# The SLEEEP Study Protocol

## Scientific Title

**Sleep, Lifestyle, Energy, Eating, Exercise Program for the management of sleep apnea patients indicated for weight loss treatment: A randomised controlled pilot study**

## Simplified Title

SLEEEP Study

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This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Part or all of the information in this protocol may be unpublished material.

Accordingly, this protocol is to be treated as confidential and restricted to its intended use.

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## AIM

In this phase 2A study we will not statistically compare the effectiveness of these two tailored isocaloric dietary interventions of “low GI/high protein” (LGHP) or a “standard hypocaloric diet based on the Australian guide to healthy eating” (AGHE) each preceded by an identical three month very low energy diet (VLED) and lifestyle modification program. We are studying the prognosis of patients given these diets while using randomisation to ensure the groups of patients are comparable. We suspect that these two treatments will have equivalent effects. Any statement of relative effectiveness of these diets will need to be tested in a larger more adequately powered trial. The difference in sympathetic activity will predict success of weight loss maintenance and be correlated with improvement in cardiovascular risk and obstructive sleep apnea profiles with the additive benefit of mechanical treatment of obstructive sleep apnea. Phenotyping the sympathetic activity response to weight loss following these two different dietary programs will allow better tailored treatment and more realistic treatment outcome prediction amongst obese patients with OSA.

## Hypotheses

1. Patients randomised to the low GI/high protein diet will maintain weight loss achieved through a very low energy diet and demonstrate a reduction in clinical symptoms associated with sleep apnea.
2. Patients randomised to the standard hypocaloric diet will maintain weight loss achieved through a very low energy diet and demonstrate a reduction in clinical symptoms associated with sleep apnea.

*N.b. we are not statistically testing the relative effectiveness of these two diets*

1. Patients with obstructive sleep apnea have lower sympathetic activity following weight loss.
2. Patients with higher sympathetic activity at baseline are more resistant to weight loss across diets
3. Patients with higher sympathetic activity at the point of randomisation following a very low energy diet will be more resistant to weight loss maintenance. Smaller reductions in sympathetic activity following a very low energy diet will be predictive of weight regain.

In addition, part of the secondary aim of this study will determine whether the magnitude of weight loss will be influenced by levels of self-efficacy whereby patients with higher self-efficacy will also have a higher quality of life as assessed through questionnaires.

## Background

Obstructive Sleep Apnea (OSA) affects over 3.5 million Australians with approximately 25% complaining of marked sleepiness and is one of the most common health complications of obesity and central adiposity.

OSA is a disorder which is characterised by repetitive episodes of partial (hypopnea) or complete (apnea) upper airway obstruction occurring during sleep. These episodes often result in snoring and oxyhaemoglobin desaturations that are usually terminated by brief arousals from sleep. OSA is associated with hypertension, cardiovascular disease, depression, impaired quality of life, excessive daytime sleepiness (EDS) and impaired neurobehavioral functioning. Continuous positive airway pressure (CPAP) is considered to be the ‘gold standard’ treatment for OSA. CPAP effectively alleviates obstructive episodes during sleep and has been found to improve parameters of sleepiness, cognitive performance and functional status in patients with severe OSA, however, compliance with this treatment as well as other mechanical alternatives is problematic.

The only major modifiable risk factor for sleep apnea is obesity but the efficacy of weight loss in reducing OSA in individual patients is extremely variable. We know that weight loss is effective for reducing the clinical problems associated with sleep apnea such as daytime sleepiness, cardiovascular risk etc. As gradual weight loss is the recommended treatment approach in OSA, many patients will not immediately improve the disturbing daytime sleepinessthat is often the chief clinical complaint and one of the factors accountable for the lack of weight loss. Furthermore, mechanical treatment compliance often limits the potential for improvement in symptoms of daytime sleepiness.

Most weight loss studies in this clinical population are of limited duration and there is little insight into the diets that are effective for long term weight maintenance in this population. Current evidence regarding dietary prescription in the OSA population is limited and usually incorporates exclusive use of very low energy diets (VLED) rather than coupling such diets with a maintenance phase for long term sustained with loss (Anandam et al. 2012). Recent studies have alluded that the macronutrient composition of diets during weight loss can influence energy expenditure during weight loss and maintenance phases (Ebbeling et al. 2012) however this concept has not been specifically investigated in a sleep apnea cohort. Current evidence indicates the use of a low glycemic index high protein diet in individuals seeking weight loss, metabolic and cardiovascular risk reduction for weight loss maintenance (Larsen et al. 2010, Brand-Miller et al. 2002, McMillan-Price et al. 2006) but this has not been tested in people with OSA. It is vitally important to test weight management interventions specifically in populations with OSA because there is evidence to suggest that this population may be particularly resistant to weight loss. Such weight loss resistance may be related to the symptoms of sleep apnea (such as daytime sleepiness interfering with exercise capacity), which are known to be associated with alterations in sympathetic activity.

Furthermore, obstructive sleep apnea is frequently associated with heightened sympathetic nervous activity and there is a complex integration between cardiovascular reflexes and central autonomic influences that control physiological sleep dependent changes in arterial blood pressure and heart rate (Cortelli et al. 2012). Perturbations in neuroadrenergic function play a key role in the genesis and progression of the metabolic syndrome and its related cardiometabolic risk (Mancia et al. 2007). In established obesity, metabolic, hemodynamic and medical (OSA) factors contribute to sustained elevation in sympathetic tone, a long term cycle that in the long term, leads to target organ damage and worse clinical prognosis (Mancia et al. 2007, Seals and Bell 2004).

Weight loss and diet induced changes in sympathetic nervous activity have implications in obese patients with OSA (Young and Landsberg 1982, Troisi et al. 1991). While evidence supports that very low calorie diets support improved baroreflex sensitivity (Kansanen et al. 1998) there is no specific available evidence regarding sustainable, gradual weight loss in OSA populations nor whether macronutrient composition or glycemic index modulates this response. It is unclear how greater levels of sympathetic activity may impact upon people with OSA’s capacity to lose weight and furthermore, their ability to maintain this weight loss. The current study will investigate how weight loss via two different dietary interventions relates to individual differences in baseline sympathetic drive as well as how weight loss may steer subsequent improvement in sympathetic neural activity via different dietary macronutrient compositions and glycemic index with the potential additive effects of non-randomised use of mechanical treatment in a clinical setting.

Energy restriction decreases sympathetic reactivity: VLED reduces sympathetic nervous activity, as indicated by significant reductions in 24-hour urinary norepinephrine excretion (Rosenbaum et al. 2000). Since sympathetic activity is an important regulator of metabolic rate, substrate oxidation (Rosenbaum et al. 2000), and bone mass (Takeda et al. 2002), and since reduced capacity to activate the sympathetic nervous system is associated with decreased weight loss in obesity (Bobbioni-Harsch et al. 2004), it is important to determine whether VLED and followed by conventional maintenance diets may have differential effects on sympathetic reactivity. Additionally, as the changes in sympathetic reactivity with weight loss may be mediated by the same hypothalamic ‘master switch’ that initiates other adaptive responses to weight loss.Deep inspiration induces vasoconstriction in skin capillaries via sympathetic activation, and dynamic weight loss has been shown to inhibit this response (Bobbioni-Harsch et al. 2004), possibly by the same hypothalamic alterations that induce the various adaptive responses to weight loss.

A standard “public health” lifestyle prescription of a healthy diet and increased physical activity may be unrealistic in individuals who are obese and experiencing significant daytime sleepiness. The one size fits all approach is not adequate for the majority of individuals trying to lose weight. A theoretically grounded lifestyle modification program that addresses the aetiology of disease onset and progression of OSA combined with health coaching behavioural interventions focused on solution focused therapy holds potential for more effective weight loss and long term maintenance. *Therefore we have designed a completely novel lifestyle intervention* ***specific*** *for obstructive sleep apnea comparing combinations of mechanical treatment versus no active treatment and low glycemic index/high protein diet or standard hypocaloric diet (Australian Guide to healthy eating) and weight loss program.*

The results from this study will not only provide insights of immediate benefit to the clinical management of patients with OSA in our clinic and others around the world, they will also provide insights into potential predictors of who will respond to the different weight loss regimes available.

## Research Plan

STUDY TYPE: This unblinded, randomised controlled trial will incorporate two intervention arms in two separate groups stratified by treatment use. The intervention arms for the SLEEEP study include:

SETTING/LOCATION:

* The Woolcock Institute of Medical Research
* Royal Prince Alfred Hospital (recruitment only)
* Potential for home visits/internet contact via email and Skype

DURATION OF THE STUDY: The SLEEEP study will recruit for a minimum of 6 months. Participants will be enrolled for a total of 12 months consisting of 3 overnight visits, 2 clinic visits lasting between 2-3 hours and 6 Skype/Phone sessions. In addition, patients will be contacted to attend a 3 year follow up visit to track progress.

TREATMENT STABILITY: Patient recently diagnosed with OSA and instructed to use mechanical treatment must demonstrate consistent compliance for a three month period prior being entered to the study. They will remain on hold during this period. This will reduce the likelihood of a treatment user moving to a no active treatment group should they reject mechanical therapy soon after a new prescription.

## Methods

STUDY POPULATION

This pilot study will recruit the maximum number of participants possible in a minimum period of six months. Potential participants must fulfil the following criteria:

* Patients with Obstructive sleep apnea
* Significant adiposity: BMI>30 kg/m2 and/or waist circumferences > 88cm for women and >102cm for men.

Patients will be aged > 18 and < 65 and will be excluded if they are actively involved in a structured weight loss program for the last 3 months, have any contraindications to exercise (e.g. known aneurism, severe aortic stenosis, unstable angina etc) or if in the study physician’s opinion would not be a suitable candidate for a weight loss program. Diagnostic polysomnography will be required to confirm presence of OSA if no recent overnight sleep study has been conducted.

STRATIFICATION: for treatment versus non treatment users

## Recruitment

Recruitment will primarily be conducted through the physicians at the Sleep Clinics of:

* The Woolcock Institute
* Royal Prince Alfred Hospital

Potentially eligible participants will be given an information sheet detailing the aims of the study, basic eligibility criteria and the study staff coordinator contact number to call if they are interested in participating. Participants who are recruited from one of the Sleep Clinics listed may fill in a form requesting to be contacted by a study investigator if they prefer. Other sources of potential volunteers include:

* The Woolcock Clinic: Treating physicians, all Woolcock affiliated, will be alerted to the study and asked to inform candidate patients of the trial. Patients will be assured that an unwillingness to participate in the trial will in no way affect their ongoing treatment and level of care.
* Local print media including newspaper advertisements, local newsletters, university mail and newsletters etc.
* Specialist/GP Referral and potential advertisements in GP wait rooms
* Sleep Disorders Australia website
* Australasian Sleep Trials Network website
* Australasian Sleep Association website
* Databases from previous studies where individuals have consented to be contacted for future studies
* Advertisements may also be displayed in health magazines, websites or papers that are targeted at similar patients. Sleep Disorders Australia and larger general practices will also be advised of the trial to advertise the trial for potential participants.

To assess the eligibility for the SLEEEP Study, interested volunteers will undergo a telephone screening. The questions on the form were designed to address all inclusion and exclusion criteria. A 15-30 minute phone call from the interviewer will allow all volunteers to answer the questions and ask any that they may have about the study. A confidential study database will maintain a record of all screens conducted and indicate potential participants and note those who wish not to be contacted in the future.

Participants will be informed about their eligibility or be placed on hold for further medical information and/or investigation(s). An information package will be sent via email or post to the potentially eligible subjects and will include an appointment to see the study physician, information regarding the location of the screening, testing venue, a permission slip for access of medical records, a study information sheet including a brief outline of the assessment procedures and a brochure outlining the weight loss program and diets. If not eligible, the researcher will ask volunteer’s permission to retain their contact details in case their situation changes over time and they become eligible at a later date. To obtain medical clarification for volunteers, letters will be sent to their relative doctors along with the signed permission slip from the volunteers indicating that the physician may release relevant medical information where this information may be lacking at the discretion of the study physician.

Potentially eligible participants will be given the informed consent and will be guided through all aspects of the information sheet and offered the opportunity to ask any questions related to the study when they attend their screening visit at the Woolcock Institute. Those subjects who agree to participate in the area will be asked to sign the consent form according to the guidelines of the Sydney Local Health District’s Ethics Review Committee. If the patient is willing to participate in the study, they will be requested to also provide written and witnessed informed consent for use of a sample for Pharmacogenetic Research. To determine final eligibility the study physician will examine, consult and review the medical records and telephone screening of each subject. Screening bloods will be collected to check against inclusion/exclusion criteria along with a 12 lead resting ECG. If necessary, a screening overnight PSG will requested to confirm OSA prior to the participant being entered into the study.

Eligible subjects will then be asked to attend a baseline visit. Baseline visits will take place overnight at The Woolcock Institute (Glebe). Eligible volunteers will all commence Optifast for the proceeding two month period prior to be randomised to one of the intervention arms as stratified by treatment versus non-treatment use.

## Inclusion and exclusion criteria

The following conditions permanently exclude the participant from the SLEEEP Study:

* Unstable aortic aneurysm
* Rapidly progressive or terminal illness
* Severe left ventricular dysfunction/end stage congestive heart failure
* Severe aortic stenosis
* Severe psychosis or behavioural disturbance or cognitive impairment
* Patients known to be involved in illegal activity

The following conditions require medical intervention or re-evaluation prior to participation in the SLEEEP Study:

* Abnormal resting ECG
* Alcohol or Caffeine dependence as patients undergo multiple 24 hours periods in our sleep laboratory without access to these.
* Angina (unstable)
* Arrhythmias or heart block (uncontrolled)
* Breathing problem or motion disorder
* Cardiac surgery (within last 6 months)
* Cataract extraction (within last month)
* CHF (uncontrolled)
* Cognitive impairment (mild-moderate)
* COPD / CAL (uncontrolled)
* Current active involvement in another diet/weight loss intervention study or in a weight loss program or drug trial within the preceding three months.
* Uncontrolled Diabetes
* Deep venous thrombosis (acute)
* Endocarditis
* Fracture (recent or delayed union)
* Haemorrhoids (severe)
* Hepatic Impairment
* Hernia (unrepaired or symptomatic; abdominal or inguinal;)
* SBP≥180 and/or DBP≥110.
* Inability to exercise
* Knee joint injury within the past 6 months
* More than 20% of AHI with central apneas.
* Myocardial infarction (acute; within last 6 months)
* Neurological disease (rapidly progressive or unstable)
* Pericarditis (acute)
* Pregnant or breastfeeding or planning to fall pregnant in the next 12 months
* Pulmonary embolism or infarction (acute)
* Retinopathy, recently treated, unstable
* Renal Impairment
* Unstable medication use in the preceding 3 months or throughout the study (variable dosages) including antidepressant or anxiolytic medications
* Severe functional limitation (unable to walk unaided by a person)

INCLUSION CRITERIA

The following inclusion criteria enable the volunteer to participate in the SLEEEP Study:

* Males & Females aged 18-65 years.
* General or central obesity: BMI: ≥30kg/m2 (≥26kg/m2 amongst non-Europeans) or waist circumference ≥88cm for women and ≥102cm for men (>90cm in men and >80cm in women who are non-European).
* Willing and medically able to participate in a supervised very low energy diet (Optifast) and the dietary and lifestyle modification groups for a 12 month period.
* Mild-severe, symptomatic OSA (degree of symptoms at the treating physician’s discretion based on overnight sleep study report)
* No history of or current presence of eating disorders , significant/extensive food allergies or significant food intolerances (e.g. coeliac disease)
* Willing and able to complete all assessments outlined in participant information sheet
* Hold a current driver’s license or have access to transport.

Participants will be required to inform the researcher if they commence any new medications or if medication dosage changes. If this will not interfere with their ability to lose weight the medication will be recorded on the concomitant medication form.

## Randomisation

Only eligible adults providing written informed consent according to the current approved protocol will be enrolled into the trial. OSA volunteers will be enrolled sequentially according to two pre- allocated randomisation lists stratified as the treatment and non-treatment users and randomised in concealed variable blocks of 4-8 into the standard low calorie diet and lifestyle modification program OR a low GI and High protein diet and lifestyle modification program following two months of VLED. The randomisation sequence will be pre-determined by a research assistant not involved in testing/training, using a computer-generated random number sequence. Sequential treatment allocations will be enclosed in numbered, opaque sealed envelopes, and distributed to each participant at their 2 month visit stratified according to treatment to evenly distribute patients between treatment groups and aid generalisability. The dietary intervention is an open label study as participants cannot be blinded to their treatment allocation.

Screening Numbers:

Prior to commencing the trial and following signing informed consent, each volunteer will be allocated a unique patient screening number in sequential, ascending chronological order. This number will be a two-digit number prefixed by “S” (e.g. S01, S02 etc) and will be used to identify patients during the screening phase prior to randomisation. As patients commence their baseline visit they will be assigned an additional number according to order of intake and this number will be a double digit prefix used to identify patients prior to randomisation following intake after scrrening (e.g. 01S001 or 05S003) whereby

Randomisation Numbers:

Randomisation will take place at visit 4 (month 2). This will involve assigning a unique patient number in sequential, ascending chronological order.

Since the trial is stratified by treatment use this number will be an ‘R’ and then three-digit number prefixed with 1 or 2 as coded for treatment or non-treatment respectively (e.g. for treatment user 1R\_001, 1R\_002 etc and for non-treatment user, 2R\_001, 2R\_002 etc) and will be used to identify stratified patients based on pre-existing mechinical treatment use. Intervention assignment will be determined according to a computer generated randomisation list as described earlier.

## Statistical Analysis

This is a pilot trial to describe the variability of weight regain in these two different maintenance diets following a very low energy diet. Recruitment will enrol a maximum number of participants within a target period of six months. No power calculations have been conducted as this is a pilot trial however we anticipate that 20 people will be recruited for each study arm for a total of n=40 over the 6 month recruitment phase. Data will be analysed on an intention-to-treat basis. Mixed model analyses of variance will be used to test each diet treatment effect. Treatment will be the fixed effect and individual patients the random effect. Main effects for the trial will be regarded as statistically significant when p < 0.05. 95% confidence intervals will be used to analyse weight rebound in order to measure the variability associated with weight regain.

## Follow up /Assessments

The primary outcome will be assessed at baseline before the start of the lifestyle modification program and immediately after completion of the VLED 2 months, 6 months and at 12 months as a follow up. Participants will also be assessed for various secondary, tertiary and explanatory outcomes at 1, 2, 6 and 12 month visits as defined in the visit schedule later in the protocol. Blinding of participants is not possible due to the nature of the dietary interventions, but they will not be aware of the investigator’s specific hypotheses.

### Primary Outcome

* *Waist Circumference:* measured using the International Diabetes Federation Guidelines. The unit will be cm loss and this outcome will be assessed at baseline, 1 month, 2 months, 6 months and 12 months.

### Secondary Outcomes

* *Apnea-Hypopnea Index (AHI):* measured via polysomnography to define sleep apnea severity. Leads will be attached to the subject’s head in order to measure chest and abdominal movement, airflow at the mouth and lips, blood oxygen level, muscle tone, eye movements, heart rate and electrical activity in the brain. The subject will be required to sleep with these leads attached. The study is scored using standard criteria and this outcome will be assessed at baseline, 2 months and 12 months.
  + *For those patients using CPAP this measurement will be via their CPAP machine which is used on the night of their sleep study.*
* *The SF-36 questionnaire:* as a tool to measuregeneral health related quality of life in the domains of physical and mental health and will be assessed at baseline, 2 months, 6 months and 12 months.

### Tertiary and Explanatory Outcomes and effect modifiers

**Sympathetic Activity (Effect Modifiers)**

* *24 hour urinary catecholamines:* Collected over a 24 hour period and split into wake versus sleep period to measure sympathetic activity (specifically dopamine, norepinephrine, epinephrine and serotonin) These will be measured at baseline, 2 months, 6 months and 12 months.
* *24 hour cardiopulmonary coupling:* to assess sleep quality via a sleep spectrogram (a visualisation or image created by CPC analysis that displays the integrated or *coupled*) biological oscillations of sleep. This will be measured at baseline, 2 months, 6 months and 12 months. CPC uses autonomic and respiration physiological data streams to mathematically capture the common activity strongly modulated by a third physiological stream: electrocorticol activity. The visualisation of sleep created by this interplay can be used to phenotype various sleep and breathing disorders including OSA. Coupling signatures are categorised as high frequency coupling (HFC:0.1-0.4 Hz) or low frequency coupling (LFC: 0.0 to 0.1 Hz).
  + HFC indicated stable sleep and is increased by conditions that improve the effectiveness or efficiency of sleep.
  + LFC is present when sleep is unstable or inefficient and increased by conditions that add disruptive influences in sleep.
  + During the course of a night’s sleep there are spontaneous switches between HFC and LFC that occur within a sleep cycle. In health, more time (more than 50%) is spent in HFC however diseases disrupting sleep can erode HFC periods, reducing their duration and the percentage of sleep in the HFC state while simultaneously increasing LFC. Patients may also be phenotyped as narrow band, broad band or complex according to spectral dispersion of the coupling sprectra.
* *24 hour heart rate variability:* heart rate is modulated by the combined effects of the sympathetic and parasympathetic nervous systems. Measurement of heart rate changes over time (i.e. heart rate variability) provide information about autonomic functioning) and can be measured as a domain of cardiopulmonary coupling. Heart rate variability (HRV) is the standard deviation of the R-R interval and we expect will increase with weight loss. This will be measured at baseline, 2 months, 6 months and 12 months.
* *Core temperature, skin temperature and sweating:* Measured using ibutton, electrodermal activity (through skin) and via a component of the CPC Embla device. Objectiveassessment via electro- dermal activity (EDA), a measurement of the activation of the eccrine sweat glands (Bouscein, 1993). EDA correlates highly with an actual sweat measurement, the ventilated capsule method (r = 0.88) (Kobayashi et al., 2003). Electrodermal activity will be measured with NoiseFree single bio-potential silver-silver ⁄ chloride electrodes connected to the Em- blaTM digital recording device. EDA will be recorded using the skin potential method by placing one electrode on the hypothenar eminence as an active site and another on a lightly abraded site on the volar surface of the forearm as an inactive site (two-thirds of the distance from wrist to elbow) on the right arm (Andreassi, 1995; Fowles et al., 1981). A thermoregulatory index will also be calculated based upon the autonomic function questionnaire.
* *Autonomic Functioning Questionnaire:* measuring self-reported autonomic regulation

**Clinical Symptoms Associated with Sleep Apnea and Phenotyping of Sleep Apnea**

* *Anthropometric measurements:* including height (only measured at baseline); change in weight (kg) , neck circumference (cm) and hip circumference (cm). This will be measured at baseline, 1 month, 2 months, 6 months and 12 months.
* Change in grams of fat mass, fat free mass, total body water, intracellular fluid and extracellular fluid measured by BIA between baseline and 2 months, baseline and 6 months.
* *Polysomnography:* Sleep shall be monitored using standard polysomnography at the Woolcock Institute for the purpose of determining sleep apnea severity via RDI, sleep quality and sleep efficiency. Leads will be attached to the subject’s head in order to measure chest and abdominal movement, airflow at the mouth and lips, blood oxygen level, muscle tone, eye movements, heart rate and electrical activity in the brain. The subject will be required to sleep with these leads attached. The study is scored using standard criteria and this outcome will be assessed at baseline, 2 months and 12 months.
* *Laboratory Analyses for metabolic risk, inflammatory markers and hormones:* lipoprotein profile, plasma leptin, insulin sensitivity (HOMA), triacylglycerol concentrations, C-reactive protein, inflammatory markers (IL-4, IL-6, TNF-α), liver function tests, cortisol, ghrelin, adiponectin, testosterone, luteinising hormone, follicle stimulating hormone and a genetic marker for the COMT polymorphism. A 20ml blood sample will be collected at baseline, 1 month, 2 month, 6 month and 12 month visits using standard venepuncture to measure the hormonal and cardiovascular markers noted. Serum will be frozen and processed by a central laboratory. If the patient consents, blood will also be taken and stored for genetic testing at a future occasion.
  + Lipids electrolytes and liver function 1 X 7ml (gold top gel tube)
  + Full blood count takes 1 X 4ml EDTA (purple top tube)
  + Hormones and fasting insulin/glucose 1 x 7 mL (gold top)
  + At the baseline visit a 4ml sample will be taken for genetic testing for the COMT polymorphisms that have been reported to predict sleepiness.
* *Vitals (resting blood pressure and heart rate):* Blood pressure (BP), and heart rate (HR), are recorded at each contact visit including the termination visit should it occur, following ESH guidelines. The BP and HR are measured using a consistent device and cuff throughout the study on the same arm used at baseline that showed the higher value. At least 2 measurements should be taken (with 1-2 minutes between) after at least 5 minutes of sitting and resting. A third measure should be taken if there is >10 mmHg discrepancy between the first two measurements.
* *Sleepiness related quality of life:*  as measured by the functional outcomes of sleepiness questionnaire (FOSQ) and Epworth Sleepiness Scale (ESS)
* *Craniofacial Photography:* a photograph of the participants face will be taken with appropriate markers attached to determine craniofacial dimensions specific to sleep apnea.

**Self Efficacy**

* *Self Regulation Questionnaire (SRQ):* measures the ability to develop, implement, and flexibly maintain planned behaviour in order to achieve one's goals.
* *General Self Efficacy Scale:* to assess a general sense of perceived self efficacy.
* *Bandura’s nutrition and physical exercise self efficacy scale*
* *The Kentucky Inventory of Mindfulness Skills (KIMS; Baer 2004)* will be used to assess the specific mindfulness skills of participants

**Quality of Life Measures**

* *Depression and Anxiety and Stress Scale (DASS):*to measure the three related negative emotional states of depression, anxiety and tension/stress.
* *Impact of Weight on Quality of Life Questionnaire:* to assess the effects of the obese condition on the quality of life of persons seeking treatment for this condition.
* *Three Factor Eating Questionnaire:* (TFEQ; Stunkard & Messick, 1985) will be used as a measure of eating behaviour, specifically assessing cognitive restraint, disinhibition of eating, and perceived hunger.

### Qualitative/Habitual Outcomes

* *Habitual physical activity, energy expenditure, sleep and sedentary behaviour:* Actigraph accelerometers will be worn during all waking hours for seven days on the non dominant wrist at all times to monitor activity. These wrist activity monitors will be used to estimate sleep and wake periods by using activity measured by wrist accelerometry. We will also be using this device’s raw activity counts as an objective measure of physical activity levels. Sensewear armbands will also be worn for a seven day period on the upper portion of the non-dominant arm to quantify energy expenditure, sleep, body temperature, intensity of physical activity and steps taken.
* *Food and Activity Diary:* Minimum 4 day collection period (3 weekdays and 2 weekend days) to assess habitual dietary intake and energy expenditure via the Bouchard Questionnaire.
* *Actiwatch Diary*
* *Food Habits Questionnaire (FHQ95):* To assess usual eating habits
* *International Physical Activity Questionnaire (IPAQ):* To provide health related physical activity data

### Screening Questionnaires

* *Eating Disorder Examination Questionnaire:* (EDE-Q; Fairburn & Cooper, 1993) will be used to assess the specific psychopathology of eating disorders. The EDE-Q is comprised of four subscales: restraint, weight, shape and eating concerns.

## Interventions

### Very Low Energy Diets (VLED): All participants

Very low energy diets are frequently used as an efficient and rapid means of controlled weight loss prior to patients transitioning to a maintenance diet. There is a strong body of evidence using VLED in overweight/obese sleep apnea patients as a precursor to other treatment options. The VLED program structure has been provided by RPAH Metabolism and Obesity Services and has been utilised in clinical services and other research trials frequently in the past. The state of ketosis is achieved as large amounts of fatty acids are broken down in response to extreme energy restriction. VLEDs also contain the recommended daily requirements for [vitamins](http://en.wikipedia.org/wiki/Vitamin), [minerals](http://en.wikipedia.org/wiki/Dietary_mineral), [trace elements](http://en.wikipedia.org/wiki/Trace_element), fatty acids and protein.

Those patients achieving desired body weight prior to completion of the 3 month shake period will be reviewed by the study physician and supervising nutritional staff to determine whether to graduate them to a maintenance diet earlier than projected. The specific VLED program can be found in the standard operating procedures manual. Patients will follow a full VLED program for an 8 week period (3 shakes per day) then an initial transition phase for 2 weeks (2 shakes, one meal) followed by a latter transition phase (1 shake, 2 meals) before initiating their randomised maintenance diet.

### Safety and Compliance VLED Pathology Measurements:

Baseline:

* Biochemistry (Electrolytes, Liver function tests, Creatinine, Glucose, Total cholesterol, LDL and HDL, Triglycerides)
* Haematology: (Full blood count, Iron studies)
* Endocrine: TFTs, glucose, insulin (HOMA)

Follow up pathology

* Electrolytes, creatinine and LFTs: after completion of first 4 weeks of the diet; if results are normal no need for further blood testing.
* Urate– second weekly, if the patient had a history of gout or baseline urate level is above the normal range.

Endocrine team to decide on the appropriate pathology follow up.

### High Protein/ Low GI Diet

Participants in this group will be coached to adopt a high protein/low GI weight loss diet based on a 500 calorie restriction (as determined by Harris Benedict Equation). The goal of the diet is to maintain a minimum of 5-10 % weight loss over a 12 month period with sustainable changes in eating patterns.

The target macronutrient contribution is 45% of energy from carbohydrates, emphasising low glycaemic sources, 30% from fat and 25% from protein. This macronutrient distribution is similar to the Australian average diet but the GI is lower. The diet will aim to be as low in GI as practical as achieved by replacing higher GI carbohydrates (e.g. conventional white bread, breakfast cereals and potatoes) with lower GI carbohydrates (e.g. Burgen® grain breads, oats, pasta, basmati rice). The GI of the low GI/GL diet will be < 50 (glucose = 100) and calculated using published data for Australian foods. The diet will emphasise lean sources of protein and restriction of saturated and transfats (but not total fat).

Participants will be provided with The Shoppers Guide to Low GI that outline the carbohydrate choices and the food amounts that constitute one serving. They will also be provided information on the whole diet to ensure energy and overall nutrient balance.

### Australian Guide to Healthy Eating

Participants in this group will be coached to adopt a variety of healthy foods from all food groups based on a 500 calorie restriction (as determined by Harris Benedict Equation). It will be modelled around the current Australian guide to healthy eating. The goal of the diet is to maintain a minimum of 5-10 % weight loss over a 12 month period with sustainable changes in eating patterns. Patients will be encouraged to choose whole grains, sources of high fibre, reduce sugar intake and decrease fat intake (specifically saturated and trans fats). The target macronutrient contribution is 60% of energy from carbohydrates, 23% from fat and 17% from protein. This macronutrient distribution is within the recommendation ranges provided by the Australian Guide to Healthy Eating.

Participants will be provided with The Australian Guide to Healthy Eating that outlines the carbohydrate choices and the food amounts that constitute one serving. They will also be provided information on the whole diet to ensure energy and overall nutrient balance.

### Lifestyle Modification Program

Individual dietary counselling is necessary to identify current dietary patterns, recommend specific changes and identify barriers and target behavioural change strategies to the individual successfully. Participants will be scheduled at the following sessions as well as being provided with a lifestyle modification booklet at baseline to be made available in each session. All patients will receive identical models of counselling for exercise and overall lifestyle modification according to the pre-designed program. The visit scheduling has been designed to minimise patient burden and make use of convenient means of communication/counselling where possible such as Skype or telephone calls.

All participants will be weighed at each clinic visit using the same calibrated scale at the laboratory, as frequent weighing has been shown to enhance weight loss significantly. The participants will also be asked to weigh themselves each morning and measure their waist circumference once a week and record this. These measurements are not data points but will be reviewed at each point of contact with the study staff. Logging of behaviour and goals has been shown to significantly enhance compliance and weight loss.

At baseline, 2, 6, and 12 months, collection of 4-day food diary will aid assessment of dietary compliance. Participants who have low adherence (<75%) will receive additional individual booster sessions either in person or by telephone if they are not attending sessions or require additional support (this will be at the discretion of the research officers and medical staff) The behavioural change principles that will be utilised to maximise adherence include the theoretically-grounded principles of decisional balance, social cognitive theory and the stages of change model.

## Participant Withdrawal

Patients who are unable to tolerate the VLED will be considered by the medical supervisory staff to determine whether they are able to reduce their VLED prescription while maintaining an acceptable rate of weight loss so as to enable them to remain in the study. These decisions will be considered on a case by case basis. Patients who are unable to be randomised due to inability to lose weight through the VLED will undertake an exit interview prior to exiting the trial and will be offered medical support as required.

### Booster Sessions

Patients presenting with low adherence to dietary program or demonstrating a need for additional support via more frequent anthropometry may be offered to participate in face to face sessions instead of skype/phonecall sessions. This will be at the discretion of the study physicians and study coordinator where a consensus must be met based on weight loss and patient compliance monitoring.

### Withdrawal:

Patients will be informed that they have the right to withdraw from the study at any time without prejudice to their medical care, and are not obliged to state their reasons. The investigator will follow up any withdrawals. Additionally the investigator may withdraw a patient at:

**Any time** for the following reasons:

1. Pregnancy
2. Severe hypertension (SBP≥180 and/or DBP≥110).
3. Excessive sleepiness with increased risk for driving-related accidents requiring immediate treatment.
4. Serious incident medical or psychiatric disease

**After Randomisation** for the following reasons:

1. Patients may be withdrawn if in the opinion of the patient, the treating physician and the data safety physician it is in their best interests. Reasonable effort should still be made to collect the outcome data and at the very least the primary outcome measures regardless of whether the patient has been undergoing the weight loss program.
2. Serious Adverse Events that preclude the ability to measure the primary outcome
3. Administrative reasons.

If a patient fails to return for follow up or discontinues for personal reasons, attempts will be made to determine what the reason for not returning is if not an adverse event (respecting that the patient is not obliged to state his/her reasons). If discontinuation occurs, an early termination visit will be encouraged with an attempt to collect the primary outcome.

### Additional Visits: in case of early termination

If in any case whereby the patient is withdrawn before study completion date, an early termination visit should be arranged as soon as possible.

The investigator should examine the following;

* Anthropometry measurements.
* Office blood pressure and heart rate.
* Collection of adverse events.
* Adverse Event Reporting.

## Exit Points:

If a patient wishes to prematurely withdraw from the trial they should be asked whether they wish to continue participation until an exit point is reached. In the event of them wanting to completely withdraw from the lifestyle program, the participant will cease all treatment however be encouraged to attend their next scheduled visit to enable collection of data for the major outcomes. Exit points exist at the following time points (2, 6 or 9 months). Every effort should be made to ensure that the major outcome measures are collected if the patient is happy to offer their time for these assessments.

## Risks and Discomforts

Minor side effects such as fatigue, constipation, diarrhoea, nausea, dizziness, headache, irritability and cold intolerance are usually transient and rarely prevent patients from completing the VLED program. Longer term side effects such as dry skin, hair loss and brittle nails usually subside with the re-introduction of a standard weight maintenance diet. In extreme cases vomiting, acute gout, acute gall bladder disease or cardiac disturbances (particularly if electrolyte disturbances) may preclude therapy.

### Study Discontinuation:

The trial as a whole may be discontinued at any time on the advice of the responsible Principal Investigators and the Data safety monitor based on new information regarding safety or efficacy. Additionally, the study may be terminated if progress is unsatisfactory.

In case of premature termination or suspension of the trial, the investigator will inform the trial subjects and ensure appropriate medical follow up. In addition, the appropriate regulatory authorities and ethics committee will be informed, where relevant.

If the study is discontinued for safety reasons, the investigators must contact all affected patients within a reasonable period to inform them of the termination of their involvement in the study.

## Participant Visits

Screening Visit

Prior to conducting the screening visit, in order to determine eligibility, the investigator must:

* Provide the participant with written information on the study.
* Discuss study participation including answering questions about procedures, randomisation, potential risks and no guaranteed benefit from participation.
* Perform the telephone screening
* Obtain signed consent.

If the investigator is satisfied that the person is potentially eligible, understands the nature and purpose of the study and is willing to participate fully in the study, he/she will be asked to sign the consent form. A signed informed consent must be obtained prior to the following procedures and tests being completed.

In order to determine eligibility, the following procedures need to be completed:

* Medical history and examination.
* Office Blood Pressure and Heart Rate.
* Venous blood sample, approximately 10mls of blood will be taken if a recent clinical blood test is not available.
* Current medication
* Resting ECG to rule out any potential contraindications to exercise
* A previously recorded nocturnal polysomnogram (PSG) report is required to confirm patient eligibility. A PSG will be scheduled if it has not already been performed within the last 24 months or the patient has recently lost or gained >5% body mass.

Patients who satisfy eligibility criteria will proceed to visit 1 (week 0) baseline.

Patients demonstrating any absolute or relative contraindication to exercise through their resting ECG must be reviewed by the safety officer Dr Keith Wong FRACP for inclusion/exclusion/ referral to a cardiologist.

Follow up with Study Doctor

For patients who do not pass the screening visit, a follow up visit should be organised with the clinic doctor.

Randomisation

Following 2 months optifast completion all participants will be randomized to their dietary group

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline o/night** | **0.25 month P/C or Skype** | **0.5 month P/C or Skype** | **1 month clinic** | **2 month o/night** | **3 month P/C or Skype** ∆ | **4.5 month P/C or Skype** | **6 month clinic** | **9 month P/C or Skype** | **12 month o/night** | **3 years** |
|  | \*# | ∆ | ∆# | ∆ | \* ∆# | \*# | \*# |
| Randomisation |  |  | 🟍 |  |  |  |  |
| Overnight PSG | 🟍 |  | 🟍 |  |  | 🟍 | 🟍 |
| Sympathetic Activity Battery (24hour urinary catecholamines, CPC, HRV, temperature, sweat & Autonomic Questionnaire) | 🟍 |  | 🟍 |  | 🟍 | 🟍 | 🟍 |
| Pathology | 🟍 | 🟍 | 🟍 |  | 🟍 | 🟍 | 🟍 |
| Anthropometry and BIA | 🟍 | 🟍 | 🟍 |  | 🟍 | 🟍 | 🟍 |
| Vitals | 🟍 | 🟍 | 🟍 |  | 🟍 | 🟍 | 🟍 |
| Questionnaires (Self Efficacy & Quality of Life) | 🟍 |  | 🟍 |  | 🟍 | 🟍 | 🟍 |
| Diaries, Habitual Questionnaires and monitors (actiwatch and sensewear) | 🟍 |  | 🟍 |  | 🟍 | 🟍 | 🟍 |
| Facial Photography | 🟍 |  | 🟍 |  | 🟍 | 🟍 | 🟍 |

\*Patients will be required to wear an actiwatch and sensewear armbands for a week prior and fill out a detailed sleep, diet and exercise diary for 4 days prior to each of these visits. Patients should try to have dinner before arriving at the sleep clinic for **7:00 pm**. At this point, the patients will follow the standard overnight visit protocol**.**

∆ All patients will be required to participate in a lifestyle modification session. These modules will be accompanied by a manual/workbook and all sessions will be conducted by an Accredited Exercise Physiologist (EM) according to methods taught by Health Coaching Australia: Health Coaching for Health Professionals.

# Patients will be required to drop off the 24 hour Embla device (to reception at the Woolcock) and to drop off 24 hour urine collection to their most convenient pathology service.

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