device). For categorical data either a Chi-square test (if n ≥ 5 in each table cell) or Fisher's exact test (if n < 5 in any single table cell), will be used, and for continuous a 2-sample t-test will be used to compare the respective subgroups.

References

Yan, Lee & Li (2009). Missing Data Handling Methods in Medical Device Clinical Trials. Journal of Biopharmaceutical Statistics, 19: 6, 1085-1098.

Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA (2006). Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch Gen Psychiatry, 63 (5): 484-9.

Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED) for ReShape Integrated Dual Baloon System. 2015.

Pre-enrollment Screening

Prior to being allowed to start the study proper, potential subjects with type 2 diabetes should be excluded by means of a fasting blood glucose test. This can be via a finger prick sample and glucose meter. Testing should be done in the morning after an overnight fast of at least 8 hours. If the reading is 126 mg/dl or above then the potential subject will be excluded from the study and asked to see their primary care physician in order to be investigated for type 2 diabetes mellitus. The rationale for excluding subjects with type 2 diabetes is explained in Appendix 3. At the same Screen Visit subjects will complete a questionnaire about their medical history and medications to ensure that they fulfil the inclusion and exclusion criteria for the study. The questionnaires will be identified using an alphanumeric code and will not have any identifiable subject data on them. The questionnaires will be securely stored at the ACTRI.

Device Use Procedure

Subjects will be provided will disposable alcohol wipes and asked to clean this area of skin before applying their device. Subjects will also be provided with an adequate supply of disposable 32mm diameter hydrogel electrodes, which are manufactured to go with the device. It is estimated that these electrodes will need to be changed about once a week. The need to change them can be judged by whether they still stick the skin.

The devices come with an instruction sheet indicating that they have buttons on them to increase and decrease the delivered current. Most people can tolerate up to 1.0mA without difficulty and subjects will be encouraged to turn the device up as much as they are comfortable with. Subjects will though be advised that not all users are consciously aware of any stimulation taking place. This is true for some users of the actual device, and also necessary because of the fact that the sham devices will not deliver any electrical current. Subjects can monitor the current being delivered by means of a smart phone app (iOS and Android) that will be installed when they are enrolled in the study. With the sham devices the app will reflect the number of button presses.

Subjects will self-administer VeNS or sham stimulation at home for a total of at least 5 hours a week. If they wish the subjects can use the devices for up to 7 hours a week. The devices are able to detect when they are applied properly, as they measure resistance, and they will record usage data, which they will store pending retrieval when the subjects next attend for review. The skin behind the ears will be visually

inspected during follow up visits and all subjects will be provided with aloe vera gel to apply as required, as this is thought to be particularly effective in preventing skin irritation by VeNS. Subjects will also be advised to contact study staff should they have concerns about skin irritation, and will be provided with contact numbers to do so. If they do then a review will be arranged for when next convenient, and the subject will be advised not to use the device until reviewed. If on review there are ongoing concerns about skin irritation, as evinced for instance by redness, then the subject will be withdrawn from the study.

Appendix 1: Study Devices and Risk Assessment

Background

The VeNS stimulators and sham stimulation devices that will be utilized are being provided free of charge by the company Neurovalens. The sham devices will externally appear identical to the VeNS stimulators, however, they will not deliver an actual electrical current to the skin behind the ears and as such the vestibular nerve will not be stimulated.

Risk Assessment

In terms of this amendment the following risk assessment was also carried out for vestibular nerve stimulation devices that can deliver up to 1mA. Under the guidance for IRBs from the FDA a device will be determined to be non-significant risk (NSR) if it does not meet the definition of a significant risk (SR) device (see https://irb.ucsd.edu/device.pdf). A SR device is one which meets at least one of the following criteria:

a. The device is intended as an implant.
b. The device supports or sustains human life.
c. The use of the device is of substantial importance in diagnosing, curing, mitigating, or treating disease, or preventing impairment of health.
d. The device could cause significant harm to any subjects.
e. The subject must undergo a procedure as part of the device study.
f. The device appears on the FDA list of significant risk devices.
g. The study or any of the study procedures could cause harm to the subjects which:
i. could be life threatening;
ii. could cause permanent impairment of a body function;
iii. could cause permanent damage to body structure;
iv. or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or preclude permanent damage to body structure.

As the device is not implanted, no procedure is required to use it, it does not support or sustain life and it is not on the FDA list of significant risk devices, criteria a, b, e and f clearly do not apply. Regarding criterion c, the aim of this study is to investigate whether vestibular stimulation can, in conjunction with lifestyle interventions, assist with fat loss. It may be the case that VeNS has such a role, but it is unlikely that this will be of "substantial importance in … curing, mitigating, or treating disease, or preventing impairment of health." Thus criterion c does not apply.

This then leaves criteria d and g, which both pertain to users suffering significant harm from the device. When the device is turned on it will start at 0mA and the current can then be increased in 0.1mA increments up to 1.0mA. The waveform is a bipolar rectangular shape with 50% duty cycle and – i.e. half the time no current is being delivered. The device is powered via a 4.25V battery and can be recharged

through a USB connection. There is also a hardware interlock to ensure the device cannot be switched on when the charging cable is being used. Please note the device is battery, and not mains, powered.

The devices are placed on the head in a manner analogous to headphones, and the VeNS devices will deliver a small electrical current (1.0mA or less) to the skin behind the ears over the mastoid processes. The device can only be used for up to one hour a day, and after being used for this time period the device will automatically lock out until the next day. Delivery of electrical current to the skin over the mastoid region is known to activate all five components of the vestibular apparatus, but lower level currents (below 3mA) are thought to particularly activate the two otolith organs responsible for detecting linear acceleration and gravity (Zink et al., 1998). It is these otolith organs that, from the animal studies, are particularly associated with a reduction in body fat. This technique – known as bilateral bipolar vestibular stimulation – has been known about since the 19th century and is known to be safe, though skin irritation behind the ears can occasionally occur (Fitzpatrick & Day, 2004).

More recently Paneri et al. (2015) reviewed the safety of repeated sessions of transcranial electrical stimulation (tES), a term that they use to encompass both the transdermal electrical modulation of cranial nerves (i.e. as in VeNS) and transcranial direct current stimulation (tDCS) of the cerebral cortex. Based on studies of tES on patient groups with depression (Brunoni et al., 2013) and migraine (Magis et al., 2013), and an array of studies of tES on normal volunteers (Brunoni et al., 2011; Kessler et al., 2012; McIntire et al., 2014; Morales-Quezada et al., 2015; Nitsche et al., 2003; Poreisz et al., 2007; Raimundo et al., 2012; Russo et al., 2013; Tadini et al., 2011), together with theoretical assessments of tES (Bikson et al., 2009; Brunoni et al., 2012), they commented that the "safety and tolerability profile previously accumulated regarding extended use of tES in clinical populations is compelling and supports a low-risk or non-significant risk designation" (Paneri et al., 2015).

Paneri et al. (2015) also assessed the safety and tolerability of repeated tES across time in a group of 100 volunteers who were split into three groups. The first group received sham stimulation, the second tES at 2mA, and the third pulses of tES at between 5 to 7 mA (this is notably higher than the 1mA maximum we are proposing to use). A total of 1905 treatment sessions were carried out in total across the three groups. The authors report no serious adverse events in any treatment condition, and that the common side effects were restricted to skin tingling, itching, and mild burning. Moreover, the incidence of these events were not statistically higher in the tES groups (Paneri et al., 2015). These mild skin sensations were not associated with withdrawal from the study and the authors report they became less salient after the first few sessions. Other adverse events, such as headache, were rare (<5%) and statistically indistinguishable across the three groups. Paneri et al. (2015) concluded that the "repeated use of limited output tES across extended periods, is well tolerated and poses no significant risks to healthy subjects, as previously observed in clinical studies".

This conclusion is in keeping with the findings of Wilkinson et al. (2009), who reported on a stroke patient who received repeated VeNS sessions as part of his rehabilitation therapy. The authors observed no adverse events during stimulation over 5 consecutive daily sessions of VeNS at 1mA for 30 minutes per day. Utz et al. (2011) studied the adverse effects of 255 VeNS sessions at 1.5mA (again higher than the 1mA we propose to use) in 55 stroke patients and 30 healthy controls. They found only a few mild adverse effects, with the most common being slight itching (mean 10.2%) and tingling (mean 10.7%) underneath the electrodes. They concluded that VeNS induces "very few and mild adverse effects in healthy and persons with stroke and [is] safe" (Utz et al., 2011). There is thus a body of literature supporting the safe usage of both tES and specifically VeNS devices delivering at least 1mA in stimulation.

Similarly, in February 2016, Halo Neuroscience, a company based in San Francisco, released additional data on the safety of tES; on this occasion for a 2mA tDCS device used on 1010 subjects.[1] They state that "there were zero reports of burn or seizure activity across all 1010 subjects, zero serious or unexpected adverse effects and zero withdrawals due to adverse events other than unpleasant sensation". They conclude that their tES study showed "a favorable safety profile and [was] associated with a very low incidence of adverse events, with no unexpected or serious adverse events".

Specific measures taken to reduce the incidence of skin irritation are the 32mm diameter of the electrodes, which are themselves hypo-allergenic, and the 50% duty cycle (i.e. half the time no current at all is being delivered), and the maximum current of 1.0mA. This means that the maximum phase current that can be delivered is only 500μC. In conclusion, there is not a significant risk of harm from using the device, and as such criteria d and g do not apply. Thus as the device does not meet the criteria of a SR device it is a NSR device.

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Appendix 2: Weight Loss Program

Both the control and experimental groups will be exposed to a double-pronged weight reduction program. The first component of this will consist of face-to-face diet counseling by the Clinical Research Dieticians, led by Cynthia Knott, at the ACTRI. The research dieticians will also be blinded to the allocation of treatment. The initial session when subjects start the study will last 30 minutes and during it the dietician will review a three-day diet record provided by the subjects, review study dietary goals, identify areas of concern, and target subject goals and then work on a time-line or "contract" with the subject. The subjects and dieticians will subsequently have 15-minute follow-up meetings scheduled when the subjects attend for review at months 3 and 6.

The subjects will also be given access to the GB HealthWatch 360 app (see: https://healthwatch360.gbhealthwatch.com/health360.php), which is operated by a San Diego based

company that provides a commercial service to both monitor trial participants' caloric intake (very thoroughly indeed), and also physical activity (via another app called Moves). Simultaneously the GB Healthwatch 360 app can advise them on a daily basis about their diet and what options would be best for weight loss. Subjects will be asked to update this app every day with a record of what they are eating, in return the app will help them monitor their caloric intake for the day and advise them on eating choices to achieve the goal of weight loss.

Weight loss will be set as a goal in the app for all subjects, causing their recommended calorie goal for the day to decrease, and the algorithm underlying their daily nutrition score to reflect how well they do meeting this goal. In addition, if their diet is too high in saturated fat, added sugar or calorie-dense foods, their daily score also will reflect this. There have been studies showing that self-monitoring of behavior and diet can be effective in producing weight loss. The GB Healthwatch 360 app also contains slideshows that review healthy food choices for weight loss, and articles that help educate users on nutrition and simple exercise regimes suitable even for the very obese. Subjects will be encouraged to view these slideshows, and to follow the dietary advice as well as participate in the suggested exercise regimes. There is a sister app for researchers that the research team can log into, which will deliver the data it has garnered in a spreadsheet form.

As described above the Healthwatch 360 app allows tracking of the subjects' daily dietary habits and also physical activities. Subjects are requested to input a description of what they have eaten into the HealthWatch 360 app every day, and their physical activity is monitored by the app pairing to the Moves of FitBit apps, and also subjects are requested to input physical activities directly into the app also. The information that subjects input allows tracking of their diet and exercise, as well as acting itself, in conjunction with the dietary counseling, as a behavioral modification. This is because, as stated above several studies have shown that self-monitoring of dietary intake and/or behavior via mobile app or other technologies can promote/result in weight loss (Burke et al., 2011; Lyzwinski 2014; Michaelides et al., 2016; Rutledge et al., 2017). Thus, all subjects, regardless of whether they are in the active or control group, will benefit from access to behavioral modification in the form of the HealthWatch 360 app, and also the face-to-face dietary counseling sessions.

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Appendix 3: Exclusion of Subjects with Type 2 Diabetes Mellitus

The decision to exclude participants with type 2 diabetes mellitus was made after reading the FDA's draft guidance (see: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071612.pdf). This notes that, "[c]ompared with nondiabetic patients, overweight and obese patients with type 2 diabetes often respond less favorably to weight-management products and may face unique safety issues such as risk for sulfonylurea-induced hypoglycemia following weight loss (if the dose of sulfonylurea is not appropriately lowered or the drug discontinued)."

The FDA then go on to advise "examining the efficacy and safety of weight-management products in trials dedicated to patients with type 2 diabetes." On the basis of this advice we made the decision to exclude patients with type 2 diabetes. This is an important patient group of course, and our intention is to investigate type 2 diabetics in due course. This current study will though include patients with impaired glucose tolerance, and this will be assessed by the oral glucose tolerance test.

If a subject is found to possibly have type 2 diabetes during the initial screening then they will be excluded and asked to notify their primary care physician. However, if a subject passes the initial screening but a suspicion of this diagnosis arises during one of the study tests, then the subject will be asked to notify their primary care physician, though they will still be allowed to complete the study.

Appendix 4: Dual Energy X-Ray Absorptiometry Scanning

Dual Energy X-ray Absorptiometry (DXA) is a technique that was originally developed to determine bone mineral density and to aid in the management of osteoporosis. More recently, the technique has been expanded to include the analysis of fat mass and lean body mass in addition to bone density. The DXA machine emits alternating high and low energy X-rays that produce precise, high quality images. A fan beam is now used and this technology allows decreased scan times so that scans are completed within seconds or minutes.

The basic principle of DXA data acquisition is based on the differences between bone and soft tissue attenuation at the high and low X-ray levels. As the X-ray beam passes through the subject, detectors register the varying levels of X-rays that are absorbed by the anatomical structures of the subject. The raw scan data, which includes values of tissue and bone, are captured and sent to a computer. An algorithm interprets each pixel, and creates an image and quantitative measurement of the bone and body tissues. The amount of radiation exposure is very low.

We will acquire a whole body DXA scans in Array mode (using the Hologic Discovery W DXA scanner at the ACTRI) at time-points 0, 3, 6 and 12 months. The technique has a precision error (1SD) of 3% for whole body fat, and automatically calculates total body fat, truncal fat and visceral adipose tissue. The radiation exposure associated with this protocol is small, and the cumulative total from all four scans has been calculated to be 0.18000mSv for each subject who participates. This amount is less than a year of background exposure in the San Diego area, which is 1.6mSv.

There is a DXA subject instruction sheet provided by Cynthia Knott at the ACTRI, that is being included with this submission. It includes instructions like avoiding strenuous exercise and large meals, and maintaining equivalent states of hydration in the hours immediately before a scan. Also all female subjects, of child bearing potential, must undergo a urinary pregnancy test prior to each DXA scan to ensure that they are not pregnant.

Appendix 5: Oral Glucose Tolerance Test (OGTT)

This test will follow the guidance laid down by the World Health Organization (see: http://apps.who.int/iris/bitstream/10665/43588/1/9241594934_eng.pdf). Note venous blood draws taken to assess glucose at time points zero, one-hour and two-hours after ingestion of 75g oral glucose load. The glucose should be dissolved in water and taken over no more than 5 minutes. This should be at 8am after a 10-hour fast. Drinking water is permitted but medications should be delayed until after the OGTT.

Bloods must be taken within 5 minutes of specified time points. The WHO guidance specifies the following diagnostic criteria:

Diabetes mellitus

Fasting plasma glucose ≥7.0mmol/l (126mg/dl)

or

2–h plasma glucose ≥11.1mmol/l (200mg/dl)

Impaired glucose tolerance

Fasting plasma glucose <7.0mmol/l (126mg/dl)

and

2–h plasma glucose ≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl)

Impaired fasting Glucose (IfG)

Fasting plasma glucose 6.1 to 6.9mmol/l (110mg/dl to 125mg/dl)

and (if measured)

2–h plasma glucose <7.8mmol/l (140mg/dl)

Appendix 6 – Good Clinical Practice Processes

As study will now have two sites these have been described in detail, and are listed in a separate appendix.

10. HUMAN SUBJECTS

The aim is to enroll a total of 150 subjects across both sites with a 2:1 split between the control and experimental groups, and a total of 60 subjects at UCSD. There will be no exclusion from the study on the basis of race, socioeconomic status, language spoken, or ethnicity. However, due to the very small dose of ionizing radiation delivered by DXA scanning, pregnant women will be excluded from participating (see Inclusion Criterion 2 below).

Pre-enrollment Screening for Type 2 Diabetes Mellitus

Prior to officially being enrolled in the study, potential subjects will be screened for type 2 diabetes mellitus by means of a fasting blood glucose test. This will be done via a finger prick sample and glucose

meter. Testing should be done in the morning after an overnight fast of at least 8 hours. If the reading is 126 mg/dl or above then the potential subject will be excluded from the study and asked to see their primary care physician in order to be investigated for type 2 diabetes mellitus.

As stated above, if a subject is found to possibly have type 2 diabetes during the initial screening then they will be excluded and asked to notify their primary care physician. However, if a subject passes the initial screening but then a suspicion of this diagnosis is made during one of the study tests, then the subject will be asked to notify their primary care physician, though they will still be allowed to complete the study.

Inclusion Criteria

1. Signed informed consent

Body mass index (BMI) ≥ 30 kg/m^2, or BMI ≥ 27 kg/m^2 with one or more of these obesity related co-morbid conditions:

a) History of treatment for systemic hypertension
b) History of treatment for dyslipidemia
c) History of treatment for sleep apnea syndrome
d) Stable cardiovascular disease (no change in medication and no active events within 1 year).

2. Males or Females. Note females of child-bearing potential must have a negative urine pregnancy test at screen and also just before each DXA scan. (As DXA involves a small dose of ionizing radiation). They should agree to follow a physician-approved contraceptive regimen for the duration of the study period (other than DMPA injections as this causes weight gain).
3. 22-80 years of age inclusive on starting the study. (In order to comply with FDA guidance: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm#s6)
4. Ability and willingness to complete all study visits and procedures.
5. Owner of a smart phone (iOS or Android) in order to access the diet monitoring and advice app (GB Healthwatch 360), activity monitoring app called Moves, and the app that reports on the status of the stimulation devices used in the study.
6. Agreement not to use of prescription drug therapy or the use of over-the-counter weight loss preparations for the duration of the trial.
7. Agreement not to start smoking tobacco or marijuana for the duration of the study.

Exclusion Criteria

1. History of vestibular dysfunction.
2. History of bariatric surgery, fundoplication, gastric resection or major upper-abdominal surgery (acceptable surgeries include cholecystectomy, hysterectomy).
3. History of skin breakdown, eczema or other dermatological condition (e.g. psoriasis) affecting the skin behind the ears, or of the head and neck.
4. History of weight loss device implantation (e.g. VBloc Maestro or Abiliti), or use of non-invasive weight loss device.
5. Untreated thyroid disorder (stable treatment for 3 months is acceptable).
6. Other endocrinological causes of weight gain (e.g. Cushing's disease, Cushing's syndrome or acromegaly)
7. Previous diagnosis of HIV infection or AIDS (HIV is known to cause a vestibular neuropathy which would prevent VeNS from working).
8. History of cirrhosis, or liver, kidney or heart failure.
9. Chronic pancreatitis.

10. Treatment with prescription weight-loss drug therapy in the year before starting the study.
11. Tobacco or marijuana smoking in the year prior to starting and for the duration of the study.
12. Known genetic cause of obesity (e.g., Prader-Willi Syndrome).
13. Body weight change of more than 10% in either direction within the previous year.
14. Physician-prescribed diet, and/ or current, active member of an organized weight loss program (e.g., Weight Watchers). (Note: study subjects may continue any personal eating plan they were on prior to study enrollment)
15. Diabetes mellitus (Types 1 & 2). (See Section 9 Research Design and Methods, Appendix 3)
16. Diagnosis of epilepsy or use of anti-epileptic medication within six months of starting the study (e.g. for the treatment of peripheral neuropathy)
17. Chronic (more than a month of daily use) treatment with opioid analgesic drugs within the last year.
18. Regular use (more than twice a month) of anti-histamine medication.
19. Use of oral or intravenous corticosteroid medication within a year of starting the study.
20. Use of the beta-blockers atenolol, metoprolol or propranolol within 3 months of starting the study.
21. Current alterations in treatment regimens of anti-depressant medication for whatever reason (including tricyclic antidepressants) (Note: stable treatment regimen for prior six months acceptable).
22. An active diagnosis of cancer.
23. A myocardial infarction within the preceding year.
24. A history of stroke or severe head injury (as defined by a head injury that required intensive care). (In case this damaged the neurological pathways involved in vestibular stimulation).
25. Presence of permanently implanted battery powered medical device or stimulator (e.g., pacemaker, implanted defibrillator, deep brain stimulator, vagal nerve stimulator etc.).
26. Psychiatric disorders (including untreated severe depression, schizophrenia, substance abuse, bulimia nervosa etc.)
27. Current participant in another weight loss study or other clinical trials.
28. Have a family member who is currently participating or is planning to participate in this study.
29. Subject weighs over 350 pounds as this is the weight limit of the DXA scanner.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

The study will recruit subjects via Research Match (see: https://actri.ucsd.edu/clinical/Pages/using-ResearchMatch.aspx). Research match is a "is a NIH-sponsored national registry of volunteers who have indicated a willingness to learn more about research studies." The aim of this registry is to connect "researchers with appropriate potential subjects." A proposed recruitment message for use on Research Match is being submitted with this Research Plan for IRB review. Best practice in the management of bias in recruitment will be followed.

In order to improve recruitment numbers we also plan to post the flyer included for review with this submission up at the ACTRI and in authorized locations on the UCSD campus.

We also intend to post an advertisement to Facebook groups relating to weight loss that operate in the Southern California area; if necessary we may ask Facebook to promote this statement via a paid advertisement. The proposed Facebook statement is also included for approval.

We also plan to suggest to active subjects, via phone or email, that they give our contact details to friends or family that may be suitable to participate. In return they will receive $25 compensation if someone they referred is then enrolled. The proposed text is included with this submission.

12. INFORMED CONSENT

In order to facilitate the identification of prospective research participants who meet the eligibility criteria for enrollment review it is proposed that pre-screening by telephone take place. In order to allow this to take place over the telephone it is requested that a waiver of consent documentation is allowed. The script for this telephone pre-screening is included for review by the IRB.

This process is considered minimal risk to the potential subjects as all data gathered via this process will be treated in the same confidential manner as data gathered at any other part of the study. Moreover, all data for subjects deemed ineligible to participate will be destroyed at the end of the phone call to pre-screen them. It is not believed that this process will adversely affect the rights and welfare of potential subjects that are pre-screened as the telephone script still includes the Elements of Consent. Potential subjects are thus requested to give verbal consent to undergo the pre-screening process. However, as it takes place over the phone it is not possible to obtain signed consent.

Without the waiver of documented consent in place the recruitment process would be much more cumbersome, a lot less practical and potentially significantly inconvenient for the potential subjects. This is because there are over 30 inclusion and exclusion criteria, several of which include the use of a variety of commonly taken medications. Thus many potential subjects would attend in person at the CTRI despite being clearly ineligible to participate in the study.

In terms of providing additional information to potential subjects, those judged eligible to proceed on the basis of the phone pre-screening will be invited to a face-to-face meeting at the CTRI. There they will be provided with a copy of the Informed Consent Form, which the research coordinator will then talk through with them.

Other than the data provided over the phone by potential subjects undergoing the pre-screening process no hospital records or other PHI will accessed as part of the telephone pre-screening process. Thus it is judged that waiver of HIPAA consent is not necessary.

Individuals that agree to participate in a research study will be informed about the purpose and the duration of the current study. Informed consent will be obtained, once the subject has been informed and wants to participate in this investigation, using the attached informed consent form.

Informed consent will be taken by clinical trial coordinators at the ACTRI. This will be done in a private room at the ACTRI in a manner that is non-coercive and using language that is understandable to the potential participants. No exculpatory language will be used and the participants will not be asked to waive any of their legal rights.

13. ALTERNATIVES TO STUDY PARTICIPATION

Subjects are free to participate or not participate as they wish. Alternatively many different techniques are available to assist individuals who are overweight in losing weight. These include a wide range of different diets and exercise regimes, as well as, if indicated, weight loss medications and weight loss (bariatric) surgery.

14. POTENTIAL RISKS

General Risks

1. Information of a personal nature will be collected in order to determine eligibility for the study, and therefore there is a risk of loss confidentiality.

2. Subjects may experience some degree of distress or anxiety due to confusion, the personal nature of

the questions, the VeNS, or their disqualification based on the exclusion criteria.

Risks relating to Screen Visit

There is a risk in the Screen Visit that a diagnosis of diabetes mellitus may be suggested.

Risks related to VeNS

A risk assessment for the device has been carried out (see Section 9 above) which indicates that it is a non-significant risk device. Due to the low current (1mA) and voltage (4.25 V), the VeNS stimulator being used in the study is safe. However, the following specific risks do exist:

1. Skin irritation at the electrode sites.
2. That the stimulation sites may be uncomfortable at the time of stimulation – an electrical tingling sensation may occur and also VeNS may induce the sensation of being pushed towards the side of the cathode.
3. A sensation of disequilibrium, analogous to being on a boat, may occur during the test that some subjects find uncomfortable.
4. VeNS may induce nausea.
5. VeNS may occasionally induce vomiting.
6. Headache has been reported to occur by Utz et al. 2011 as a side-effect from VeNS, but in all cases was mild and self-limiting.

Risks related to DXA Scanning

1. It has been calculated that subjects will be exposed to a combined total radiation dose of 0.18000mSv from the four whole body scans they will receive over the course of a year participating in the study. The scanner used at the ACTRI is a Hologic Discovery W DXA scanner, and the scans administered will be whole body scans in Array mode. Ionizing radiation is known to carry a dose related increased risk of cancer.
2. The scan sequences we are proposing to use were selected to provide the greatest possible information about body mass composition while exposing the subjects to the lowest possible dose of ionizing radiation. We note in this regard that the total dose we are proposing over the one year period of the study is less than the average background from living in San Diego for a year which is 1.6 mSv.
3. In order for the DXA scanner to function properly all metal must be removed from the subjects' bodies and they must change into a hospital gown. Some subjects may find doing so to be embarrassing or uncomfortable.

Risks relating to weight loss programs

1. Subjects will have to discuss their dietary habits and weight loss aspirations with a professional dietician and some subjects may find doing so to be embarrassing or awkward. Also has with any personal data there is a risk of loss of confidentiality.
2. Data pertaining to the subjects' diet and physical activity will be collected on the GB Healthwatch 360 app and, although this is a platform specifically designed for researchers, there is as with the collection of any data the risk of loss of confidentiality.

Risks relating to Audiograms

1. Some subjects may find the process of otoscope examination of the ear canal prior to the audiogram to be uncomfortable.
2. It is theoretically possible that the otoscope examination could cause some local trauma to the ear canal.
3. It is possible that the audiogram test may reveal some hearing loss that the subject was not previously aware of and that this could cause them psychological distress.
4. Minor discomfort or pressure may be experienced from headphones.

Risk of Loss of Confidentiality

This is a general risk that applies to all of the data gathered as part of the study. The processes for managing the risk of loss of confidentiality are described in Section 16.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Risks relating to Screen Visit

If a diagnosis of diabetes mellitus is suggested during the Screen Visit then the subject will not be able to continue in the study. Instead the subject will be advised that this is a possibility and that they should see their primary care physician for further assessment regarding this possible diagnosis. Some patients may not be aware that they have diabetes, but if it is diagnosed it allows treatment to be undertaken which can significantly reduce the risk of the various ill-effects that diabetes can cause.

Risks Related to Vestibular Nerve Stimulation (VeNS)

1. The devices being used have been judged to be non-significant risk devices in the risk assessment, carried out according to FDA criteria, that is detailed in Section 9.
2. Any potential subjects a history of irritation to the skin behind the ear will be excluded (See Criterion 3 in Exclusion Criteria).
3. Hypoallergenic hydrogel electrodes of 32mm diameter will be used in order to minimize the likelihood of skin irritation.
4. Subjects will be provided with a gel containing aloe vera and as a means minimizing skin irritation. They will be asked to apply this after using the device.
5. If skin irritation occurs after using the device the subjects will be advised to apply the aloe vera gel, and they will also be given a contact number at the ACTRI they can call in order to arrange a review.
6. Prior to the beginning of the study the possible discomforts of VeNS will be described to the participant in lay language, and the investigator will make sure that the subject understands what will happen when using the device.
7. The usage of the device is electronically limited to just 60 minutes per day.
8. Usage is voluntary, and subjects will be informed at the beginning of the study that they may withdraw at any time, for any reason, with no negative repercussions.
9. Subjects will be warned about the sensation of disequilibrium and will be advised that the device should be used only while seated.
10. The maximum current the device can deliver is 1mA but there is no requirement for the subjects to use it as this level. Instead they will be asked to increase the current (using buttons on the device)

to a level that is comfortable. The minimum setting is 0.1mA and the current can be increased in 0.1mA increments.

11. If subjects find the sensation invoked at the level they have the current set, to be uncomfortable (e.g. in terms of nausea or disequilibrium) then they can lower the stimulation level to a more comfortable setting.
12. The subjects can always take off the devices at any point they wish.

Risks Related to DXA Scan

1. All female participants will have to provide a negative urinary pregnancy test prior to DXA scanning due to the very small amount of ionizing radiation involved in DXA scanning.
2. If participants become claustrophobic during the scanning process, the scan will be stopped and the participant will be able to leave the room. Given the scans can be conducted in around 5 minutes this risk should be minimal.
3. Thorough prescreening of all patients prior to the DXA scan to make sure they have no metal on their bodies or clothing. Participants will also be asked to wear a hospital gown, which will be available to them at the ACTRI. They will be provided with a private area to change back and forth from their clothes into the gown.
4. The dose of ionizing radiation from these scans is very small (it has been calculated that it will add up to a total of 0.18000mSv for the four whole body scans over the year) and much less than the annual background from living in the San Diego area, which is 1.6 mSv. Exposure to this small dose of radiation will be explicitly mentioned in the consent document.

Risks pertaining to weight loss programs

1. The Dietician at the ACTRI who will administer the weight loss advice is Cynthia Knott who is a qualified professional, employed by the ACTRI, with experience of such studies in the past.

Risks relating to Audiograms

1. The examinations will only be carried out by trained clinical professionals who are all UCSD employees.
2. Participants will be free at any time to indicate that they wish to stop the procedure.
3. The risk of revealing a previously unknown hearing impairment will be described in the Informed Consent Form.
4. If headphones are not tolerated, then a different type of ear phone will be employed, which consist of a soft foam which is placed at the entrance to the ear canal.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

1. Subject's information will be kept strictly confidential to the extent provided by law. An alphanumeric code will be assigned to each subject, and this code will be used in place of a name when reporting data. The hardcopy corresponding subjects with codes will be kept in a locked data cabinet in the ACTRI, along with all results of all screening inventories, assays, and questionnaires. The computer to be used for data collection and analysis will require a password for access, which only personnel directly involved in the study will have. Data in any format will only be available for those on the

protocol. Information collected in the study will not be reused or disclosed for other purposes. Data collected in the study will be destroyed after seven years.

2. All aspects of the study will be explained to the subject in lay language, and the experimenter will make sure that the subject understands what will happen prior to his/her participation. The experimenters will inform the subject of the precautions that will be taken with regard to personal information collected during the course of the study. The study will be as short as possible. Participation is voluntary, and subjects will be informed at the beginning of the study that they may withdraw at any time, for any reason, with no negative repercussions. The research should in no way result in social stigmatization or any other long-term distress to the subjects.

3. In order to minimize the risk of coercing subjects to participate, and in keeping with the UCSD HRPP guidance in this area no attempts to recruit subjects during undergraduate classes will be made.

4. Similarly, due to the risk of coercion the following will be excluded from participating: graduate students in Psychology; undergraduate students working as research assistants at the CBC; employees in Psychology.

5. We consulted GB HealthWatch 360 about their app's security/confidentiality set-up. Their reply is as follows:

   "All HealthWatch 360 application data and user data are encrypted and remotely backed up on a daily basis, in which all the data transmission and storage is protected with AES-256 encryption. This means the only risk is losing up to the most recent 24 hours of data.

   You can download/export your project data from the research portal at any time. We build our application and databases on a leased dedicated server hosted in a secure datacenter in Atlanta, GA. The datacenter successfully completed a rigorous audit from a certified independent CPA to validate that it is operating in compliance with new SSAE 16 (SAS70) standards (the SSAE 16 audit validates that all IT Infrastructure hosted within the facilities are secured through the implementation of IT controls that adhere to the new SSAE 16 guidelines).

   As we are using a dedicated server, we have total control and implement the highest level of security policies to protect our server from hacking and intrusion. In addition, while using the research portal, all participant data is exported masked with randomly assigned participant IDs."

17. POTENTIAL BENEFITS

The current study will contribute to the field of knowledge about the neurological mechanisms that control body mass composition. We will also determine whether the relatively inexpensive, and non-invasive technique of VeNS is an effective treatment for obesity and fat loss. This is of particular importance given the current obesity pandemic and the serious public health challenge that this poses.

A potential benefit for participants is that they may experience some degree of weight loss as a result of participation. This is true for both the experimental and control groups, as both will be receive weight loss counseling from the ACTRI's dietician, Ms C. Knott, as well as receive one year's access to the GB Healthwatch 360 app. This app will assist them in making healthy dietary decisions, and exercises they can undertake, in order to reduce their weight.

18. RISK/BENEFIT RATIO

The risks to participants in this study are relatively small (skin irritation, mild discomfort, possible nausea and, compared to background, a very small dose of radiation), as well as transient in nature; the discomfort and nausea will stop soon after stopping VeNS. Conversely, in terms of the importance of the knowledge that a positive study would yield, the potential benefits are significant. The global obesity pandemic poses significant public health challenges, and developing novel strategies to combat it are of paramount importance.

The current study explores the possibility that the noninvasive and relatively inexpensive technique of VeNS may be useful as a weight loss adjunct. Given the importance of the knowledge that may be gained, we believe the small risks to the subjects are reasonable.

19. EXPENSE TO PARTICIPANT

There will be no monetary expense to the subject for participation in the study. All study visits will take place at the ACTRI, and parking and reasonable traveling costs will be reimbursed. Scheduling of the sessions will be made to avoid inconvenience. The VeNS devices used in the study will be provided to the subjects free of charge, and the same applies to access to dietetic advice, as well as the weight loss app (GB Healthwatch 360).

20. COMPENSATION FOR PARTICIPATION

Participants in the study will receive $250 for their complete participation in this study. If they terminate their involvement early then they will receive $50 for each 3 months they have completed. If they wish subjects can be paid on a pro rata basis as they attend ($50 at months 3 and 6, and another $150 at the final visit), or alternatively $250 on completion of the study. If they end their involvement before completing the three-month DXA scan they will be asked to return their device and in return receive $15. This compensation is payment for the participants' time and not any type of coercion to participate. If subjects are excluded during the Screen Visit then they will receive travel/parking expenses but no additional compensation.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Dr V.S. Ramachandran, MD PhD Professor of Psychology and Neuroscience at UCSD and Director of the Center for Brain and Cognition is the PI.
Dr Paul D. McGeoch, MB ChB MD MRCP FRCS(SN) Visiting Scholar, Center for Brain and Cognition UCSD is a co-investigator. He will be involved in general ongoing oversight of the study.
Cynthia Knott, RDN, CCRC, Clinical Research Dietitian, ACTRI, UCSD, will administer dietetic counseling and also operate the DXA scanner.
Jeff Ledford-Mills BA is an ACTRI research coordinator who will be involved in recruitment, consent, data gathering and coordination of the study.
Denya Arellano MD is a research coordinator at the ACTRI who will be involved in recruitment, consent, data gathering and coordination of the study.
Sharon Quigley is a Project Manager at the ACTRI who may act as a study contact.
Mark Wallace MD is a co-investigator as in order to order labs at UCSD Health it is necessary to have a physician who practices there place the order requests.
Maeve Taaffe RN is the senior nurse at the ACTRI who will oversee nursing activities undertaken in the study.
Rachel Croft BA is Dr Ramachandran's research assistant, who may if necessary transport consumables for study use (e.g. cash to compensate subjects and spare electrode pads) from Dr Ramachandran's lab to the coordinator at the ACTRI.
James Proudfoot MSc is the study statistician. He is based at the ACTRI.
Jason McKeown MD is a Visiting Scholar at the Center for Brain & Cognition and a co-investigator in the

study. His role is limited to training the coordinators on how to use the study device.
Deeba Pourmand MS is a research coordinator at the ACTRI who is carrying out the role of study monitor.

22. BIBLIOGRAPHY

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23. FUNDING SUPPORT FOR THIS STUDY

The funding support for this investigator-initiated protocol will be from a grant arranged via OCGA to the Center for Brain and Cognition from Neurovalens (see Section 27).

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

A risk assessment has been carried out according to the criteria outlined by the FDA (see Section 9, Appendix 1) which indicates that the device has a non-significant risk status.

26. IMPACT ON STAFF

Not applicable – study to be carried out at the ACTRI.

27. CONFLICT OF INTEREST

Dr Ramachandran and Dr McGeoch are named as co-inventors on patent held by the Regents of the University of California that pertain to using electrical stimulation of the vestibular nerve as a means of altering body mass composition. Dr McGeoch was involved in co-founding Neurovalens, which has licensed the right to commercially exploit this technology from the University of California.

Neurovalens is funding the research via a grant negotiated with OCGA (see Section 23). Relevant forms are being filed with the COI office at UCSD, and the study will be executed at the ACTRI by its own research staff.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable.