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Clinical Study Protocol: Version 5 dated 27 August 2018

Project Title: Cardio-metabolic health effects of CPAP treatment for sleep apnoea during weight loss: A Randomised Controlled Pilot Trial

Principal Investigators:

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This protocol has been approved by the Sydney Local Health District Ethics Committee (X17-0039) and is registered on the Australian New Zealand Clinical Trials Registry (ANZCTRN12617000823370)

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

1. Study Synopsis

1.1 Investigators:

Chief Investigators:

Medical: Professor Ron Grunstein FRACP
Non-Medical: A/Prof Craig Phillips PhD

Chief Associate Investigator: Dr Camilla Hoyos PhD

Associate Investigators under the supervision of the Principal Investigators:
Professor Stephen Twigg
A/Prof Brendon Yee
A/Prof Keith Wong
A/Prof Tania Markovic
A/Prof Nathaniel Marshall
A/Prof Amanda Salis
Doctor Dev Banerjee
Doctor Elizabeth Cayanan
Doctor Nicholas Fuller
Doctor Peter Buchanan

1.2 Funding

Diabetes Australia – Research Grant
University of Sydney DVC Research – Bridging Support Grant
Sydney Medical School Foundation - Project Grant

1.3 Declaration of interests

Nil financial or other competing interests for principal investigators to declare.

1.4 Background

Obstructive Sleep Apnoea (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 (apnoea) 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.

Numerous cross-sectional studies show insulin resistance in OSA as measured by Homeostasis Model Assessment (HOMA) or Oral Glucose Tolerance Test (OGTT). In addition, nocturnal glucose during sleep measured with continuous glucose monitoring (CGM) has been shown to be elevated in both non-diabetic and diabetic OSA.

Randomised Controlled Trials involving treatment of OSA with CPAP versus sham CPAP or conservative treatment have been equivocal with positive effects from CPAP being more evident with high compliance, in more severe OSA and in pre-diabetes. Apart from one small study no benefit has been shown in diabetes with respect to lowering of glycosylated haemoglobin (HbA1C).

One RCT explored the combined effect of weight loss and CPAP on cardio-metabolic parameters including insulin sensitivity and blood pressure and demonstrated greater improvements with combined treatments. No studies that have looked at CGM in weight loss and OSA treatment interventions.

The only major modifiable risk factor for sleep apnoea is obesity but the efficacy of weight loss in reducing OSA in individual patients is extremely variable. As gradual weight loss is the recommended treatment approach in OSA, many patients will not immediately show an improvement in the disturbing daytime sleepiness that is often the chief clinical complaint.

The purpose of the current study is to determine in obese people with pre-diabetes, the efficacy of treating OSA with CPAP during weight loss, to achieve improvements in glucose tolerance (a measure of diabetes risk), abdominal fat loss, blood pressure and other cardio-metabolic measures at three months.

1.5 Outline of the Proposed Research

Project Title: Cardio-metabolic health effects of CPAP treatment for sleep apnoea during weight loss**:** A Randomised Controlled Pilot Trial

Objective: To determine in obese people with pre-diabetes, the efficacy of treating OSA with CPAP during weight loss, to achieve greater improvements in glucose tolerance (a measure of diabetes risk), abdominal fat loss and other cardio-metabolic measures at three months. All patients will be invited to attend a follow up visit at 12 months with reassessment of outcomes, after following a low glycaemic index (GI)/high protein diet and exercise program for nine months.

Design: A three month Randomised Controlled Trial (RCT) in obese pre-diabetic patients with OSA randomised to a very low energy diet (VLED) (control) or CPAP plus VLED (intervention). Following the randomised controlled phase, patients will be re-assessed for OSA severity. Any patients with persistent OSA will commence or continue on CPAP treatment if recommended by their treating sleep physician. In addition, all patients will receive education about how to maintain a healthy weight using a low GI/high protein diet and exercise program. Optional support from a dietitian will be offered. All patients will be invited to attend a follow up visit at 12 months with reassessment of outcomes.

Hypotheses: Treatment of OSA with CPAP during a VLED, compared with a VLED alone for three months, will better improve:

1. Glucose tolerance and HbA1c
2. Central Blood Pressure
3. Abdominal and total fat mass
4. Lipid profiles

Patients: Female and male centrally or generally obese adults with pre-diabetes and moderate-severe OSA.

Primary Outcome: Glucose tolerance, as measured by two hour blood glucose level following an oral glucose tolerance test, assessed at three months.

***Secondary Outcomes*:** Abdominal and body fat, metabolic syndrome components (glucose, lipids, BP), insulin sensitivity, 24 hour blood glucose levels, 24 hour central blood pressure, health related quality of life and cost effectiveness measures.

2. Participants

2.1 Sample

Sample size:	30 patients randomised using a 1:1 ratio for VLED plus CPAP or VLED alone
Study Population:	Female and male adults with pre-diabetes and moderate-severe OSA recruited from obesity and sleep clinics and advertisements.

2.2 Inclusion / Exclusion Criteria

Inclusion
1. Community dwelling adults aged 18-65 years 2. Body Mass Index (BMI): ≥27 kg/m^2 and/or waist circumference: females >88cm, males >102cm (non-European: females >80cm, males >90cm) 3. Pre-diabetes defined per World Health Organisation as any of the following recent (<3 months) findings: ▪ Impaired fasting glucose with BGL between 5.5 and 7.0 mmol/L ▪ Impaired glucose tolerance with BGL between 7.8 and 11.0 mmol/L after a formal 75g Oral Glucose Tolerance Test (OGTT) ▪ HbA1C between 6 and 6.5% 4. Moderate-severe hypoxaemic OSA with AHI ≥20/hr and ODI ≥10/hr prior to VLED, based on recent (<12 months) polysomography
Exclusion
1. Any known contraindications to VLED or exercise 2. Recent weight loss that in the opinion of the treating physician is clinically significant 3. Current or recent (<3months) treatment of OSA 4. Professional drivers who are sleepy 5. Recent (6 month) history of fall-asleep car crashes or near miss accidents 6. Excessive sleepiness that in the opinion of the treating physician requires immediate CPAP treatment 7. Severe medical (including renal failure) or psychiatric co-morbidity 8. Unstable medical conditions (hypertension, cardiac) 9. Recent use of illicit drugs or alcohol dependence 10. Current or recent (<3 months) use of hypoglycaemic agents 11. Current or previous diagnosis of diabetes mellitus (previous gestational

diabetes mellitus not excluded)
12. Respiratory failure including obesity hypoventilation syndrome (OHS) (OHS as diagnosed by physician, based on standard criteria including: BMI >30kg/m^2, arterial PaCO2 >45 and evidence of prolonged periods of hypoventilation and hypoxemia during sleep)

Participants will be required to inform the researcher if they are on any other medications. If this will not interfere with the study intervention and poses no greater risk to the patient, the medication will be recorded on the concomitant medication form found in Appendix C.

2.3 Participant Withdrawal

Withdrawal criteria

Participants 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. If any of the study exclusion criteria are diagnosed
2. Protocol violations
3. Adverse or serious adverse events

Discontinuation of the study

The study may be discontinued at any time on the advice of the responsible principal investigators on the basis of new information regarding safety or efficacy. Additionally, the study may be terminated if progress is unsatisfactory or if the principal investigators fail to secure additional funding to continue the trial.

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

Procedure to withdraw

If a participant fails to return for follow up or discontinues for personal reasons, attempts will be made to determine whether the reason for not returning is not an adverse event (bearing in mind that the participant is not obliged to state his/her reasons).

Participants with clinically significant abnormalities requiring discontinuation will be followed until recovery from the abnormality, if possible.

For the reasons above, if discontinuation occurs, an early termination visit will be encouraged with an attempt to collect the primary outcome.

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

Participants discontinuing from the study may be replaced. A new randomisation number must be issued for the new participant.

2.4 Modification of Protocol

If any important protocol modifications are made, standard steps will be taken to gain approval from ethics for relevant documents and to re-consent affected participants with the new protocol.

2.5 Recruitment Approaches

Hospitals:

Approximately 30 participants will be entered in the pilot trial. Participants will be recruited via Woolcock, Royal Prince Alfred Hospital, University of Sydney, other affiliated sleep, endocrine and obesity physicians and advertisments.

Woolcock Databases:

The Woolcock Volunteer database hosts patient's details who have provided consent to be contacted about clinical trials. Any appropriate candidates may be contacted from this list.

Woolcock Clinic:

Woolcock affiliated treating physicians will be alerted to the study and asked to inform potential participants of the trial. Patients will be assured that an unwillingness to participate in the trial will in no way affect their ongoing treatment or level of care.

Advertising:

Advertisements will be displayed in and around waiting rooms and on websites of the institutions listed above. Advertisements may also be displayed in magazines, websites or papers and in local shops. Sleep Disorders Australia and larger general practices will also be advised of the trial to advertise the trial for potential participants.

Media coverage:

Media organisations will be engaged through our media liaison to outline the research study and engage public interest. Potential participants will be directed to the Woolcock Insititute website where they can answer a series of eligibility questions prior to choosing whether to provide their contact details to discuss the study.

3. Study Design and Procedures

3.1 Study Design

Study Design and Duration:	A three month randomised controlled parallel group trial in obese pre-diabetic patients with OSA randomised to a VLED (control) or CPAP + VLED (intervention). The study incorporates a superiority framework. Following the randomised controlled phase, patients will commence usual clinical care of their weight maintenance and their OSA. At 12 months they will be invited to attend a follow up visit.
Outcome Measures:	Primary Outcome: Glucose tolerance as measured by an oral glucose tolerance test at three months. Secondary outcome measures of abdominal and body fat (determined from DXA scans), metabolic syndrome components (glucose, lipids, BP), health related quality of life and cost effectiveness measures will also be assessed.
Location:	Study procedures will be conducted at the Woolcock Institute of Medical Research, except the DXA scan which will be undertaken at the Charles Perkins Centre, University of Sydney.

- *The study timeline can be found in Appendix A.*

3.2 Enrolment and Randomisation to Treatment

Only eligible adults providing written informed consent, according to the protocol approved by the local ethics committee, will be enrolled into the trial.

Patients will be enrolled sequentially according to the randomisation list. After screening and baseline assessment, all participants will be randomised in a 1:1 ratio into either:

1. CPAP + VLED (Intervention) OR
2. VLED alone (Control)

This is an open label study; it is not possible to blind the study due to the nature of CPAP treatment.

3.3 Assignment to Treatment Groups

Informed consent:

Enrolment of participants into the trial will be performed by a combination of study doctors and coordinators as eligibility needs to established. All participants will first be provided with a participant information sheet to read which includes details of all the study procedures, commitments and risks. The study staff member who enrols the participant will also verbally explain the study to the participant in detail and provide opportunity to ask questions. All participants will then be asked to sign the informed consent form before proceding to undergo formal screening.

Screening:

All patients who undergo screening will be automatically allocated a screening number in ascending chronological order against which their personal details will be entered into the Research Tools^{TM} database - including name, DOB, address and contact numbers. This number will be a three-digit number prefixed by "S" (e.g. S001, S002 etc.) and will be used to identify participants during the screening phase prior to randomisation. All data to allow assessment for trial eligibility will also be required to be entered into the Research Tools database.

Randomisation:

Randomisation will take place at baseline. Secure randomisation will be achieved through Research Tools. Participants will be enrolled sequentially according to a computer generated randomisation list using a random block size (2, 4 or 6) that is not available to staff who enrol participants. A unique participant randomisation number will be assigned sequentially, in ascending order and will comprise a three digit number prefixed by "R" (e.g. R001, R002 etc.). This randomisation number will be used to internally identify the treatment group the participant is assigned to.

At randomisation, the randomisation module in Research Tools system requires that the trial coordinator enter a screening number and then confirm that the displayed participant name and DOB match the participant they intend to randomise. All previously entered eligibility data are then automatically assessed. If the participant meets all inclusion/exclusion criteria then the trial coordinator is able to commit online to automatically randomising the participant. Once this occurs, the participant is irrevocably allocated the next available randomisation number and previously concealed treatment assignment. Both the randomisation number and allocated treatment are then displayed and permanently recorded against that participant's online record.

To ensure the participant's anonymity, documents will use the participant's unique participant screening and randomisation numbers.

3.4 Concomitant medication, activities and procedures

Any other medication considered necessary for the participant's welfare and which does not interfere with the study objectives, assessment or treatment may be given at the discretion of the investigator. Allowed medications must be maintained at consistent dose as far as possible. Dose changes or the use of additional prescribed or non-prescribed medication should be recorded: noting drug, dosage, duration and reasons for use or dose change.

Any additional diagnostic, therapeutic or surgical procedures performed during the study period should also be recorded, including date, reason for and description of procedure and its outcome.

3.5 Risks and Discomforts

VLED: 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.

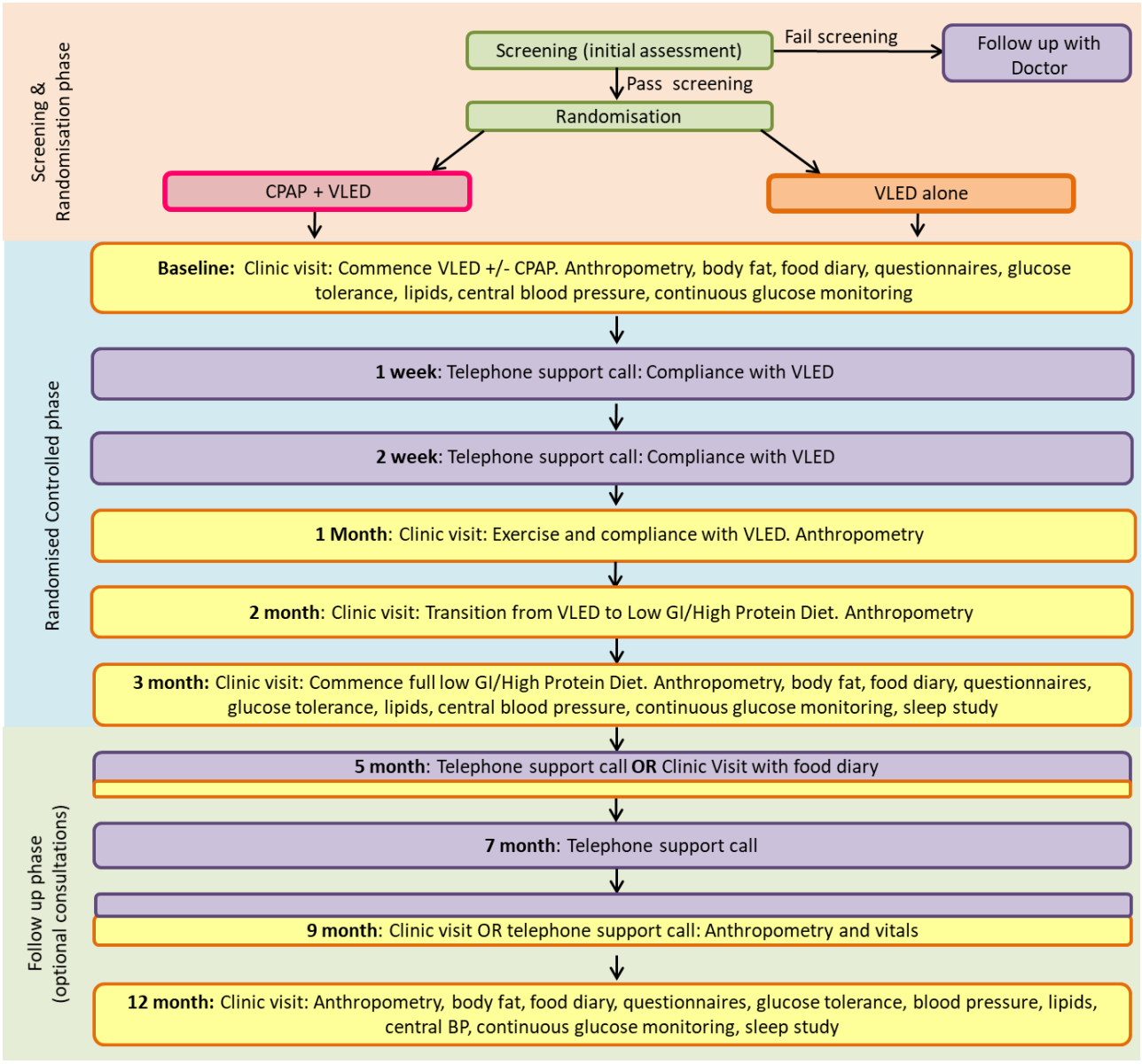
Blood Test: There may be some discomfort from the venepuncture and cannular insertion at the site from which blood is taken. There is also a risk of some minor bruising at the site, which may last one to two days.

DXA Scans: This research study involves exposure to a very small amount of radiation. The dose from routine diagnostic X-ray and nuclear medicine procedures is 2 mSv to 20 mSv. The effective radiation dose from this study is about 0.54 mSv. At this dose level, no harmful effects of radiation have been demonstrated and the risk is very low.

In addition to the risks or discomforts listed here, there may be other known and unknown risks that are not disclosed here; patients should talk to the study doctor if they would like more information.

In addition, patients may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if their injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). Patients do not give up any legal rights to compensation by participating in this study.

3.6 Study Flow Chart



3.7 Schedule of study procedures

Visit 1: Screening (face-to-face)

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, use of study devices and products, randomisation, potential risks and no guaranteed benefit from participation.

- 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
- Epworth Sleepiness Scale (ESS) and/or clinical report of debilitating daytime sleepiness.
- 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 12 months or the patient has recently lost or gained >5% body mass.

Patients who satisfy eligibility criteria will proceed to visit 2 (week 0) baseline. **OPTIONAL:** Patients who pass this level may be enrolled directly into the study and have Visit 2 consecutively beginning the same day.

Patients demonstrating any absolute or relative contraindication to exercise through their resting ECG must be reviewed by the study doctor to determine if suitable for the study.

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

Visit 2: Baseline assessment (0 weeks - face-to-face)

Participants will need to attend this visit in the fasting state. The investigator will verify eligibility according to inclusion and exclusion criteria. If entry criteria are met, the volunteer can be enrolled in the study, and then commence the VLED. Each participant will be provided with written instructions on how to self-administer the VLED and with information on potential side effects to monitor.

The following examinations will be performed at this visit (not necessarily performed in this order):

1. Insulin sensitivity (MINMOD) which incorporates an oral glucose tolerance test
2. Total body fat & lean mass (DXA)
3. Anthropometry & Vitals
4. Bio-impedance spectroscopy
5. Blood markers
6. 4 Day food diary
7. Questionnaires
8. Lifestyle consultation
9. 24 hour continuous blood glucose monitoring
10. 24 hour central blood pressure monitoring

Participants will be provided with VLED packages and study staff will schedule a date for telephone support calls (Visit 3 and 4) after this face-to-face visit.

Visit 3 & 4: Telephone support call (1 & 2 weeks - telephone)

Phone based follow-up. Patients will converse with the study clinician (exercise physiologist/dietitian) to confirm compliance and identify any side effects or problems with the VLED.

Visit 5: Clinic (1 month - face-to-face)

A brief clinical appointment reassessing anthropometry, vitals and bio-impedance spectroscopy to confirm progress for patient feedback. Lifestyle consultation and session one of the program (Exercise, Planning, Doing, Tracking) will also be conducted.

Visit 6: Clinic (2 months - face-to-face)

A clinical appointment reassessing anthropometry and vitals to confirm progress for patient feedback. Lifestyle consultation to educate on transitioning from VLED to the weight maintenance diet (low GI, higher protein) and session one of the programme (Exercise, Planning, Doing, Tracking) will also be performed.

Visit 7: Clinical assessment following VLED (3 months - face-to-face)

The following examinations will be performed at this visit (not necessarily performed in this order):

- Insulin sensitivity (MINMOD) which incorporates an oral glucose tolerance test
- Total body fat & lean mass (DXA)
- Anthropometry & vitals
- Bio-impedance spectroscopy
- Blood markers
- 24 hr food recall
- Questionnaires
- Lifestyle consultation and confirm compliance with the weight maintenance diet
- 24 hour continuous blood glucose monitoring
- 24 hour central blood pressure monitoring
- Arrange referrals and/or follow up for handover to usual clinical care of weight maintenance and OSA.
- Sleep Study – performed one week after Visit 7. Particpiants assigned to CPAP will undergo a a one week CPAP washout prior to the sleep study

Visit 8 – Clinical Monitoring (5 months – phone call or face to face) – optional

The following examinations will be performed at this visit (may not necessarily be performed in this order). At 5 months, (visit 8) the 4-day food diary will be collected to ensure compliance with the dietary prescription following completion of the VLED.

- Anthropometry & Vitals
- 4-day food diary
- Questionnaires
- Lifestyle consultation and session two of the program (Food Thoughts and Lapses)

Staff will schedule a date for Visit 9 and 10.

Visits 9 and 10– Lifestyle Support Call (7 and 9 months – phone call) - optional

Phone based intervention lifestyle support call. Patients will converse with the study clinician and undertake a 24-hour food recall at visits 9 and 10 (7 months and 9 months and respectively). Visit 9 and 10 (phone calls) will cover the topic Maintaining the change while visit 10 will cover patient specific lifestyle re-assessment, goal setting and review.

Staff will schedule a date for Visit 11, approximately 3 months after visit 10.

Visit 11 – Outcomes collection (12 months - face-to-face) - optional

The following examinations will be performed at this visit (may not necessarily be performed in this order).

- Fasting blood glucose test, if results indicate patient remains in a pre-diabetic state (5.5-7 mmol/L) an oral glucose tolerance test is clinically indicated and will be requested by study staff.
- Total Body Fat & Lean Mass (DXA)
- Anthropometry & Vitals
- Bio-impedance spectroscopy
- Blood markers
- 4-day food diary
- Questionnaires
- Lifestyle consultation
- Sleep Study: for symptomatic untreated individuals
- Patients who have continued using CPAP since the 3 month timepoint will be requested to bring their device memory card for download and confirm compliance.

Booster Sessions

Patients presenting with low adherence to the weight loss program (<75% adherence as determined by food diary or 24 hour food recall) 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.

3.8 Study Procedures and Assessments

Personnel training

Relevant study personnel will be trained by investigators on outcome collection.

Informed consent

Each potentially eligible participant will be informed of the study's objectives and overall requirements using the Patient Information Sheet and Informed Consent Form. A copy of the form will be provided for the participant. If the volunteer is willing to participate in the study, they will be requested to provide written and witnessed informed consent prior to participation in the trial.

Anthropometry

Anthropometric measurements will be taken at every meeting. These will include:

- Height (at screening only)
- Weight
- BMI
- Neck circumference (triplicate)Waist circumference (triplicate)

Office Blood Pressure

- Blood pressure (BP), and heart rate (HR) will be recorded at each contact visit including the termination visit should it occur, following European Society of Hypertension guidelines.
- Throughout the study, BP will be measured using the same type of device and a standard sized BP cuff will be used, except a larger and smaller cuff will be used for large arms (>32cm) and small arms, respectively.
- BP will be measured on both arms at baseline to detect possible differences. In this instance, the arm with the higher value will be taken as the reference.
- At least 2 BP measurements will be taken, in the sitting position, spaced 1-2 minutes apart, and additional measurements if the first two are quite different.

24 hour Central Blood Pressure Monitoring

Pulse wave analysis measures arterial stiffness by assessing peripheral and central blood pressure using a non-invasive device combined with an ambulatory 24 hour

brachial sphygmomanometer (Oscar 2™ system from SunTech Medical®). This is a portable automatic blood pressure machine, which takes measurements blood pressure, central pressure and arterial stiffness. Patients will be fitted with the machine by the study coordinator at baseline (Visit 2) and follow-up (Visit 8 and Visit 9). The patients will be asked to wear the device for 24 hours at each time point.

Wrist accelerometer

Sleep and wake periods and activity will be gauged using a commercially available device (Respironics Actiwatch2). We will also be using this device's raw activity counts as an objective measure of physical activity levels.

Glucose control

Oral Glucose Tolerance Test

Glucose tolerance will be assessed by 2 hour blood glucose level following a 75g oral glucose load. A total of 10ml of blood will be collected at each time point (baseline, 3 months and 12 months).

Insulin Sensitivity

Insulin sensitivity will be assessed by modified minimal model (MINMOD) analysis of multiple measurements of insulin, glucose and c-peptide (at 0, 10, 20, 30, 60, 90, 120, 150 and 180 mins) after a 75g oral glucose load, using a previously published method (Dalla-Man et al, Diabetes 2005; 54:3265-3273). A total of approximately 100ml of blood will be collected at each time point (baseline, 3 months and 12 months). This measurement will incorporate measurement of glucose tolerance.

Continuous Blood Glucose Monitoring

A small sensor device (Medtronic Guardian) is worn by the participant for 24 hours. It is inserted comfortably under the skin, normally on the stomach, using a special insertion device secured with tape or a bandage, by a researcher, and the participant will be instructed on how to use it. The sensor measures glucose levels every few seconds and sends the information to a monitor that can be worn on a belt or in a pocket. Blood sugar levels will be checked to calibrate the device, using a regular glucometer and the widely used fingerprick technique, which only provides minimal discomfort. Potential side-effects include minor bruising, mild discomfort and a small risk of infection. The risk of any of these side effects is low.

Metabolic Syndrome Markers and Anabolic Hormones

A fasting approximately 20ml blood sample will be collected for assessment of lipids and HbA1c. Samples will also be stored at -80C for later measurement of IGF1 and IGFBP1 and other markers.

Body composition (DXA scan)

Dual Emission X-Ray Absorptiometry uses a very low dose of radiation. This scanning machine provides a measure of body composition that is practical within a clinical setting. (Protocol can be found in **Appendix G**). These scans will be performed at 0, 3 and 12 months time points at the Charles Perkins Centre by a trained technician.

Bioimpedance Spectroscopy (4 compartment model)

Bioimpedance spectroscopy will be performed at 0, 3 and 12 months time points. (Protocol can be found in **Appendix I**)

Questionnaires

The following questionnaires will be completed at 0, 3and 12 months:

1. The Epworth Sleepiness Scale (ESS)
2. Functional Outcomes of Sleep Questionnaire (FOSQ)
3. Depression, Anxiety and Stress Scales (DASS)
4. Impact of Weight on Quality of Life questionnaire (IWQOL)
5. International Physical Activity Questionnaire (IPAQ)

All questionnaires can be found in Appendix E

Weight Loss and Maintenence

Weight loss and maintenance education will be provided by the study dietitian/nutritionist to all patients during the three month randomised controlled phase at the 0, 1, 2 and 3 month visits and the 1w and 2w phone or video conference consultations. The focus during this period is complying with the VLED.

After the three month randomised controlled phase all patients will be offered continued weight maintenance from the study dietitian/nutritionist for the nine month follow up phase. The frequency of the follow up visits is at the discretion of the patient. The recommended schedule of clinic visits is at 9 and 12 months and

telephone or video conferencing consultations at 5 and 7 months, which is based upon a previously published Woolcock Institute clinical trial. The weight maintenance program consists of a manualised dietary and exercise component, aiming to maintain a minimum 10% weight loss over a 12 month period with sustainable changes in eating patterns and prescribed physical activity.

Dietary Component

All participants will undergo a VLED in the first 2 months to enable rapid weight loss of approximately 10% body weight. The VLED will be followed by a transitional period of 4 weeks into a low GI/high protein weight maintenance diet. During the maintenance diet, total daily energy intake is prescribed according to a participants' energy requirements, estimated using the Harris-Benedict equation with an appropriate activity factor and 2000 kJ (500 calorie) per day deficit to encourage moderate weight loss (approximately 0.5 kg per week) among participants. Dietary compliance will be monitored with a 4-day food diary administered at 0, 3 and 12 months.

Exercise Component

The exercise component aims to encourage patients to achieve greater than 250 minutes of exercise a week which is conducive to clinically significant weight loss and metabolic improvements. In addition, they will be prescribed a minimum 2 days per week self-managed strength training to promote lean muscle gain. Physical activity will be assessed at 0, 3 and 12 months using the International Physical Activity Questionnaire (IPAQ). In addition, all subjects will be issued with a wrist accelerometer to objectively measure but also potentially enhance physical activity. Activity data from these devices will be available online to investigators.

OSA and CPAP Management

Team sleep clinicians and CPAP therapists will manage OSA and CPAP therapy according to standard clinical practice. Patients will use auto-titrating CPAP during the randomised controlled phase of the trial. After the 3 month followup visit, all patients who commence or continue with CPAP therapy may use either auto-CPAP or fixed CPAP as deemed appropriate by the treating sleep physician. Clinic CPAP

therapists will download compliance data at 2 weeks, 3 months and as clinically indicated.

Diaries

Patients will be asked to document diet, exercise, and sleep habits daily at periods during the trial. They will also be asked to complete a 4-day food diary at 0 months, 3 months, 9 months and 1 year. 24-hr food recall will also be undertaken at 0 weeks, 2 months, 3 months, 5 months and 7 months to confirm dietary compliance. See Appendix F.

Overnight Sleep Studies: Polysomnography (PSG)

At three points during the study (screening, 3 and 12 months[if clinically indicated]) patients will undertake overnight polysomnography at the Woolcock Institute for the purpose of determining sleep apnoea severity measured primarily via the apnoea hypopnea index (AHI). This requires the attachment of leads to the patient 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 study is scored using standard criteria.

3.9 Adverse Event Reporting

Collection of adverse events will commence from the time that the participant signs the consent to participate in the study. Routine collection of adverse events will continue until the participant completes the study or withdraws.

Adverse events are defined as any untoward medical occurrence in a patient that occurs during the trial, which does not necessarily have a causal relationship with the interventions.

If the investigator believes that the adverse event is causally related to the VLED or CPAP device then adjustment or ceasing the use of the diet or device should be considered. This will be assessed by the investigators, study doctors and other members of the study team.

Serious adverse events (SAE's) are defined as any untoward medical occurrence that:

- Results in death
- Is an immediately life-threatening condition
- Requires hospitalisation or prolongs hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Results in any other important medical condition.

The Ethics Committee must be notified of any SAE's within 72hours.

4 Statistical Methods

Sample Size:

30 patients will be required to complete the randomised phase of this pilot study. Allowing for an approximate 20% dropout, n=38 will need to be randomised.

Data management:

Electronic Case Report Forms reside on a secure server that is regularly backed up. Data is entered manually by keyboard in the Research Stools Database. All participants have unique screening and randomisation numbers. Participant personal details (name, DOB etc) are de-identified in each record but are linkable via the allocated screening number.

Data input has range checks for most variables. Double data entry will be used for all outcomes that require manual keyboard entry.

The investigator team will have access to the final trial dataset. Any other persons would require approval from the investigator team.

All data will be stored securely for at least 15 years.

Data Analysis:

Outcome data will be analysed using Linear Mixed Model Analysis of variance due to expected inter-patient variability and repeated measures. Patients will be random

factors. Treatment and time (0 & 3 months) will be fixed factors. The Treatment x Time interaction will be examined to see the specific difference between treatments at just the 3 month time point. Analysis will be by intention to treat and will include all participants who are randomised at 0 months including drop-ins to CPAP and participants who do not adhere to treatment.

Exploratory mixed models analyses of OSA severity accounting for CPAP compliance and weight change will also be conducted using 12 month followup data.

Data Monitoring: As all treatments are routinely applied in clinical care, a Data Monitoring Committee will not be appointed. Instead, all adverse events and serious adverse events will be monitored by the investigating team and discussed at regular monthly meetings. Patients who develop excessive sleepiness in the weight loss alone arm will be assessed by the study sleep physicians to determine the cause of the sleepiness and be considered on a case-by-case basis for being placed on CPAP therapy. Side effects attributable to the VLED will be managed by the dietician in consultation with the endocrinology/metabolic physician team.

There are no planned interim analyses. The final decision to terminate the trial lies with the Principal Investigators. Stopping guidelines will be based on (1) safety data and (2) ongoing trial funding. The investigators will conduct a 6 monthly review of all SAEs (pre-defined on page 22) and if after discussion the rate of SAE's is deemed unacceptable by the PI's then the study will be stopped and the HREC will be advised of the decision.

Internal procedures for monitoring trial conduct will be followed. Where available an external monitor will be engaged.

Dissemination:

Findngs will be disseminated via conferences, publications and media, as applicable. Patients will be informed of results of the study at the conclusion of the trial. Eligible authors will include investigators who are involved in the conception and design of the study, the conduct of the trial, the analysis of the results and authorship and

presentation of study findings. The full protocol will be added to the ANZCTR registry.

Appendix A: Time Frame for Study Visits	**Visit number**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
	Month	**0**	**1W**	**2W**	**1M**	**2M**	**3M**	**5M**	**7M**	**9M**	**1Y**
Study Phase	**Screen**	**Randomised Controlled**					**Follow up (optional consultations)**				
Lifestyle Modification Phase		Very Low Energy Diet (VLED)				Trans -ition	Low GI/High Protein Diet				
CPAP Phase		Randomised to CPAP or No CPAP					Usual Care for CPAP				
Eligibility & Informed Consent	X										
Randomisation to CPAP		X									
Reassessment of OSA and transfer into follow up phase with optional support							X				
Glucose Tolerance (OGTT, MINMOD)		X					X				X**
Total Body Fat & Lean Mass (DXA) & Bioimpedence		X					X				X
Anthropometry, Vitals		X			X	X	X				X
Blood Markers (Lipids,HbA1c,IGF1,IGFBP1)		X					X				X
24 Hour Testing (Continuous Central Blood Pressure & Continuous Glucose Monitoring)		X					X				X
4-day Food Diary		X						X			X
24-hr Food Recall					X	X	X		X	X	
Questionnaires		X					X				X
Sleep Study	X						X				X*
Lifestyle Consultation		X			X	X	X		X		X
Lifestyle Support Call			X	X				X		X	

* PSG if clinically indicated by symptoms of obstructive sleep apnoea

** If clinically indicated by elevated fasting blood glucose result

Appendix B – Schedule of Participant visits

Screen (Visit 1)	• Woolcock screen visit with physician and study coordinator to assess study eligibility • Issue 4-day food diary • Includes overnight sleep study if not conducted within preceding 12 months to confirm OSA severity
Baseline (Visit 2)	• **Full Assessment** including dietary and exercise assessment and all other study procedures listed during a half day clinic visit • Measurement of glucose tolerance, insulin sensitivity, total body fat and lean mass • Measurement of anthropometry, vitals, metabolic blood markers • Assessment of food diary and education on VLED diet • Complete diet, exercise and quality of life questionnaires • Issue VLED shakes – Stage 1 • 24 hour central blood pressure monitoring and 24 hour continuous blood glucose monitoring
1 week (Visit 3)	• **Phone call or Skype** contact lasting 15-30minutes • Emphasis: VLED compliance and safety
2 weeks (Visit 4)	• **Phonecall or Skype** contact lasting 15-30 minutes • Emphasis: VLED compliance and safety
1 month (Visit 5)	• **2 hour clinic session** • Anthropometry & vitals • 24 hour recall • Session: Exercise, Planning, Doing, Tracking
2 month (Visit 6)	• **2 hour clinic session** • Anthropometry & vitals • Education on Low GI/High Protein Diet and transition phase diet
3 month (Visit 7)	• **Full Assessment** including dietary and exercise assessment and all other study procedures listed during a half day clinic visit • Sleep study performed one week after Visit 7. Those using CPAP will have a one week washout prior to sleep study • Measurement of glucose tolerance, insulin sensitivity, total body fat and lean mass • Blood test, body measurements, bioelectrical impedance analysis, blood pressure, heart rate, wrist accelerometer and sensewear & diary and lifestyle consultation • 24hr food recall • 24 hour central blood pressure monitoring and 24 hour continuous blood glucose monitoring •
5 month (Visit 8)	• **2 hour clinic session OR Phone call/ Skype** lasting 30- 60

– optional	minutes • Clinical assessment involving: anthropometry and vitals, bio-impedance spectroscopy, questionnaires and lifestyle consultation • Session: Headspace and Food Choices • 4 day food diary
7 month (Visit 9) – optional	• **Phone call or Skype** lasting 30- 60 minutes • 24 hour food recall • Lifestyle consultation
9 month (Visit 10) – optional	• **Phone call or Skype** lasting 15 - 30 minutes • Session: Maintaining the Change
12 month (Visit 11) – optional	• **Full Assessment** including dietary and exercise assessment and all other study procedures listed during a half day clinic visit • Sleep study for those clinically indicated • Measurement of fasting blood glucose (and glucose tolerance/ insulin sensitivity if clinically indicated), total body fat and lean mass • Blood test, body measurements, bioelectrical impedance analysis, and lifestyle consultation. • 24 hour central blood pressure monitoring and 24 hour continuous blood glucose monitoring • 4 day food diary completed • Study complete

Appendix C: Concomitant Medications

Were any medications, including over-the-counter and health/dietary supplements, taken by the patient during the study? ☐

Yes → Enter information on this sheet. ☐ No

Line #	**Name of Medication**	**Dose**	**Units**	**Freq**	**Route**	**Indication** If med. taken due to AE, record AE # →	**AE #**	**Date**		**Ongoing at end of study?**
1								Start		
								End		
2								Start		
								End		
3								Start		
								End		
4								Start		
								End		
5								Start		
								End		
6								Start		
								End		
7								Start		
								End		

Appendix D: Risk Stratification

ADULT PRE-EXERCISE SCREENING TOOL

This screening tool does not provide advice on a particular matter, nor does it substitute for advice from an appropriately qualified medical professional. No warranty of safety should result from its use. The screening system in no way guarantees against injury or death. No responsibility or liability whatsoever can be accepted by Exercise and Sports Science Australia, Fitness Australia or Sports Medicine Australia for any loss, damage or injury that may arise from any person acting on any statement or information contained in this tool.

Name: _____

Date of Birth: _____ Male ☐ Female ☐ Date: _____

STAGE 1 (COMPULSORY)

AIM: to identify those individuals with a known disease, or signs or symptoms of disease, who may be at a higher risk of an adverse event during physical activity/exercise. This stage is self administered and self evaluated.

Please circle response

1.	Has your doctor ever told you that you have a heart condition or have you ever suffered a stroke?	Yes	No
2.	Do you ever experience unexplained pains in your chest at rest or during physical activity/exercise?	Yes	No
3.	Do you ever feel faint or have spells of dizziness during physical activity/exercise that causes you to lose balance?	Yes	No
4.	Have you had an asthma attack requiring immediate medical attention at any time over the last 12 months?	Yes	No
5.	If you have diabetes (type I or type II) have you had trouble controlling your blood glucose in the last 3 months?	Yes	No
6.	Do you have any diagnosed muscle, bone or joint problems that you have been told could be made worse by participating in physical activity/exercise?	Yes	No
7.	Do you have any other medical condition(s) that may make it dangerous for you to participate in physical activity/exercise?	Yes	No

IF YOU ANSWERED 'YES' to any of the 7 questions, please seek guidance from your GP or appropriate allied health professional prior to undertaking physical activity/exercise

IF YOU ANSWERED 'NO' to all of the 7 questions, and you have no other concerns about your health, you may proceed to undertake light-moderate intensity physical activity/exercise

I believe that to the best of my knowledge, all of the information I have supplied within this tool is correct.

Signature _____ Date _____

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Appendix E: Questionnaires

Epworth Sleepiness Scale (ESS)

Imagine yourself in the following situations, and rate your chance of dozing or falling asleep within the last two weeks. Even if you do not find yourself in the situation (eg driving), imagine how they would have affected you. Indicate your answer by putting a tick "✔" in the appropriate box.

Situations	Chance of Dozing			
	Would never doze 0	Slight chance of dozing 1	Moderate chance of dozing 2	High chance of dozing 3
1.Sitting and reading				
2.Watching TV				
3.Sitting, inactive in a public place (e.g., a theatre or a meeting)				
4.As a passenger in a car for an hour without a break				
5.Lying down to rest in the afternoon when circumstances permit				
6.Sitting and talking to someone				
7.Sitting quietly after lunch without alcohol				
8.In a car, while stopped for a few minutes in the traffic				
Total score				

SIGNATURE: _____

DATE: _____

Functional Outcomes of Sleep Questionnaire (FOSQ)

Note: In this questionnaire the words "sleepy" or "tired" are used, it describes the feeling that you can't keep your eyes open, your head is droopy, that you want to nod off or that you feel the urge to take a nap. These words do not refer to the tired or fatigued feeling you may have after you have exercised.

FOSQ questions are answered using numbers from 0-4.

- 0 = I don't do this activity for other reasons
- 1=Yes, extreme
- 2=Yes, moderate
- 3=Yes, a little
- 4=No

	I don't do this activity	Extremely	Moderately	A little	No
Q1 - Do you generally have difficulty concentrating on the things you do because you are sleepy or tired ?	☐0	☐1	☐2	☐3	☐4
Q2 - Do you generally have difficulty remembering things because you are sleepy or tired ?	☐0	☐1	☐2	☐3	☐4
Q3 - Do you have difficulty finishing a meal because you become sleepy or tired ?	☐0	☐1	☐2	☐3	☐4
Q4 - Do you have difficulty working on a hobby (for example: sewing, collecting, gardening) because you are sleepy and tired?	☐0	☐1	☐2	☐3	☐4
Q5 - Do you have difficulty doing work around the house (for example: cleaning house, doing laundry, taking out the trash, repair work) because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q6 - Do you have difficulty operating a motor vehicle for short distances (**less** than 100 miles) because you become sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q7 - Do you have difficulty operating a motor vehicle for long distances (**greater** than 100 miles) because you become sleepy or tired?	☐0	☐1	☐2	☐3	☐4

Q8 - Do you have difficulty getting things	☐0	☐1	☐2	☐3	☐4

done because you are too sleepy or tired to drive or take public transportation?					
Q9 - Do you have difficulty taking care of financial affairs and doing paperwork (for example: writing checks, paying bills, keeping financial records, filling out tax forms , etc.) because you are sleepy or tired.	☐0	☐1	☐2	☐3	☐4
Q10 - Do you have difficulty performing employed or volunteer work because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q12 - Do you have difficulty visiting with your family or friends in **your** home because you become sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q13 - Do you have difficulty visiting your family or friends in **their** home because you become sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q14 - Do you have difficulty doing things for your family or friends because you are too sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q15 - For question 15 answer using only 1,2,3 or 4. Has your relationship with family, friends or work colleagues been affected because you are sleepy pr tired?	☐0	☐1	☐2	☐3	☐4
Q16 - Do you have difficulty exercising or participating in a sporting activity because you are too sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q17 - Do you have difficulty watching movie or videotape because you become sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q18 - Do you have difficulty enjoying the theatre or a lecture because you become sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q19 - Do you have difficulty enjoying a concert because you become sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q20 - Do you have difficulty watching television because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q21 - Do you have difficulty participating in religious services, meetings or a group or club because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4

Q22 - Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q23 - Do you have difficulty being as active as you want to be in the morning because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q24 - Do you have difficulty being as active as you want to be in the afternoon because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q25 - Do you have difficulty keeping pace with others you own age because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q26 - For question 26, answer only using the scale 1 = very low, 2=low, 3=medium, 4= high. How would you rate your general activity?	☐0	☐1	☐2	☐3	☐4
Q27 - Has your intimate or sexual relationship been affected because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q28 - Has you desire for intimacy or sex been affected because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
29 - Has your ability to become sexually aroused been affected because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4
Q30 - Has your ability to have an orgasm been affected because you are sleepy or tired?	☐0	☐1	☐2	☐3	☐4

Depression, Anxiety and Stress Scale

DASS21

Name: Date:

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

Impact of Weight on Quality of Life Questionnaire

Please answer the following statements by circling the number that best applies to you in the past week. Be as open as possible. There are no right or wrong answers.

Physical Function		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble picking up objects.	5	4	3	2	1
2.	Because of my weight I have trouble fastening my shoes or tying my shoelaces.	5	4	3	2	1
3.	Because of my weight I have difficulty getting up from chairs.	5	4	3	2	1
4.	Because of my weight I have trouble using stairs.	5	4	3	2	1
5.	Because of my weight I have difficulty putting on or taking off my clothing.	5	4	3	2	1
6.	Because of my weight I have trouble with mobility (getting around).	5	4	3	2	1
7.	Because of my weight I have trouble crossing my legs.	5	4	3	2	1
8.	I feel short of breath with only mild exertion (e.g. climbing a single flight of stairs).	5	4	3	2	1
9.	I am troubled by painful or stiff joints.	5	4	3	2	1
10.	My ankles and lower legs are swollen at the end of the day.	5	4	3	2	1
11.	I am worried about my health.	5	4	3	2	1
Self-esteem		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I am self-conscious.	5	4	3	2	1
2.	Because of my weight my self-esteem is not what it could be.	5	4	3	2	1
3.	Because of my weight I feel unsure of myself.	5	4	3	2	1
4.	Because of my weight I don't like myself.	5	4	3	2	1
5.	Because of my weight I am afraid of being rejected.	5	4	3	2	1
6.	Because of my weight I avoid looking in mirrors or seeing myself in photographs.	5	4	3	2	1
7.	Because of my weight I am embarrassed to be seen in public places.	5	4	3	2	1

Sexual Life		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I do not enjoy sex.	5	4	3	2	1
2.	Because of my weight I have little or no desire for sex.	5	4	3	2	1
3.	Because of my weight I have difficulty with sexual performance.	5	4	3	2	1
4.	Because of my weight I avoid sexual encounters whenever possible.	5	4	3	2	1

Public Distress		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I experience ridicule, teasing, or unwanted attention.	5	4	3	2	1
2.	Because of my weight I worry about fitting into seats in public places (e.g. theatres, cinemas, restaurants, cars, or aeroplanes).	5	4	3	2	1
3.	Because of my weight I worry about fitting through aisles or turnstiles.	5	4	3	2	1
4.	Because of my weight I worry about finding chairs that are strong enough to hold my weight.	5	4	3	2	1
5.	Because of my weight I experience discrimination by others.	5	4	3	2	1
Work (Note: For those not in paid employment, answer with respect to your daily activities.)		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble getting things done or carrying out my responsibilities.	5	4	3	2	1
2.	Because of my weight I am less productive than I could be.	5	4	3	2	1
3.	Because of my weight I feel that I don't receive appropriate raises, promotions or recognition at work.	5	4	3	2	1
4.	Because of my weight I am afraid to go for job interviews.	5	4	3	2	1

International Physical Activity Questionnaire (IPAQ)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**
_____ **minutes per day**

This is the end of the questionnaire, thank you for participating

Appendix F: Protocol for Administering Lifestyle Diaries

Protocol for administering Food Diaries and Food Recall Confirmation Method

Participants provided with food diaries at their baseline testing appointment should have completed them for a four day period (three usual week-days and one usual week-end day). Dietary assessment will be performed at baseline, 2,3,4,5,7,9 and 12 month time points. Diaries should be completed prior to each visit and will be mailed out or provided in advance depending on the more convenient method. 24 hour dietary recall will occur at the visit or over the phone and does not require any prior preparation by the patient.

Computer analysis of four day food diaries and corresponding dietary recall confirmation will be performed for each time-point (to assist with prediction of energy requirement and to guide dietary feedback). The 24 hour dietary recall at 2,3,5, and 7 month visits will not be analysed.

Four day Food Diaries:
Four day food diaries (three usual "work days", one usual "rest" day) to monitor dietary intake and support behaviour modification. To reduce reporting bias, participants will be encouraged to maintain their usual or modified eating habits as they will not be perceived as "good or bad" but simply guide dietary manipulation. Participants will be trained in how to record intake using household weights and measures during baseline testing and provided the opportunity to ask questions while being offered support throughout the trial.
Reported quantities should be checked by a research dietitian/nutritionist with the aid of a photographic atlas of food portion sizes and standardized measuring equipment if required.

Food Recall Process- Multiple Pass Method:
Upon collection of four day food diaries, a food recall method should be used to confirm both portion sizes and detailed dietary descriptions that may have been missing. A multiple-pass dietary recall may be conducted by a university trained nutritionist to aid in evaluation of participant dietary intake.

3D and 2D visual aids may be used to aid in determining portion size and to reduce error (e.g. metric cups, ruler, 7 concentric circles, diagrams of a square, cylinder and wedges, diagram of fish fillet, photos). Portion sizes may be estimated in numbers and measures rather than weights. The technique of probing should be used for more detail and to aid in memory recall.

- Step 1: Quick List (uninterrupted, previous day)
- Step 2: Forgotten Foods List (series of food questions)
- Step 3: Time and Occasion
- Step 4: Detail Cycle (description, amounts, additions, review)
- Step 5: Final Review Probe

Nutrient Analysis
Nutrient analysis will be conducted with Foodworks Version 8 (Xyris Software, Brisbane, Australia) by a university trained nutritionist using the profile for an age and gender matched individual engaged in sedentary activity and a standard protocol

for entry of food items. Food selections will be made using the description closest to the item. Due to limitations in the database, analysis may not be performed for all nutrients (e.g. Vitamin B12, Vitamin E, Vitamin D and fatty acids).

Daily Diary

Week 1					
	Medication	**Sleep**		**Diet**	**Exercise**
Date	**I have taken my medication today**	**Last night and this morning's sleep time**	**My sleep was**	**Today I ate**	**Details of my exercise today:**
Day 1	☐☐Yes ☐☐No	___ Bedtime ___ Waketime	☐Disturbed ☐Normal ☐Great	___ Meals ___ Snacks	Type: _____ _____mins
Day 2	☐☐Yes ☐☐No	___ Bedtime ___ Waketime	☐Disturbed ☐Normal ☐Great	___ Meals ___ Snacks	Type: _____ ____mins
Day 3	☐☐Yes ☐☐No	___ Bedtime ___ Waketime	☐Disturbed ☐Normal ☐Great	___ Meals ___ Snacks	Type: _____ ____mins
Day 4	☐☐Yes ☐☐No	___ Bedtime ___ Waketime	☐Disturbed ☐Normal ☐Great	___ Meals ___ Snacks	Type: _____ ____mins
Day 5	☐☐Yes ☐☐No	___ Bedtime ___ Waketime	☐Disturbed ☐Normal ☐Great	___ Meals ___ Snacks	Type: _____ ____mins
Day 6	☐☐Yes ☐☐No	___ Bedtime ___ Waketime	☐Disturbed ☐Normal ☐Great	___ Meals ___ Snacks	Type: _____ ____mins
Day 7	☐☐Yes ☐☐No	___ Bedtime ___ Waketime	☐Disturbed ☐Normal ☐Great	___ Meals ___ Snacks	Type: _____ ____mins

Food & Exercise Diary Combined

Day: _____ Date: ___ / _____ / _____ Weight: _____ Actiwatch worn: Yes / No

		Food Eaten		Drinks	
Meal	Time	Description eg. Weetbix	Quantity eg. 3 biscuits	Description eg. Coca Cola	Quantity eg. 600ml
Breakfast					
Snacks					
Lunch					
Snacks					
Dinner					
Supper / Dessert					

Physical Exercise Diary

	Hour																							
Minute	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
0-15																								
16-30																								
31-45																								
46-60																								

Appendix G. Procedure for DXA Scan

1) Equipment

It is essential that the same DEXA machine is used for the patients' measures during the study. The equipment must be calibrated regularly, maintained, and used according to the manufacturer's guidelines.

To ensure consistent technique when taking endpoint measures, the investigator should ensure that, where possible, the same staff member that completed the initial measurements on the patient continues to measure the patient at each subsequent visit.

2) Methodology

a) Prepare the patient:

1. Ensure that all attenuating material (belts, metal buttons etc) are first removed. This is best achieved by dressing all subjects in a light gown without shoes.
2. Lie the patient onto the scanner table and position so that the patient's hands are palms down and flat on the table with arms alongside the body.
3. Ensure that the patient is aligned in the centre of the scanner table, as per the manufacturer's recommendations.

b) To measure total body density:

1. A correct total body image shows the patient's entire body. Ensure that the head, feet and arms are all shown in the image.
2. Make sure the patient's head is 3 cm below the horizontal line of the table pad. Use the velcro straps to secure the patient's knees and feet to prevent movement during the measurements.
3. When analysing the image make sure the cuts are correctly positioned:
    - Head. The head cut should be located immediately below the chin.
    - Left and right arm. Both arm cuts pass through the arm sockets and are as close to the body as possible. Ensure the cuts separate the hands and arms from the body.
    - Left and right spine. Both spine cuts are as close as possible to the spine without including the rib cage.
    - Left and right pelvis. Both pelvis cuts pass through the femoral necks and do not touch the pelvis.
    - Pelvis top. The pelvis top cut is immediately above the top of the pelvis.
    - Left and right leg. Both leg cuts separate the hands and forearms from the legs.
    - Centre leg. The centre leg cut separates the right and left leg

Appendix G. Procedure for DXA Scan

CERTIFICATE OF COMPLIANCE

Certificate: No: DI 042507

Radiation Guideline 6: Registration requirements & industry best practice for ionising radiation apparatus used in diagnostic imaging

One form is to be completed for each apparatus

NSW GOVERNMENT | Environment, Climate Change & Water

I. DETAILS OF OWNER

Name: The University of Sydney — Contact person: Sally McClintock

(company or individual) Level 2 Charles Perkins — Position:

Street address: centre D17, The University of Sydney

(not a PO Box): — Tel: 0402 832 401 Fax:

2. APPARATUS DETAILS (tick one box only)

☐ Mammography ☐ Radiography only ☐ Fluoroscopy only
☐ Radiography/Fluoroscopy ☐ Dental ☐ Veterinary ☑ Computerd Tomography & Bone Mineral Densitometry

Site name and address: as above

(not a PO Box)

Specific site location: DEXA Room 1220

(Eg. Building C, room 227)

Reason for inspection
☐ New registration
☑ Registration renewal
☐ Annual "mean glandular dose" measurement ONLY
Other (please specify):

Registration Number

Details		Manufacturer	Type/Model No.	Serial No./Registration No.
Console/Generator		Hologic inc.	Discovery QDR	86936
X-ray tube housing (one or more)	1	Hologic inc.	101-05479	SQ-159AP
	2			
X-ray tube insert (one or more)	1	Lohmann	160/25 HA10 DEG	160915002
	2			

3. ASSESSMENT DETAILS - The apparatus fails to meet the following mandatory requirements of Radiation Guideline 6

Subclause (e.g. 2.4.1 Filtration)	Details

4. MINOR OR EASILY REPAIRABLE FAULTS - The apparatus meets the mandatory requirements of Radiation Guideline 6 provided that the following faults are corrected by the date specified (which must not exceed 3 months).

Date:

Subclause (e.g. 2.10.3 Markings)	Details

5. DECLARATION

I have assessed the apparatus for compliance with Schedule 1 of *Radiation Guideline 6*, which are prescribed in the *Radiation Control Regulation 2003* as the minimum mandatory requirements for the registration of ionising radiation apparatus used in diagnostic imaging under section 7 of the *Radiation Control Act 1990*.

The apparatus complies with the minimum mandatory requirements for registration: *☑ Yes ☐ No

Name Vivien Munoz-Farrell Signature — Date of inspection 18/10/16 — Accreditation No. (CRE) 27

*Subject to the conditions in part 4 of this certificate

Notes:

1. The original of the certificate of compliance must be completed by the CRE and provided to the owner of the apparatus within 21 days of the date of compliance testing for the purpose of certification for registration, regardless of whether the apparatus has passed or failed.
2. In addition, the CRE must within a reasonable period after the inspection issue the owner with a report, including readings and calculations, details of non-compliance with mandatory requirements of *Radiation Guideline 6* and may include recommendations relating to matters outside mandatory requirements in the Guideline (for example, recommended best practice). The report should note any mandatory requirements that are not applicable to the apparatus. The non-removable carbon copy must be retained by the CRE for audit purposes
3. The owner should send a photocopy of the certificate to the Authority only when the apparatus is certified compliant (including annual *mean glandular dose* measurement of mammography apparatus). The owner must keep the original certificate and report for audit purposes.
4. If the inspection is for a registration application the owner must send a photocopy of the original certificate to the Authority with the appropriate form.

Return form to the DECCW (NSW), Radiation Control Section, PO Box A290, SYDNEY SOUTH, NSW, 1232
Tel: (02) 9995 5959 Fax: (02) 9995 6603

The Environment Protection Authority is part of the Department of Environment, Climate Change and Water (NSW) REG_DIA_CERTC_JAN2011

1.3	**Radiation Shielding:**	
1.3.1	Fixed protective shield present	N/A
1.3.2	Radiation Dose Rate	
Radiation dose rate	to public ≤ 20μSv/week	√
	to radiation workers ≤ 100μSv/week	√
Where shielding deemed necessary		
1.3.4	Shield correct height and marked	N/A
1.3.5	Communicate with and see patient	N/A
1.3.6	Viewing window marked	N/A
1.5	**Radiation Warning Signs**	
1.5.1	Entry doors	√
1.5.2	Warning lights	N/A
1.5.3	Warning lights – correct operation	N/A
2.1	**QA Program:**	
2.1.1	Program instituted and maintained	√
2.1.3	Program standardised and documented	√

Instrument Calibration			
Instrument	***Serial No***	***Date Due***	***Organisation***
PTW DIADOS-E	T11035-0113	01/03/2017	Gammasonics
Compliance Tester (Print/Type)	***Vivien Munoz-Ferrada***		
Compliance Tester (signature)		***Date 18 Oct 2016***	

Gammasonics
Institute For Medical Research Pty Ltd

'We specialise only in Technology'

Divisions:
Radiological Services Pty Ltd - 90 Queens Rd.
Canada Bay Medical Centre Pty Ltd - Suite 502, 49-51 Queens Rd.
Oncothermia Clinic - Suite 24/ Level 7, Prince Of Wales Private Hospital
Procon Aerospace & Marine Pty Ltd - 90 Queens Rd.
Lead Glass and Shielding Protection Pty Ltd - 90 Queens Rd.
ABN: 96 001 853 881

Mailing Address:
P.O.Box 323 Drummoyne, NSW 1470, Australia

90 Queens Road, Five Dock, NSW 2046, Australia
Phone: +61 (2) 9713 0000
Fax: +61 (2) 9713 1238
Email: pa@gammasonics.com
Web: www.gammasonics.com

ISO 9001 International Standards Certifications
ISO 13485 International Standards Certifications

BONE MINERAL DENSITOMETRY
NSW

Testers must complete all relevant sections

Note: Boxes should be completed with a √, a ×, or N/A.

Owner: The University of Sydney	**Phone No:** 0402 832 401
Address: Level 2 Charles Perkins Centre D17	
Contact Person: Sally McClintock	**Date of Test:** 18 Oct 2016
Equipment location: DEXA Room 1220	
EPA Registration No:	

2.10 Markings:

2.10.2 X-ray Control:

Manufacturer: Hologic Inc.	Model: Discovery QDR
S/n: 86936	Date of Manufacture: Sep 2012

2.10.3 X-ray Tube:

Insert manufacturer: Lohmann	
Insert model: 160/25 HA10 DEG	Insert s/n: 16091500Z
Housing name: Hilogic Inc.	
Housing type no: 101-0579	Housing s/n: SQ-15988
Housing Max kVp: 140kV	Total filtration: 6.8 mm Al @ 140 kV
Focal spot size(s): 0.4x1.2mm	Position of focal spot marked:

Comments
The unit complied with the mandatory requirements of the EPA Radiation Guideline #6. The Certificate of Compliance No.: DI042507 is enclosed with this report. Employing a technique of Full body, 7 min scan (3.5 nSv) scatter measurements were registered at the designated positions given. The calibration phantom was employed as the scattering medium. Estimated Max workload: 150 scans per week Estimated dose at operator's position: 0.525 µSv/week. NB: Radiation warning light deemed not necessary as no dose above background detectable at door way during exposure. It was found to be adequate to maintain radiation doses to occupationally exposed persons and members of the public within the prescribed limits.

Appendix H. Lifestyle Modification Programs

Lifestyle Consultation Protocol

All participants will undergo dietary and exercise assessment at baseline and will be prescribed individualised programs for physical activity and diet. The lifestyle modification sessions are designed to provide specific information about lifestyle changes and to reinforce behavioural changes in a supportive environment. Ongoing sessions allow for review of personalised prescriptions.

Diets

Participants will be coached to adopt a high protein/low GI weight loss diet. The dietary goal is to maintain weight loss of ≥5-10% over 12 months with sustainable changes in eating patterns and moderate energy restriction (similar to the diabetes prevention programs).

Energy intake for weight loss

Total daily energy intakes will be prescribed according to participants' energy requirements. As estimated using the Harris-Benedict equation with an appropriate activity factor (it is suggested all activity be underestimated to ensure a conservative approach) and 2000kJ/500calorie /day energy deficit. This will encourage moderate weight loss amongst participants (minimum 5% weight loss over 12 months). Four levels of daily energy will be used in this study (5,7,9 or 11 MJ/day) and participants will be prescribed an energy level which is closest to their energy intakes as calculated above.

Macronutrient distribution

Desired macronutrient distribution will comprise 45% daily energy intake from carbohydrate, 25% from protein, 30% from fat and <1% from alcohol.

- The diet will aim to be as low in GI as practical and achieved by replacing higher GI carbohydrates (e.g., conventional white or wholemeal bread, breakfast cereals, potatoes) with lower GI carbohydrates (e.g., Burgen® grain breads, oats, pasta, Basmati rice). The GI will be <50 (glucose = 100) and calculated using published data for Australian foods..
- Participants' diets will be focused on the consumption of more low GI foods (GI value of 55 or less) and less medium (GI value of 56-69) or high GI foods (GI value greater than 70).
- Adhering to a moderately low carbohydrate consumption (45% of daily energy), GL will be achieved by advising a moderate reduction in carbohydrate portion sizes leading to reduced overall carbohydrate consumption (g) throughout the day.
- A GI diet (average over 7 days) value of <50, and a low GL diet with a value of 77 will be the goal for participants.

- Participants will be encouraged to consume a diet reflecting the set macronutrient distributions by means of set food 'units' per day, sample meal plans and individual advice given by a nutritionist.
- Dietary modelling has been undertaken to determine the number of 'units' of food groups participants should aim to consume each day in order to follow the study diet.
- Food groups will be based on groups identified in the CSIRO Total Wellbeing Diet (Noakes & Clifton, 2006) (e.g. breads, cereals, dairy foods, fruit, vegetables, meats and alternatives, etc)..

- Sample meal plans and food group daily recommendations ('units') will aim to meet Nutrient Reference Values (NRVs) for participant age and gender groups, and will include popular foods consumed by many Australians.
- Dietary advice will emphasise lean sources of protein and restriction of saturated and trans fats (but not total fat).

Dietary Counselling

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 provided with educational materials that outline the carbohydrate options and the food amounts that constitute one serving. The nutritionist/dietitian will also provide information on the whole diet to ensure energy and overall nutrient balance and be available for telephone queries outside of scheduled visits.

All participants will be weighed at each lifestyle modification visit on 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. They will also be encouraged to keep a record of their food and exercise throughout the trial in a log and these logs will be reviewed each study visit. Logging of behaviour and goals has been shown to significantly enhance compliance and weight loss.

At 2,3,4,5,7,9 and 12 month time points 24-hour food recall interviews or 4-day food diaries will be collected to assess dietary compliance. Participants who have low adherence (<75%) will be offered additional individual booster sessions in person or by telephone if they require further assistance. 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. The study clinician will be a multi-skilled health professional educator with expertise in both the dietary and exercise components of the lifestyle modification program. This is critical to oversee the intervention and nurture participant perception of weight loss and that these elements are inextricably linked to successful long-term weight control and sleep management.

Baseline Dietary assessment:

- Introduction to the VLED including detailed discussion surrounding the information sheet.
- Risks, tips and strategies for compliance will be discussed alongside confirmation of the best means of maintaining the pattern of eating.
- Health coaching techniques will supportive behaviour change and techniques are based on the *Health Coaching Australia* techniques in which the study clinician is trained.
- Patients will be provided with educational material and safe/sustainable dietary recommendations to support weight loss and maintenance.

Baseline Exercise assessment:

- Individual suitability for exercise (as previously assessed by medical screen)
- Exercise specific risk stratification **(Appendix E)**

- Exercise history and assessment of current levels of participation in structured, non-structured and incidental physical activity.
    - Specific physical assessment to determine existing joint instability or muscular weakness/imbalance
        - Active and passive range of motion
        - Postural assessment
        - Indicated functional testing (e.g. lumbopelvic stability test, balance assessment etc)
- Prescription of specific strength and cardiovascular training program for weight loss with consideration of existing co-morbidities or musculoskeletal limitations.
    - Programs based on the "Australian Physical Activity Guidelines" as recommended for healthy for all Australians irrespective of weight.
        - $\geq$ 30 minutes physical activity on most, preferably all days
        - Vigorous activity for health and fitness where possible (per the principles of progressive overload)
    - Programs also draw from the *American College of Sports Medicine* guidelines for weight loss and weight maintenance
        - > 250 minutes/week of moderate- intensity physical activity for clinically significant weight loss
        - Strength training as part of the health and fitness regimen to increase fat-free mass and further reduce health risks
- Exercise specific goal setting based on weight loss targets and Australian guidelines for physical activity

The Lifestyle Modification Program

The lifestyle modification program has been designed for delivery in a clinical setting over a period of 10 months for sustainable and healthy weight loss. Sessions will consist of a combination of diet and exercise reinforcement and will provide the opportunity to progress exercise prescriptions as well as monitor dietary compliance. The lifestyle modification program is based on content from the The NSW Department of Health "Live Life Well" program and the RPAH Metabolism and Obesity Services "Bodylines" program. Dietary counselling and design is based on "The Lo Study" and advice from the Boden Institute of obesity, nutrition, exercise and eating disorders.

Participants will be advised on safe exercise habits and prescribed exercise at a frequency, intensity and volume that evidence supports as promoting weight loss (ACSM guidelines) and this will be tailored to the individual by addressing potential co-morbidities or musculoskeletal limitations. Emphasis will be on the progression of duration and frequency before intensity.
There will also be emphasis on goal setting and potential behavioural lapses along with educational components to address dietary changes.

The program emphasises healthy eating patterns and recommends ways to incorporate and plan physical activity into one's lifestyle.
During sessions, participants will be encouraged to track their progress in achieving those goals set in their baseline consultation. They will also be offered the opportunity to identify difficulties in making the recommended lifestyle changes and will have access to professional advice to assist them. All participants will be advised of their basal metabolic rate and encouraged to track energy in and energy out to promote a consistent

effort towards energy deficit and therefore weight loss. Patients will be provided with resources to aid them in these calculations throughout the trial (see below).

Patient Resource Aid

Welcome

About the Program:

The Lifestyle Modification Program is designed around the Sydney Diabetes Prevention Program and the Royal Prince Alfred Hospital's "Bodylines" program to promote healthy weight loss and reduce cardiovascular risk. This program seeks to aid sustainable lifestyle changes by delivering a specific, informative and factual series of sessions to assist you in losing weight amongst other health benefits. This program will help you to better understand the factors influencing your health and provide practical assistance in making better long term health choices.

The Program Goals are to:

- Reduce weight by 5%
- Increase Fibre intake
- Incorporate more low GI foods in your diet / Reduce saturated fat intake
- Reduce total fat intake
- Increase physical activity: at least 30 minutes a day

Who developed the program and why?

Our program is based upon the Sydney Diabetes Prevention Program 's Live Life Well Manual that is designed to reduce the risk of diabetes through lifestyle changes modelled on the Australian recommendations for healthy eating and physical activity. This program was designed by the NSW Department of Health, together with experts in diabetes, nutrition and physical activity. It aims to lower the risk of disease and improve health by eating better and moving more and is based on the best scientific evidence available.

Our program also draws some guidance from the "Bodylines" program- promoting weight loss through lifestyle changes modelled on consistent exercise and dietary changes. This program was designed by the Metabolism and Obesity Services at Royal Prince Alfred Hospital, and combines hospital based expertise in nutrition and physical activity. It aims to lower the risk of disease and improve health through exercise and behavioural education as accompanied with a comprehensive focus on specific components of diet.

What does the program involve?

The program will be conducted by experienced health professionals. It starts with a comprehensive consultation tailored to you. The program will teach you the lifestyle skills necessary to live with healthier lifestyle habits in a manageable and achievable manner with the greater aim of losing weight and keeping it off.

You will learn about:

- The risks associated with being overweight and the benefits of a healthy lifestyle
- The goals of the program and personal goals to track your progress
- Healthier eating with a specific diet
- Physical activity with a personalised exercise program
- Overcoming the barriers to change and staying on track

We hope that you enjoy the program, appreciate any feedback and would remind you that our professional team is an important and open source of support throughout the process of change ahead. We wish you the best of luck. All sessions are delivered by an exercise physiologist/dietitian.

Program Overview

Baseline Individual Consultation	• Your cardiovascular risk • Identifying your current behaviours and beliefs - Current physical activity - Dietary Assessment • Identifying realistic weight loss targets • Developing a personal action plan - Commence very low energy diet - Exercise prescription • Goal setting and identifying potential barriers
One month **Session One (Understanding self & committing to change, Get moving)**	• Identify overweight/obesity and disease relationships • Reducing the risk of cardiovascular disease • Reviewing the program goals and individual goals • Tracking your progress • Assess commitment and motivation to change • Challenging overweight myths • Physical Activity - Unstructured physical activity - Demonstration of unstructured physical activity - Aerobic activity and strength training - Intensity of aerobic activity - Demonstration of strength training • Stepping it up- progressive overload • Building exercise into our day • Review of personal programs
2 month **Session Two (Food for Thought)**	• Reviewing the program goals in light of personal goals • Tracking your progress • Introduction of the maintenance diet and portions • The importance of low fat and nutritionally balanced diet in losing weight • "Supermarket" tour: - The influence of dietary fat on obesity - Carbohydrates and fibre - The impact of alcohol on weight management - Defining GI - swapping foods • Reading Labels • Practical GI decisions • Eating out/social eating- tips and aversions • The role of snacking • Evaluating health claims

	• Review of strength training - Assessing exercise intensity
3 month **Progress Phone call & Session Three (The psyche of weight loss, Staying on Track)**	• Tracking your progress - Reaffirm positive outcomes • Re-visit the maintenance diet • Food and emotions • Distinguishing psychological hunger • Body image and self esteem • Stress and overeating • Negative self talk - Demonstration of positive self talk • Passive vs aggressive vs assertive • Self nurturing
5 month **Progress Phone call & Session Four (Look how far you have come and preventing relapse)**	• Modifying Goals - Why does weight loss stop? • Preventing relapse • Evaluate lifestyle and maintaining lifestyle changes • Review changes in body weight and body shape Physical Activity Review
7 month **Session Five (The Ideal you review and maintaining weight loss)**	· Review diet and exercise prescription considering weight loss · Review personal goals · Review program goals and discuss compliance and % achieved · Q & A regarding health · Back up plans and behaviour lapses · Maintaining motivation
9 month **Session Three (The psyche of weight loss, Staying on Track)**	· Review diet and exercise prescription considering weight loss · Review personal goals · Review program goals and discuss compliance and % achieved · Q & A regarding health · Back up plans and behaviour lapses · Maintaining motivation
12 month **& Session Three (The psyche of weight loss, Staying on Track)**	· Review diet and exercise prescription considering weight loss · Review personal goals · Review program goals and discuss compliance and % achieved · Q & A regarding health · Back up plans and behaviour lapses · Maintaining motivation · Self maintenance plan and exit interview

Appendix I: Bioimpedance spectroscopy (Impedimed SFB7™, Impedimed Ltd., Pinkenba, Queensland, Australia)

This single channel tetra polar bioimpedance spectroscopy device scans 256 frequencies between 4 kHz and 1024 kHz to estimate body composition. The device uses Cole modelling with Hanai mixture theory to determine the four compartment model and therefore no population specific prediction algorithms are required (BioImp™, version 5.4.0.3, California, USA).

Participants lie in a flat supine position with their arms by their sides, separated from their body, with palms down, and legs separated to minimise skin-to-skin contact. They lie for five minutes for even fluid distribution and the four electrode sites are cleaned with an alcohol swab before attachment and participants shaved where appropriate to reduce artefact. Two upper limb Impedimed™ dual tab electrodes are placed on the right wrist, over the midline between prominent ends of radius and ulna of wrist and the second five centimetres away over the midline of third metacarpal-phalangeal joint on dorsal hand surface. Two lower limb Impedimed™ dual tab electrodes are placed over the midline between the medial and lateral malleolus of ankle and the second 5 cm away over the midline of the third metatarsal-phalangeal joint on anterior surface of foot according to the manufacturer's standard operating procedures. Individual characteristics of height, weight and age must be entered into the device (as measured on the same morning) and the measurement takes two to three seconds.

WOOLCOCK
LEADERS IN BREATHING & SLEEP RESEARCH

TITLE OF PROJECT: Cardio-metabolic health effects of CPAP treatment for sleep apnoea during weight loss: A Randomised Controlled Pilot Trial

INFORMATION FOR PARTICIPANTS

Introduction

You are invited to take part in a research study which will investigate the health effects of using CPAP (Continuous Positive Airway Pressure) to treat your sleep apnoea in conjunction with a weight loss programme. The study is suitable for people with pre-diabetes, obstructive sleep apnoea and obesity. The study will look at changes in your glucose tolerance (which is a marker of diabetic risk related to blood glucose control) as well as assessing other measures of your health over a 12 month period.

If you choose to enrol in the study you will firstly be randomly allocated to one of two groups. The first group will receive CPAP plus a Very Low Energy Diet (VLED) for three months. Participants assigned to this group will then be offered sleep apnoea support and weight maintenance support for nine months.

Participants assigned to the second group will receive a VLED alone for three months. They will then be offered a three-month trial of CPAP. They will also be offered sleep apnoea support and weight maintenance support for nine months.

The study is being conducted within this institution by the following researchers:

Chief Investigators:	A/Prof Craig Phillips	
Associate Investigators:	Prof Ronald Grunstein, Dr Camilla Hoyos, Prof Stephen Twigg, A/Prof Brendon Yee, A/Prof Keith Wong, A/Prof Tania Markovic, A/Prof Nathaniel Marshall, A/Prof Amanda Salis, Dr Dev Banerjee, Dr Elizabeth Cayanan, Dr Nicholas Fuller, Dr Peter Buchanan	
Study Coordinator:	Dr Elizabeth Cayanan	(ph 9114 0411)
	Ms Freya Grove	(ph 9114 0236)

What is Obstructive Sleep Apnoea?

Obstructive sleep apnoea (OSA) is a common condition. It is characterised by repetitive apnoeas (breathing pauses) and hypopneas (shallow breathing) during sleep. Symptoms include loud snoring and inappropriate day time sleepiness. OSA is typically caused by a blockage of the upper airway, usually when the soft tissue in the rear of the throat collapses during sleep. At least 20% of adults are thought to suffer from mild forms of this condition. OSA is associated with an abnormally high frequency of cardiovascular and metabolic disease (hypertension, stroke, coronary heart disease, diabetes) and excessive daytime sleepiness (responsible for an increased frequency of work and road accidents). Whilst treating OSA has been shown to reduce daytime sleepiness and memory problems as well as reduce blood pressure, the effect on other measures of cardiovascular and

metabolic health as well as life expectancy remains uncertain. The study aims to address some of these uncertainties.

What is the treatment for Obstructive Sleep Apnoea?

The standard treatment for OSA is continuous positive airway pressure (CPAP). CPAP machines work by applying a pressure of air through a nose mask to your airway during sleep. This pressure keeps your airway open and prevents it from collapsing which improves the quality of sleep.

What is the purpose of this study?

In this study, we will test:

- Whether the use of CPAP in conjunction with a weight loss programme achieves better glucose tolerance, abdominal fat loss and cardio-metabolic health at three months compared to weight maintenance alone. All patients will be invited to attend a follow up visit at 12 months with reassessment of outcomes, after following a low glycaemic index (GI)/high protein diet and exercise programme for nine months.

What is involved in the study?

This study will last for twelve months. During the first three months, you will be asked to visit the clinic for an initial short screening that may include an overnight sleep study followed by two half day visits, two short clinic visits, one full day visit including one overnight sleep study and participate in two phone or video conference consultations.

Following the initial three months, your OSA severity will be re-assessed during the abovementioned overnight sleep study. Any patients with persistent OSA following weight loss will commence or continue with CPAP treatment if recommended by their treating sleep physician.

Should you be using CPAP during the study, you will be offered clinic or phone call consultations with the CPAP therapist, according to your needs and standard clinical care. These consultations may be in addition to the scheduled study visits.

Following the initial three months, you will be offered weight maintenance support, consisting of three consultations conducted face-to-face in clinic or by phone or video conference. The frequency and method of attendance at these consultations is at your discretion.

You will be invited to attend a final assessment at twelve months that involves a full day visit and an overnight sleep study if clinically indicated.
A schedule of these visits can be found at the end of this document along with more detailed descriptions of the procedures being undertaken. Involvement in this study may take more time and more tests than your usual clinic visits would, some of which may have no direct benefit to you. **Scheduling of the visits will be as convenient for you as possible.** The overnight stays will be at the Woolcock Institute Sleep Unit in Glebe where you will be provided with your own room and bathroom facilities.

Very Low Energy Diet and Weight Maintenance Diet
The first two months of the trial requires you to follow a VLED which is primarily composed of nutritionally complete liquid shakes, soups or bars. We ask that you try to maintain compliance during this short, intense phase in order to achieve maximal weight loss as is healthy for you. You

will be encouraged to exercise throughout this phase. You will undergo a dietary and lifestyle assessment prior to starting the diet and will be supervised and supported throughout.

During a one month transition phase you will begin to eat normal food with the shakes, and then stop the shakes and start on a *Low Glycaemic Index (GI)/high protein diet.* The goal of this diet is to maintain a minimum of 5-10% weight loss over a 10 month period with sustainable changes in eating patterns. You will learn about low GI foods and be taught how to select these types of foods. You will receive an eating plan providing 45% of energy from carbohydrates (with emphasis on low GI sources), 30% from fat and 25% from protein. The diet will emphasise lean sources of protein and restriction of saturated and trans fats (but not total fat). You will be provided information throughout the entire diet to ensure energy and overall nutrient balance.

The weight loss programme involves free health coaching and weight management delivered by a multidisciplinary team that includes an accredited exercise physiologist and dietitian /nutritionist.

The CPAP Device
Should you be randomly allocated into the group using CPAP plus a VLED, you will receive an auto-titrating CPAP machine free for three months, after which time you may choose to continue using CPAP at your own expense. This machine automatically adjusts to the pressure you require. You will be supported by a team of sleep clinicians and CPAP therapists who will help manage your OSA and CPAP therapy according to standard clinical practice for 12 months.

Should you be randomly allocated into the group using a VLED alone, you will not receive CPAP for the initial three months. However, you will then be offered a free three month trial of CPAP, after which time you may choose to continue using CPAP at your own expense. You will be supported by a team of sleep clinicians and CPAP therapists who will manage your OSA and CPAP therapy according to standard clinical care for nine months.

Study Procedures

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. You will be asked to undergo the following testing procedures at the baseline visit, three month visit and 12 month visit. Intervals are shown in the study schedule later in this document:

- *Blood Tests:* Fasting blood samples (30 ml per sample) will be collected to measure your metabolic health. This will be taken from a vein in your arm and the whole process takes 10 minutes.
- *Body measurements/Anthropometry:* Measurements will be taken of your height, weight and circumferences of your neck, waist and hips. This will take 10-15 minutes.
- *Bioimpedance spectroscopy analysis***:** This is a simple test to measure body fluid and body fat percentage. It is a non-invasive test using a very small current through your body which is not painful and takes about 2 minutes. You lie down during the test and 4 electrodes are attached to the wrist and ankle while lying down.
- *Resting blood pressure and pulse:* will be measured 2-3 times at each visit using an electronic device as you would have encountered at the doctor's surgery.
- *Insulin Sensitivity test (MINMOD test, incorporating an oral glucose tolerance test (OGTT)).* A cannula will be inserted into a vein in your arm and you will consume a drink which is high in glucose. Approximately 10ml of blood will be taken from the cannula 9 times over 3 hours.
- *Dual x-ray absorptiometry (DXA) scan* will be performed to measure the fat content in your body. You will be asked to lie on a bed for approximately 15-20 minutes.

- *Questionnaires:* You will be asked to complete a set of questionnaires which will seek information on your general health and psychological wellbeing, your sleep, self-efficacy and the way you see yourself, your diet and exercise habits. They will take approximately 30 minutes to complete.
- *Diaries:* We will also ask you to provide information on your dietary intake and physical activity via 4 day food and exercise diaries at 0, 5 and 12 months and a 24 hour food recall during a phone call at 1, 2, 3, 7 and 9 months. You will also be asked to wear a physical wrist activity monitor for a week prior to each consultation with the exercise physiologist/dietician.
- *Overnight sleep study/Polysomnography:* You may have had one of these sleep studies when you were originally diagnosed with sleep apnoea. It involves an overnight stay in the Woolcock Clinic in a private bedroom whilst we monitor your sleep to measure the severity of your sleep apnoea. This sleep study involves a set of electrodes being attached temporarily to your head and chest region, a process which is painless. Sleep technicians will monitor you throughout the night. (This study will be a part of the screening process and will be repeated at the three month visit and 12 month visit if clinically indicated; there is no baseline sleep study).
- *24 hour continuous blood pressure monitoring:* This involves measurement of your blood pressure over a 24-hour period using a portable blood pressure monitoring device, which automatically measures blood pressure, central blood pressure and arterial stiffness at half-hourly intervals across 24 hours. The blood pressure cuff is similar to what you may have seen in a doctor's office and is attached to a small monitor that is worn and secured by a belt.
- *Optional: 24 hour continuous blood glucose monitoring*: A small sensor device that is widely used to monitor blood glucose levels in people with diabetes will be worn will be worn. It is inserted comfortably under the skin, normally on the stomach, using a special insertion device secured with tape or a bandage, by one of the research team, and you will be instructed on how to use it. It is removed by gently pulling the sensor from the body. The transmitter and sensor are worn continuously both day and night, and can be worn when washing and swimming for up to 30 minutes and with regular exercising, however should not be worn during hot baths or in saunas. The monitor device is not waterproof and must be removed before any water activities. The device should not be worn during any X-rays, CT or MRIs, and the transmitter should be turned off during air travel (although the sensor can remain in place).

In addition, the researchers may ask your doctor's permission to have access to your medical records to obtain information relevant to this study where not already available.

Risks

All medical procedures - whether for diagnosis or treatment, routine or experimental – involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown and unforeseeable. In spite of all precautions, you might develop medical complications from participating in this study.

Should you be randomised into the group receiving weight loss support alone for three months, you will not receive any mechanical treatment (CPAP or any other device) for your sleep apnoea for the first three months you are enrolled in the study. If you are in this group, there is a risk that you may develop sleepiness. We will ask you about your sleepiness whenever we contact you or see you at face-to-face meetings. Apart from these times, we recommend that if you develop sleepiness at any time, that you notify the study staff as soon as possible and that you avoid driving. If you develop sleepiness, we will

arrange for this to be investigated by one of our study doctors before deciding on the best way to manage it.

The risks of participating in this study include some discomfort from blood sampling at the site from which the blood is taken. There is also a risk of some minor bruising at the site, which may last one to two days.

The total amount of blood taken for the entire study is 360ml, which is less than the amount taken in a standard blood donation. We advise that you refrain from donating whole blood for at least 12 weeks before and after completing a glucose tolerance test within the study.

There is little discomfort and no risk with 24 hour blood pressure monitoring. There may be some inconvenience related to wearing the monitor and the low noise the monitor makes during the half hourly measurements.

Exposure to radiation: This research study involves exposure to a very small amount of radiation. Exposure is measured in units called millisieverts (mSv). As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 to 3 millisieverts (mSv) each year. The dose from routine diagnostic X-ray and nuclear medicine procedures is 2 mSv to 20 mSv. The effective radiation dose from this study is about 0.54 mSv. At this dose level, no harmful effects of radiation have been demonstrated and the risk is very low.

Please inform us if you have participated in any other research studies using radiation in the last five years. Please keep this information in a safe place for the next five years in case you volunteer for any more studies using radiation, when you should show it to the Investigator.

The procedure itself is safe but you may get feelings of claustrophobia for a short time.

Sometimes when you first start a very low energy diet you may feel the cold more, feel tired and irritable, feel nausea, feel dizzy and have a slight headache but these symptoms should soon pass as your body gets used to the VLED. Let the study staff or doctor know if you have any side effects that persist. These diets are nutritionally complete and you will be monitored for any side effects. 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.

We suggest that you avoid alcohol and drugs of dependence during participation in the study. If you are dependent on drugs or alcohol, please be aware that you will not have access to these during your overnight stay and the lifestyle coaching will encourage you to reduce overall consumption.

Women previously infertile may become fertile while on a weight loss programme and should take appropriate birth control precautions. If at any time you think you may have become pregnant, it is important to let the researchers know immediately as a VLED will not meet the increased nutrient requirements for pregnancy.

There may be some inconvenience related to the frequency of clinic consultations however this is no more intensive than standard effective weight loss therapy sessions. Where possible, visit scheduling will be as flexible as possible. In addition to the risks or discomforts listed here, there may be other known and unknown risks that are not disclosed here; talk to your study doctor if you would like more information.

Benefits

If you adhere to the diet and exercise programme that is set for you, you will lose weight, improve your health, lifestyle and possibly your sleep apnoea. This study has been designed to enable you to lose weight and keep it off for a long period of time through lifestyle changes if adhered to as recommended. As well as this, our research study will further medical knowledge and may improve treatment of obstructive sleep apnoea in the future, even if it is not of direct benefit to you. You will also be provided with medical care as a participant in the trial. Should you be randomised into the group using CPAP in addition to weight maintenance, you will also receive CPAP.

Compensation for injuries or complications

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In addition, you may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You do not give up any legal rights to compensation by participating in this study.

Costs

Participation in this study will not be paid however you may be reimbursed for your travel expenses for study visits to be determined after discussion with the study team. You will be provided with free VLED shakes, soups and bars as part of the study. If you are randomly allocated to CPAP plus VLED, you will be provided a CPAP machine for the initial three months. After this time you may wish to continue to use CPAP at your own expense. If you are allocated to the VLED only group, you will be offered a CPAP machine trial for three months after the initial three months. After this time you may wish to continue to use CPAP at your own expense.

What will happen to my research samples?

Samples will be stored in -80C freezers at the Woolcock Institute until analysis. Only the investigator team will have access to these samples. Samples will be analysed at the Royal Prince Alfred Hospital and then they will be destroyed. All samples from patients who withdraw from the study will be destroyed.

Voluntary Participation

Participation in this study is entirely voluntary. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with the staff who are caring for you. If you decide to terminate your participation in this study, you should notify on the study coordinator on (02)9114 0411 or at Elizabeth.cayanan@sydney.edu.au .

Confidentiality

All the information collected from you for the study will be treated confidentially, and only the study investigators will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

What will happen to my research data?

All data will be stored securely for at least 15 years.

Further Information

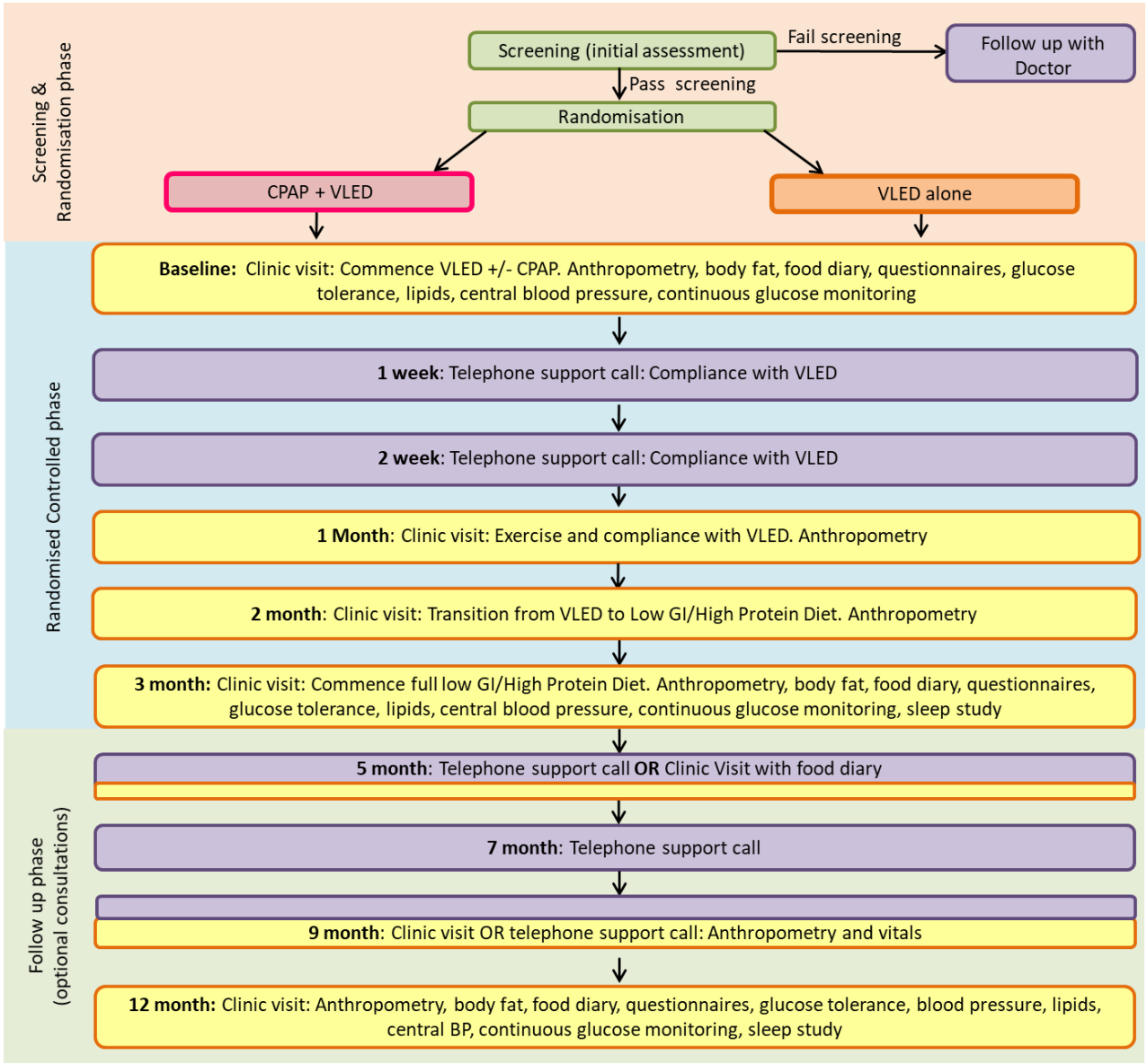
When you have read this information, *the study coordinator* will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact them on *[02] 9114 0411.*

Ethics Approval and Complaints

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X17-0039.

The conduct of this study at The Woolcock Institute has been authorised by the governance committee, any person with concerns or complaints about the conduct of this study may also contact the Research Governance Officer, Joanne Elliot on (02) 9114 0412, email: jelliot@woolcock.org.au and quote project number X17-0039.

This information sheet is for you to keep.


Screening & Randomisation phase
Screening (initial assessment)
Fail screening
Follow up with Doctor
Pass screening
Randomisation
CPAP + VLED
VLED alone
Randomised Controlled phase
Baseline: Clinic visit: Commence VLED +/- CPAP. Anthropometry, body fat, food diary, questionnaires, glucose tolerance, lipids, central blood pressure, continuous glucose monitoring
1 week: Telephone support call: Compliance with VLED
2 week: Telephone support call: Compliance with VLED
1 Month: Clinic visit: Exercise and compliance with VLED. Anthropometry
2 month: Clinic visit: Transition from VLED to Low GI/High Protein Diet. Anthropometry
3 month: Clinic visit: Commence full low GI/High Protein Diet. Anthropometry, body fat, food diary, questionnaires, glucose tolerance, lipids, central blood pressure, continuous glucose monitoring, sleep study
Follow up phase (optional consultations)
5 month: Telephone support call OR Clinic Visit with food diary
7 month: Telephone support call
9 month: Clinic visit OR telephone support call: Anthropometry and vitals
12 month: Clinic visit: Anthropometry, body fat, food diary, questionnaires, glucose tolerance, blood pressure, lipids, central BP, continuous glucose monitoring, sleep study

Time Frame for Study Visits	Visit number	2	3	4	5	6	7	8	9	10	11
	Month	0	1W	2W	1M	2M	3M	5M	7M	9M	1Y
Study Phase	**Screen**	**Randomised Controlled**					**Follow up (optional consultations)**				
Lifestyle Modification Phase		Very Low Energy Diet (VLED)				Trans-ition	Low GI/High Protein Diet				
CPAP Phase		Randomised to CPAP or No CPAP					Usual Care for CPAP				
Eligibility & Informed Consent	X										
Randomisation to CPAP		X									
Reassessment of OSA and transfer into follow up phase with optional support							X				
Glucose Tolerance (OGTT, MINMOD)		X					X				X**
Total Body Fat & Lean Mass (DXA) & Bioimpedence		X					X				X
Anthropometry, Vitals		X			X	X	X				X
Blood Markers (Lipids, HbA1c, IGF1, IGFBP1)		X					X				X
24 Hour Testing (Continuous Central Blood Pressure & Optional Continuous Glucose Monitoring)		X					X				X
4-day Food Diary		X						X			X
24-hr Food Recall					X	X	X		X	X	
Questionnaires		X					X				X
Sleep Study	X						X				X*
Lifestyle Consultation		X			X	X	X		X		X
Lifestyle Support Call			X	X				X		X	

***** PSG if clinically indicated by symptoms of obstructive sleep apnoea

** If clinically indicated by elevated fasting blood glucose result

WOOLCOCK
LEADERS IN BREATHING & SLEEP RESEARCH

RESEARCH STUDY

Cardio-metabolic effects of CPAP treatment for sleep apnoea during weight loss: A Randomised Controlled Pilot Trial

PARTICIPANT CONSENT FORM

I, ... *[name]*

of .....*[address]*

have read and understood the Information for Participants on the above named research study and have discussed the study with

..... *[name of individual obtaining informed consent]*

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or potential side effect and of their implications as far as they are currently known by the researchers.

I understand that my participation in this study will allow the researchers to have access to my medical record, and I agree to this.

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

_____ _____

_____ _____

_____ _____

Name of participant _____ Signature _____ Date _____

Name of witness _____ Signature _____ Date _____

Name of individual _____ Signature _____ Date _____
Obtaining informed consent

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH ETHICS AND GOVERNANCE OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
EMAIL: SLHD-RPAEthics@health.nsw.gov.au
REFERENCE: X17-0039 & HREC/17/RPAH/48
9.11/SEP18

Health
Sydney
Local Health District

19 September 2018

A/Prof Craig Phillips
Research Fellow
Woolcock Institute of Medical Research
431 Glebe Point Rd
GLEBE NSW 2037

Dear Professor Phillips,

Re: Protocol No X17-0039 & HREC/17/RPAH/48 – "Cardio-metabolic health effects of CPAP treatment for sleep apnoea during weight loss: A Randomised Controlled Pilot Trial"

The Executive of the Ethics Review Committee, at its meeting of 19 September 2018 considered your correspondence of 27 August 2018 and gave its approval of the following:

- Study Protocol (Master Version 5, 27 August 2018)
- Participant Information Sheet (Master Version 5, 27 August 2018)
- Participant Consent form (Master Version 3, 27 August 2018)
- Study Advertisement 1 (Master Version 2, 27 August 2018)
- Study Advertisement 2 (Master Version 3, 27 August 2018)
- Study Doctor Quick Info Sheet 1 (Master Version 1, 27 August 2018)
- Study Doctor Quick Info Sheet 2 (Master Version 2, 27 August 2018)
- Study Doctor Quick Info Sheet 3 (Master Version 3, 27 August 2018)
- Study Doctor Informative Criteria (Master Version 1, 27th August 2018)

- Wording for Woolcock Website and other media (Master Version 1, September 2018)
- Screening Questionnaires (undated)

Yours sincerely,

Sanaa Thomas
Executive Officer, Clinical Trials Sub-committee (RPAH Zone)

for:

Merela Ghazal
Acting Executive Officer
Ethics Review Committee (RPAH Zone)

HERC\EXECOR\18-09