ORIGINAL RESEARCH

The Sleeping Well Trial: Increasing the effectiveness of treatment with continuous positive airway pressure (CPAP) using a weight management program in overweight adults with obstructive sleep apnoea: A stepped wedge randomised trial protocol

Running head: The sleep well trial Protocol

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Abstract

Background: The majority of adults diagnosed with obstructive sleep apnoea (OSA) are overweight or obese. Continuous positive airway pressure (CPAP) is the most common effective therapy for OSA. However, adherence declines over time with only 50% of patients prescribed CPAP continuing to use it long term. Furthermore, a recent prospective analysis indicated that those more adherent with CPAP therapy have enhanced weight gain trajectories which in turn may negatively impact their OSA.

Aim: The Sleeping Well Trial aims to establish whether the timing of starting a lifestyle weight loss intervention impacts on weight trajectory in those with moderate-severe OSA treated at home with CPAP, whilst testing the potential for smart phone technology to improve adherence with lifestyle interventions.

Methods: A stepped wedge design with randomisation of individuals from 1-6 months post-enrolment, with 5 months of additional prospective follow-up after completion of the stepped wedge. This design will investigate the effect of the 6 month lifestyle intervention on people undergoing CPAP on body weight, body composition and health-related quality of life.

Discussion: This trial tests whether the timing of supporting the patient through a weight loss intervention is important in obtaining the maximum benefit of a lifestyle change and CPAP usage, and identify how best to support patients through this critical period.

Trial Registration: The protocol (v1) is registered prospectively with the International Clinical Trials Registry (CTR) ACTRN12616000203459 (public access). Any amendments to protocol will be documented via the CTR. Recruitment commenced March 2016 with data collection scheduled to finish May 2018.

Key words: modified fasting, obesity, obstructive sleep apnoea, weight management.

Introduction

Obesity and sleep disordered breathing are highly correlated.¹ The increased prevalence of obesity and, subsequently, obstructive sleep apnoea (OSA) has led to increased demand for treatment of this sleep disorder. Currently, moderate–severe OSA is estimated to affect 10% of men and 3% of women aged 30-49 years which increases to 17% of men and 9% of women aged 50-70 years.² Although not all with OSA are overweight, a significant proportion are (70%) and severe OSA is an independent risk factor for cardiovascular disease, insulin resistance, Type 2 diabetes and stroke.¹ Many patients who lose weight experience an improvement in their OSA.³ However, the situation is not simple and the relationship is not unidirectional. A systematic review to explore the relationships between

OSA and body weight concluded that there was strong evidence that obesity contributes to the pathogenesis of OSA.⁴ However, the review also reported that the presence of OSA can reinforce the obese state via alterations to energy metabolism, appetite and satiety (via neural control feedback mechanisms), thereby making it harder for those with OSA to manage their weight and maintain weight loss.

Continuous positive airway pressure (CPAP) is accepted as 'best practice' treatment for moderate–severe OSA. In a report prepared for the Australasian Sleep Association,⁵ CPAP treatment was found to be both clinically and cost effective, with an incremental cost effectiveness ratio of \$5K per quality adjusted life year. However, the report also highlighted that patient adherence with CPAP therapy is suboptimal with less than 50% using this therapy long term. Adherence with treatment appears to decline quickly despite reduction in daytime sleepiness.⁶ On-going support and the patient's initial experiences with CPAP have been shown to be predictors of success.⁷

Importantly, CPAP may have a negative impact on a subject's weight. A meta-analysis involving 25 randomised trials on patients with OSA found that commencing CPAP treatment resulted in a significant increase in weight and BMI.⁸ Despite this, patients on CPAP do have the ability to lose weight, further leading to an improvement in cardiovascular risk profile. Chirinos *et al.*⁹ reported that weight loss plus CPAP was more effective than CPAP alone at improving insulin sensitivity, blood pressure and serum triglycerides. In this study, there was an impressive 11kg difference in weight between groups, with those

randomised to receiving support to lose weight achieving sufficient weight loss to be clinically important in reducing their cardiovascular risk (5-10% body weight).

A comprehensive review of the literature concluded that weight loss via diet and/or exercise interventions are effective in the treatment of OSA.³ In the included meta-analysis, a mean weight loss of 13.76kg (95%CI 8.32, 19.21) and a mean reduction in Apnoea Hypopnea Index (AHI) of 16.09 (95%CI 6.54, 25.64) was observed. What was also apparent from this meta-analysis and from other studies¹⁰ is that loss of body weight is important in enabling remission of sleep symptoms (daytime sleepiness, morning headaches) independent of any improvement in OSA severity and that diet approaches are the most effective. Most of these studies had follow up periods extending out to 1 or 2 years. To date, only one study has had a long term (60 month) follow-up.⁷ This study was observational and designed to determine if weight loss from a 1 year randomised controlled trial could be maintained and prevent progression of OSA over the long term. The authors reported an 80% improvement in the progression of OSA in those whom maintained weight loss. However, a key limitation of this work is that it only recruited those with mild OSA so it remains contentious if lifestyle interventions can objectively cure those with moderate or severe OSA.⁷ Recently, fasting regimes which reduce energy intake on specific days per week and without restriction on remaining days have gained popularity, are simple to follow and have proven just as effective for weight reduction, at least in the short term, than a consistent reduction in daily energy intake.¹¹ Previously we have reported success in younger adults, with a modified 5:2 fasting regimen which incorporates a 2 day 'fasting' per week and 5 days

of healthy eating, which will be used in this study.¹² Changes in diet (energy in) and activity (energy out) are the cornerstones of any lifestyle intervention¹³ but require sustained behaviour changes to counteract the physiological compensatory processes which favour weight re-gain.¹⁴ Those newly diagnosed with OSA have to contend with the use of a CPAP machine, which requires shifts in behaviour both for the patient and potentially any bed-partner. Behaviour change theory clearly indicates that asking people to undertake multiple simultaneous changes is fraught with difficulty.¹⁵ We have highlighted the importance of actively addressing obesity alongside CPAP, but simultaneously commencing CPAP and making multiple complex changes to their diet and exercise regime concurrently (i.e. lose weight plus start CPAP) increases the risk of failure.¹⁶ Adherence to CPAP itself declines up to 83% over the first 3 months of treatment in some studies, indicating that more support is required on initiation to establish this new behaviour, particularly before moving forward with additional lifestyle changes.¹⁷ Therefore, current practice may present potential barriers for patients; multiple concurrent lifestyle changes are expected (CPAP initiation plus weight loss) but with little support. Strategies that separate the initiation of these two therapeutic interventions, such as in using step-wedged intervention designs, where commencement of the intervention of interest are staggered,¹⁸ enable each participant to be exposed to the interventions and does not require an untreated control group.

Providing long term support to patients is challenging in a health service model designed to prioritise acute care. Following initial education, patients may be left to implement changes on their own. Motivation, improving self-efficacy and social support are

key adjuncts to successful long-term behaviour change and any intervention that can incorporate behaviour modification in addition to pure 'education' is likely to have a longer term impact.¹³

Accessibility to lifestyle interventions has moved into a new age with the wide spread uptake of smart phone technology. New technology and smart phones in particular can be used to remind and enable self-monitoring of progress, from which participants gain motivation.¹⁹ Sleeping Well uses an application called MyPace™ – designed by psychologists grounded in behaviour change theory and tested in the context of weight loss. This app provides tailored motivational text messages, reminder messages to prompt desired behaviours, a weight tracker to show progress towards agreed goals and additional support to the user as they can message their dietitian in between face-to-face appointments.²⁰ Research on the integration of technology into healthcare suggests that the right application may be positively accepted by both consumers and practitioners.²¹ Further, healthcare systems in Europe, Australia and the United States are currently actively encouraging and investing in technological innovations to support available routine care.²² Time spent in face-to-face contact between individual patients and a health care professional represents a significant use of resources. Any additional contact time needs to have demonstrable benefits and outcomes.

Thus, the aims of the trial are as follows;

Primary aim 1) Investigate the effectiveness of a 6 month lifestyle intervention for reducing body weight in overweight subjects with moderate-severe OSA commencing CPAP;

Primary aim 2) Determine whether timing of commencement of a lifestyle intervention affects the change in weight and trajectory of weight experienced 12 months following CPAP commencement;

Secondary aim 1) Examine whether people who commence CPAP gain body weight;

Secondary aim 2) Examine the potential for smart phone technology to improve adherence with interventions, both lifestyle (diet and physical activity) and with self-administered CPAP and extend the reach and impact of face-to-face advice which is the traditional model of care in hospitals.

METHODS

Trial design and participants: We employ a stepped wedge design with randomisation of individuals with 5 months of additional follow-up following completion of the stepped wedge (7 months, Figure 1). The stepped wedge design¹⁸ will be used to investigate the effect of the lifestyle intervention on OSA patients receiving CPAP therapy on body weight, body composition and health-related quality of life. We chose not to use sham CPAP as a control as there are ethical issues in not providing CPAP treatment to this patient group. Crucially, this design enables us to test whether the timing of the intervention delivery impacts on both the absolute change and rate of change in weight by the 12 month post recruitment assessment.

Figure 1 Trial design using a 6 stepped wedge

Ethics approval has been granted from Monash Health and Monash University Human Research Ethics Committee (CF1) HREC/15/MonH/93 Ref 15357A. Dissemination will be via peer reviewed publications and international presentations. This manuscript was written in accordance with the SPIRIT and CONSORT guidelines.

Recruitment: The recruitment phase for this trial commenced in March 2016 and was completed in May 2017. Participants were recruited from two separate Academic sleep centres (Monash Health and Eastern Health) in Melbourne, Australia, which both follow best practice OSA treatment guidelines.²³ Eligible participants were identified and referred by their treating sleep physicians, or self-referred via approved advertising posters displayed in clinic.

Inclusion Criteria: Patients with moderate-severe OSA (defined by an apnoea hypopnoea index (AHI) ≥ 20 /hour determined from overnight polysomnography (PSG) according to standard AASM criteria)²⁴ and starting CPAP therapy were included. Additional inclusion criteria: patients between 19-68 years, self-reported sedentary lifestyle (as per trial registration, engaged in physical activity (PA) less than 2 days per week and a duration of less than 45 minutes per session).

Exclusion criteria: Those of Caucasian descent who have a BMI within the healthy range (BMI <24.9); of Indian and Chinese descent with a BMI <23 ; persons with a BMI >43 . Those with an urgent need for CPAP (e.g. commercial or drowsy drivers defined by Epworth Sleepiness Score >16),²⁵ those who were unable to provide informed consent in English,

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were already on a diet/exercise program or diagnosed with concomitant obesity hypoventilation syndrome were excluded after their PSG study. Additional exclusion criteria: pregnant women, an inability to exercise, receiving VPAP/BPAP, previous treatment for OSA, previous bariatric surgery or persons already on a diet, and those suffering from angina pectoris/atrial fibrillation.

Procedure: Patients identified by their treating sleep physician and meeting eligibility criteria provided verbal consent to be further contacted by the trial team by telephone. Self-referring participants were encouraged to phone or email researchers directly (eligibility subsequently confirmed by treating sleep physician). Individuals expressing interest in participating in the trial were then invited to attend a morning screening session after a fast of 10-12 hours the evening prior where inclusion/exclusion criteria were confirmed. Upon written consent, participants were enrolled into the trial, allocated to a treatment group and informed of their wait list period (CB, KD, LG). Group 1 began the lifestyle intervention 1 month after starting CPAP therapy; Group 2 after 2 months, Group 3 after 3 months and so forth, up to a maximum 6 month waiting period. Participants have been asked to continue with their normal lifestyle until their intervention period commences. Once the lifestyle intervention has commenced, it continues for 6 months. This design enables us to randomise each individual participant into groups and then enrol each group to the lifestyle intervention at different time points. Treatment allocation was stored in opaque envelopes and remained unknown until revealed to the researcher on the day each participant was allocated to a group. Randomisation took place using allocation concealment by the trial statistician (TH).

Masking participants to group allocation was not possible due to the necessity to participate in the diet intervention. Participants were asked not to reveal their group allocation to their treating CPAP technicians or sleep physician who were blinded to group allocation. Visits for data collection at the university used a staggered by appointment time, thus minimising any likelihood of participants meeting each other. Following randomisation (LG, CB, KD), participants' weight was assessed using a calibrated digital scale (Seca®, Hamburg, Germany). Subsequently, their blood pressure, height, waist and neck circumference was measured using standard laboratory operation procedures. A qualified phlebotomist then obtained a 17 ml blood sample from each participant. Blood samples were immediately spun via centrifuge and stored in Eppendorf tubes in a -80°C biohazard freezer in the research laboratory at Monash University. After blood collection, a light breakfast was provided to participants whilst they complete a series of validated questionnaires (see *Diet, eating behaviour, sleep, activity and psychosocial measures*). An appointment for the participant to visit the CPAP provider within 1 week of the screening session was organised by the researchers at the end of the session.

Patients underwent mask fitting and education regarding OSA and were provided with a CPAP machine by staff at Air Liquide Healthcare, and access these staff for ongoing support at no cost. Patients are initially commenced on Autotitrating CPAP using a Resmed S9 CPAP machine. After one week of treatment, patients are switched to fixed pressure CPAP based on the 95th centile pressure determined during the autotitration week. Routine equipment troubleshooting is provided by Air Liquide staff at the CPAP centres. The

participants' treating sleep physician coordinates all CPAP care and is responsible for any decisions regarding treatment changes. Participants are required to use their CPAP devices regularly for the 12 month period (beginning from consent date). Upon completion, participants will be encouraged to continue standard treatment in collaboration with their treating sleep physician.

Monitoring: After enrolling into the trial, all participants are contacted monthly to determine a time for a 10-minute visit at home or at clinic to be weighed. Participants are also asked to provide their CPAP device at the end of the 12 month period so data on usage can be extracted from its built-in memory. These data will provide objective measures of adherence with CPAP therapy and their weight trajectory over time. Any participant who withdraws from the trial will be encouraged to continue standard treatment with their initial referring sleep physician and their weight will be collected from their medical record.

Lifestyle Intervention: Participants are prescribed a modified fasting diet regime (5:2) with PA recommendations of 3 x 30 minutes per week of light/moderate PA (e.g. increase step count, begin resistance training, low-impact swimming etc.) for the initial 3 months, followed by a 3 month maintenance phase (Table 1). The dietary regimen consists of 5 days of restricted daily energy intake of 6300-7500 kilojoules (kJ) per day and 2 days of very low energy intake between 2200-2760 kJ per day. On very low energy intake days, participants are provided with low energy milk shakes, multivitamins with fish oil, fibre and iron (women only) supplements contained in labelled sachets. A single trial dietitian (KR) supports each subject by a face- to-face monthly visit (initial 60 minutes, follow-up 30 minutes) using

behaviour change and motivational interviewing techniques augmented in between appointments via communication via the MyPace™ app. The app enables out-of-clinic communication between the dietitian and the participant, including regular reminders, troubleshooting, motivational messages/encouragement and progress reports. The six face to face consultations with an Accredited Practicing Dietitian are designed to enable the participant to set their individual goals in relation to change in diet choices and activity, which develops the individuals' capability to manage their food and activity in the context of their own physical, social and psychological environment. These goals are then programmed into the app which generates automated but pre-determined motivational and supportive messages to the participant. Adherence can be assessed via monitoring the closed communication with the dietitian which occurs via the MyPace™ app. Participant satisfaction with the intervention is requested at the end of the trial and collected via an anonymous semi-structured questionnaire. Analysis of these questionnaires enables researchers to gain participant insight into aspects of the intervention content, delivery style and structure.

Table 1 The Sleeping Well Trial lifestyle intervention outline

Outcomes: The trial is powered on the primary outcome of weight change over time. Weight (kg) is measured using standard techniques at each centre on diagnosis, at the start of CPAP and then monthly at follow up visits at either the CPAP centres, routine hospital visits or

dietitian visits. Digital weighing scales (Seca®) are provided at each site or centre to ensure patients are weighed on the same device each month and all staff trained in the standard operating procedure, with routine calibration throughout the duration of the trial. Home visits are available for those who are unable to attend any other options. MyPace™ application adherence is monitored via in-app message usage. Participants are also asked to rate the MyPace App's usefulness in an end-of-trial feedback form.

Other outcome measures: CPAP adherence is measured by regular machine downloads to document hours and days used. In addition, residual AHI on treatment is continually measured via participants' CPAP device, with a final reading taken at 12 months at both the CPAP centre (by CPAP technicians) and main research facility at Monash University (by the study coordinator). Body composition is measured using the reference technique of GE Lunar iDXA (GE Medical, Software Lunar DPX enCORE 2012 version 14.0, Madison, WI). Waist and neck circumferences are measured at the same time points as weight verification and blood pressure monitored.

Blood samples are drawn at screening, baseline, at the end of the lifestyle intervention and at 12 months to measure cholesterol (HDL:LDL), triglycerides, glucose and insulin for monitoring of metabolic cardiovascular risk factors. To gain insight into the molecular mechanism underlying weight change in OSA patients undergoing CPAP, Peripheral Blood Mononuclear Cells (PBMCs) are isolated from a blood sample at the beginning and end of the weight loss phase to analyse transcriptome modulation in a sub-set (approx. 10) of

participants. The transcriptome analysis will involve RNA sequencing, cluster analysis and pathway enrichment to determine over-expressed pathways in this population.

Diet, eating behaviour, sleep, activity and psychosocial measures: The following validated questionnaires are completed at screening, baseline, at the end of the lifestyle intervention and at 12 months with data collected from the participant via an iPad® and directly uploaded to the trial database: Functional Outcomes of Sleep (FOSQ),²⁶ Epworth Sleepiness Scale (ESS),²⁵ eating behaviour (TFEQ-R18),²⁷ Health-Related Quality of Life (EQ-5D),²⁸ self-reported activity (IPAQ-SF),²⁹ general health status (SF-36),³⁰ and history of depression (BDI),³¹ and anxiety (HADS).³²

Diet is measured using a standardised 24 hour recall by the trial dietitian at the beginning of the intervention period and after 6 months. Nutrient analysis of macro and micro-nutrients will be performed using Foodworks® 7 (Xyris Software Pty Ltd., QLD, Australia) and performed in duplicate by two independent researchers. Adherence to the dietary plan is monitored by counting unused milkshake and supplement sachets provided over the dietary intervention period and monitoring of the App usage and in-built messaging is used as an indicator of adoption of behaviours and engagement with the support and goal setting provided via the App. Activity is recorded using FitBit® 'Flex' devices (FitBit®, San Francisco, CA) supplied to participants' at time of enrolment, these data being stored on participants' online accounts and accessible by researchers for the duration of the trial. Participants are requested not to change their account password from the one provided at time of set up for the duration of the trial.

Statistical analysis plan: Analyses will be undertaken using the 'intention-to-treat' approach, where all evaluable data is analysed in the treatment group according to which the participant was allocated. Statistical significance will be defined as $\alpha < 0.05$. All tests conducted will be two-tailed.

We will use multilevel, mixed effects, generalised linear models to investigate primary aims 1) and 2). We will address primary aim 1) from the short- to medium-term perspective using data only from the stepped wedge portion of our design (analysis 1), and from the medium to long term perspective using combined data from the stepped wedge portion of our design and the prospective follow-up (analysis 2). The dependent variable will be the rate of weight loss or gain relative to their previous assessment [(previous weight subtracted from present weight) divided by period of time between these assessments]. Participant number will be treated as a random effect within the model to account for the dependency of observations within each participant. A categorical fixed effect coding for month since trial commencement will be included to account for maturation effects as per guidelines for analysis of stepped wedge trials.^{33,34} We will address primary aim 2) using analysis 2, but with the addition of an intervention-by-month of commencement interaction effect. Month of commencement will be entered into the model as a categorical variable. Primary aim 2) will additionally be investigated using an ANCOVA-style linear regression analysis approach (analysis 3). Here, only the final baseline assessment of weight treated as a raw score will be used as the dependent variable. Month of commencement of the intervention will be used as a categorical independent variable. The first weight

measurement treated as a raw score will be used as a covariate. If this analysis reveals a linear, quadratic or other trend in the effect of month of commencement on the dependent variable, then an additional analysis will be undertaken (analysis 4) where the month of commencement independent variable is entered into the same model as a continuous variable with or without transformations as indicated. Average CPAP treatment adherence since the previous assessment will be used as a covariate in each of these analyses.

Secondary aim 1) will be assessed using only pre-intervention period data from the stepped wedge portion of this trial. These data will test secondary aim 1 using a pre-post intervention design which generates a quasi-experimental standard of evidence as potential maturation biases cannot be accounted for. Here, weight measurements taken at the baseline assessment (prior to CPAP commencement) will be compared to those taken after this following commencement of CPAP. This aim will be examined using a multi-level, mixed effects, generalised linear model (analysis 5). Trial participants will be treated as a random effect and the presence or absence of CPAP will be used as a fixed independent variable. The impact of CPAP will be further examined using a contamination-adjusted intention-to-treat analysis (analysis 6)³⁵ which will account for participants with poor CPAP adherence potentially contaminating the estimate of the impact of CPAP commencement on body weight. A further analysis will be conducted including a CPAP-by-time since CPAP commencement interaction effect into the same model as analysis 5 (analysis 7). This interaction effect will be examined for a linear, quadratic or other trend in the effect of month of commencement on the dependent variable. If a pattern is identified, an additional

analysis will be undertaken (analysis 8) where the month since commencement of CPAP independent variable is entered into the same model as analysis 5 but as a continuous variable with or without transformations as indicated.

The effect of average CPAP treatment adherence since the previous assessment will be used as a covariate multi-level, mixed effects, generalised linear model. The dependent variable will be the rate of weight loss or gain relative to their previous assessment.

Sample size calculation: The stepped wedge component of this design has six separate “steps”. By recruiting seven participants for each of the six starting time points of the lifestyle intervention, we have 90% power to detect a standardised effect size of 0.40 for the rate of change in body weight outcome for analysis 1. This assumes a conservative ICC of 0.10, a two-tailed $\alpha=0.05$, and treats each individual participant as its own cluster (as this is the unit of randomisation). Collecting 10 participants per group to maintain trial power will provide coverage within the trial for a potential drop-out/missing data rate of over 30%.

Trial management and dissemination: The trial will continue to be conducted according to research governance principles set out by MHREC whom maintain the right to audit the trial at any stage. Participant data are collected, entered and stored according to standard confidentiality procedures on a secure server with password-only access and in locked filing cabinets during and following the trial period. All data will be cross-checked by an independent researcher throughout the trial and may only be accessed by the research team. Trial progress will continue to be monitored via monthly collaborative group meetings

with the research team whom are ultimately responsible for any decisions regarding the fate of the trial. The trial findings will be presented at conferences and will be reported in peer-reviewed journals by the research team. Any dissemination of the research findings will be by group level data only to protect privacy and confidentiality rights.

Results

A total of 60 participants have been recruited into the trial (between 22 March 2016 and 11 May 2017). Recruitment was initially predicted to last 6 months, but took longer due to the BMI criteria excluding some potential participants (both higher and lower than inclusion criteria) and being confirmed as having 'mild' rather than 'moderate-severe' OSA after their overnight sleep study. Figure 2 details the recruitment process from both hospital sites. The majority of participants are male (n 44 (73%)), with a mean (SD) age of 49.35 years (± 10.74). The mean (SD) BMI is 34.26 (± 4.6) with a range of 25.7–43 and with moderately-severe OSA as defined by AHI (mean 46.85 (± 21.14)). Twelve (20%) participants reported being on antidepressants at the time of enrolment and 14 (23%) on medication for hypertension.

Discussion

As there is growing evidence that CPAP alone may at best support the obese state and at worse lead to increasing weight in a population vulnerable to weight gain, there is a strong rationale for adding a lifestyle based weight loss intervention to the treatment of all overweight or obese OSA patients prescribed CPAP at home. It is also important to

understand the impact of a lifestyle intervention on metabolic outcomes and psycho-social behaviours. This trial tests whether the timing of supporting the patient through a weight loss intervention is important in obtaining the maximum benefit of a lifestyle change and CPAP usage, and identify how best to support patients through this critical period.

It will extend our knowledge of the aetiology of weight trajectory in patients with moderate to severe OSA who are prescribed CPAP therapy, which is currently lacking. Importantly, the findings will extend our knowledge of treatment pathways that are applicable in practice settings, particularly whether the timing of weight management starts and how that impacts on outcomes. It also examines whether extending the impact and reach of lifestyle interventions with a comprehensive program, including the use of smart phone technology, improves adherence and therefore treatment effectiveness. Thus, the 'Sleeping Well' trial has the potential to encourage a movement towards more personalised interventions to achieve maximal benefit and engagement based on delivery timing and method of communication between dietitian and patient.

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Conflict of interest

All other authors declare no conflict of interest.

Authorship

HT conceived the trial and the dietary intervention, drafted the manuscript and takes responsibility for the trial fidelity. BE contributed to the research design and trial conception and contributed to drafting and review of manuscript. DD provided guidance to the sleep related aspects of trial design, oversaw recruitment of patients from sleep clinics at Eastern Health, contributed to drafting and review of the manuscript. AY provided input into the sleep-related aspects of trial design at Eastern Health, oversaw recruitment of patients from this site and reviewed the manuscript. LG assisted with recruitment of participants, data collection and management procedures and contributed to drafting and review of manuscript.

CB assisted with recruitment of participants, data collection and management procedures and contributed to drafting and review of manuscript. KR was responsible for delivering the lifestyle intervention, assisted in reviewing and editing of manuscript. MB contributed to the study design in relation to cardiometabolic markers and review of manuscript. CM provided

technical input in blood sample collection and analysis of gene expression. KD provided technical input into the trial and data collection and management procedures, assisted in reviewing and editing the manuscript. TH contributed to development of the research design, development of the random allocation approach, development of the statistical analysis plan, reviewing and editing of the manuscript, and contribution to the project management committee. GH provided clinical input and guidance to the sleep related aspects of trial design, oversaw recruitment of patients from sleep clinics at Monash Health, contributed to drafting and review of manuscript. All authors read and approved the final manuscript and declare that this work has not been published elsewhere. The authors would like to acknowledge the staff at AirLiquide centres in Dandenong, Richmond and Eltham for their assistance with the trial.

References

- 1 Gottlieb DJ, Yenokyan G, Newman AB *et al.* Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure. *Circulation* 2010; **122**: 352-60.
- 2 Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; **177**: 1006-14.
- 3 Mitchell LJ, Davidson ZE, Bonham M, O'Driscoll DM, Hamilton GS, Truby H. Weight loss from lifestyle interventions and severity of sleep apnoea: a systematic review and meta-analysis. *Sleep Med* 2014; **15**: 1173-83.
- 4 Ong CW, O'Driscoll DM, Truby H, Naughton MT, Hamilton GS. The reciprocal interaction between obesity and obstructive sleep apnoea. *Sleep Med Rev* 2013; **17**: 123-31.

- 5 Hamilton G, Antic N, Rajaratnam S. Australasian Sleep Association submission re. Adult Sleep Apnea Surgery. Australasian Sleep Association, 2013. (Available from: <https://www.sleep.org.au/documents/item/521>, accessed 21 June 2017).
- 6 Wolkove N, Baltzan M, Kamel H, Dabrusin R, Palayew M. Long-term compliance with continuous positive airway pressure in patients with obstructive sleep apnea. *Can Resp J* 2008; **15**: 365-9.
- 7 Tuomilehto H, Seppä J, Uusitupa M *et al*. The impact of weight reduction in the prevention of the progression of obstructive sleep apnea: an explanatory analysis of a 5-year observational follow-up trial. *Sleep Med* 2014; **15**: 329-35.
- 8 Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Benseñor IM, Lotufo PA. Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax* 2014; <http://dx.doi.org/10.1136/thoraxjnl-2014-205361>.
- 9 Chirinos JA, Gurubhagavatula I, Teff K *et al*. CPAP, weight loss, or both for obstructive sleep apnea. *New Engl J Med* 2014; **370**: 2265-75.
- 10 Dixon JB, Schachter LM, O'Brien PE *et al*. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *JAMA* 2012; **308**: 1142-9.
- 11 Tinsley GM, La Bounty PM. Effects of intermittent fasting on body composition and clinical health markers in humans. *Nutrition Rev* 2015; **73**: 661-74.
- 12 Mata F, Treadway M, Kwok A *et al*. Reduced Willingness to Expend Effort for Reward in Obesity: Link to Adherence to a 3-Month Weight Loss Intervention. *Obesity* 2017; **25**: 1676-81.
- 13 National Health and Medical Research Council (NHMRC). Clinical practice guidelines for the management of overweight obesity in adults, adolescents and children in Australia. National Health and Medical Research Council Melbourne, 2013. (Available from: www.nhmrc.gov.au/guidelines/publications/n57, accessed 21 June 2017).
14. Coutinho SR, Halset EH, Gåsbakk S *et al*. Compensatory mechanisms activated with intermittent energy restriction: A randomized control trial. *Clinical Nutrition* 2017; <https://doi.org/10.1016/j.clnu.2017.04.002>
- 15 Prochaska JO. Transtheoretical model of behavior change. In: Gellman M, Turner JR, editors. *Encyclopedia of behavioral medicine*. New York: Springer, 2013; 1997-2000.
- 16 Hood M M, Corsica J, Cvengros J, Wyatt J. Impact of a brief dietary self-monitoring intervention on weight change and adherence in patients with obstructive sleep apnea. *J Psychosom Res* 2013; **74**: 170-4.
- 17 Sin D D, Mayers I, Man G C, Pawluk L. Long-term compliance rates to continuous positive airway pressure in obstructive sleep apnea. *Chest* 2002; **121**: 430-5.

- 18 Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. *BMC Med Res Methodol* 2006; **6**: 54.
- 19 Webb TL, Joseph J, Yardley L, Michie S. Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. *J Med Internet Res* 2010; **12**: e4.
- 20 Barnett JC, Harricharan M, Fletcher D, Metzger N, Wills J. Tools for sustaining the support of health professionals: the example of MyPace. In: *Medicine 2.0: World Conference on Social Media, Mobile Apps, Internet/Web 2.0*. Toronto: JMIR Publications Inc., 2013.
- 21 Kelders SM, Van Gemert-Pijnen JE, Werkman A, Nijland N, Seydel ER. Effectiveness of a Web-based intervention aimed at healthy dietary and physical activity behavior: a randomized controlled trial about users and usage. *J Med Internet Res* 2011; **13**: e32.
- 22 Kennedy CM, Powell J, Payne TH, Ainsworth J, Boyd A, Buchan I. Active assistance technology for health-related behavior change: an interdisciplinary review. *J Med Internet Res* 2012; **14**: e80.
- 23 Australasian Sleep Association. Best Practice Guidelines for Provision of CPAP therapy. 2009.V2.2. (Available from: <https://www.sleep.org.au/professional-resources/sleep-documents/best-practice-guidelines-for-provision-of-cpap-therapy>, accessed 8 August 2017).
- 24 Berry RB, Brooks R, Gamaldo CE, Harding SM, Marcus C, Vaughn B. *The AASM manual for the scoring of sleep and associated events. Rules, Terminology and Technical Specifications*. Darien: American Academy of Sleep Medicine, 2012.
- 25 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; **14**: 540-5.
- 26 Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). *Arthritis Care Res* 2011; **63**: S287-S96.
- 27 De Lauzon B, Romon M, Deschamps V *et al*. The Three-Factor Eating Questionnaire-R18 is able to distinguish among different eating patterns in a general population. *J Nutr* 2004; **134**: 2372-80.
- 28 Rabin R, Charro Fd. EQ-SD: a measure of health status from the EuroQol Group. *Ann Med* 2001; **33**: 337-43.
- 29 IPAQ Research Committee. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)—short and long forms, 2005.

(Available from: https://sites.google.com/site/theipaq/questionnaire_links, 8 August 2017).

- 30 Ware JE SK, Kosinski M, Gandek B. *SF-36® Health Survey Manual and Interpretation Guide*. Boston: New England Medical Center, The Health Institute, 1993.
- 31 Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of Beck Depression Inventories-IA and -II in Psychiatric Outpatients. *J Pers Asses* 1996; **67**: 588.
- 32 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiat Scand* 1983; **67**: 361-70.
- 33 Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials* 2007; **28**: 182-91.
- 34 Hemming K, Haines T, Chilton P, Girling A, Lilford R. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ* 2015; **350**: h391.
- 35 Sussman JB, Hayward RA. An IV for the RCT: using instrumental variables to adjust for treatment contamination in randomised controlled trials. *BMJ* 2010; **340**: c2073.

Participant Information Sheet/Consent Form

Health/Social Science Research - Adult providing own consent

Be Active Sleep & Eat (BASE) facility in Notting Hill

Title *The Sleeping Well Trial: enhancing the effectiveness of continuous positive airway pressure (CPAP) treatment with a weight management program for overweight adults*

Short Title *The Sleeping Well Trial*

Protocol Number *HREC/15/MonH/93*

Principal Investigator *Professor Helen Truby*

Associate Investigator(s) *Assoc. Prof Garun Hamilton, Ms Ladan Ghazi, Dr Alan Young, Prof Matthew Naughton. Dr Bradley Edwards, Dr Denise O'Driscoll, Dr Maxine Bonham, Prof Terry Haines, Dr Simon Joosten, Ms Teanau Roebuck, Ms Kirsty Yull, Ms Kaitlin Day, Dr Chiara Murgia, Mrs Kerry Roem, Miss Kellie Hamill, Miss Claire Bristow (Study Coordinator).*

Location *Be Active Sleep & Eat (BASE) facility in Notting Hill (adjacent to Clayton campus) / Monash University*

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, which is called 'The Sleeping Well Trial: enhancing the effectiveness of continuous positive airway pressure (CPAP) treatment with a weight management program for overweight adults' (Trial ID: ACTRN12616000203459). You have been invited because you have obstructive sleep apnoea and are currently recommended to undergo continuous positive airway pressure (CPAP) therapy. Your contact details were obtained from your sleep physician at Monash Medical Centre, Box Hill hospital, or the Alfred hospital, after they have informed you about this study.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the processes involved with taking part. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local health worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to be involved in the research described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Obstructive sleep apnoea (OSA) is a condition in which the upper airway of patients closes off during sleep. This leads to low levels of oxygen and multiple awakenings during the night.

Being overweight and having OSA are related to each other. Although not everyone with OSA is overweight, about 70% of people are and because OSA itself is an independent risk factor for cardiovascular disease, insulin resistance, Type 2 diabetes and stroke, losing weight is an important part of managing OSA.

Previous studies have shown that changing your lifestyle by diet and activity are effective ways to lose weight. However, starting CPAP is also very important and trying to both lose weight and have time to adapt to using your CPAP machine at home is challenging. We know that changing one thing at a time is often more helpful in the long term for maintaining new behaviours.

In this study we are investigating how best to support patients through a process of adaption to using CPAP and losing weight. We are trying to establish if the timing of introducing a lifestyle intervention is important to the successful management of OSA over a 12 month period. Success on this study will help us to be able to deliver interventions that support people living at home with CPAP as we will know the best time to start each intervention.

This study involves researchers from Monash University and health service partners which includes your consultant. Some of the findings from this research will be used by Ms Ladan Ghazi for a higher degree (PhD).

3 What does participation in this research involve?

A summary table of your involvement in this 12 month study is provided on page 9. Once you have provided consent, you will be eligible to enrol into the study and undergo a screening visit. For the screening visit, you will need to fast overnight.

Screening Visit (total time ~60-90 minutes)

This will involve:

- Filling in your personal information in the provided participant's data collection sheet.
- Measuring your height, blood pressure, neck circumference, and weight (using a calibrated digital scale)
- A Blood test. You will be asked if you have fasted overnight (for 10-12 hours) before coming to the session. The phlebotomist will obtain a 17 ml sample of your blood, which lets us assess your total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, insulin, leptin and other metabolites. Also it will help us examine whether life style change affects how genes are expressed at different timepoints. This is *not a genetic test* and does *not* involve identification of a gene mutation that can be transmitted to offspring.
- You will be provided with a light breakfast (cereal, fruit, milk, coffee/ tea) after the blood test.
- Completion of some questionnaires about your health status, daytime sleepiness and its effect on your quality of life, eating behaviour, activity level, health-related quality of life, depression and anxiety status.

- Group allocation. You will be randomised into one of the 6 groups in this study. The group to which you are allocated, will determine the number of months (i.e. 1-6 Months) that you will wait before starting the lifestyle intervention program. The allocated waiting time is based on randomisation and cannot be changed but everyone will receive the intervention.
- Collecting a free Fitbit Flex wireless activity and sleep tracker wristband with instructions on how to use it. As part of your involvement in this study, you are expected to use your Fitbit tracker during 12 months of the study. You will need to sign a receipt after obtaining your Fitbit tracker. We will then create a personal online account for you in Fitbit website which saves your activity history. To update the information in the website, you need to sync your tracker with your smartphone or tablet device whenever connected to Wi-Fi. By signing the consent form, you are providing us with the permission to access this data from your personal account in Fitbit Website.
- Organising an appointment to visit a CPAP clinic within 2 working days, which will assist you with commencing your CPAP therapy.
- Receiving a document folder which you can take home at the end of the session. This folder contains a fact sheet about OSA, a list of general tips for sleeping well, a copy of your signed information sheet and consent form, a flow chart that helps you to easily understand your pathway during 12 months of this study.

CPAP therapy:

At the screening visit, if you are eligible for the study, the researcher will make a time for you to visit an 'Air Liquide' outlet to receive your CPAP machine. There, you receive your CPAP education and mask fitting. The staff at Air Liquide will provide support for your CPAP treatment, in conjunction with your treating doctor. For the first week the CPAP machine will adjust its pressure automatically. Based on these initial results, the pressure will then be set to a constant level for the remainder of the study. Adjustments to the CPAP pressure and/or mask will be at the direction of your sleep specialist in collaboration with Air Liquide. As part of your involvement in this study, you are expected to use CPAP regularly for a duration of 12 months. Overall, during 12 months of CPAP therapy, you will need to attend 5 face to face consultation sessions with Air Liquide (at time of set up, day 7, 1 month, 6 month, and 12 month), and 2 follow up calls (at 3 and 21 days following the time of set up) arranged by Air Liquide. During each consultation session, you will be asked to provide your CPAP machine and allow CPAP clinicians to extract its data. The extracted data will be uploaded in your personal account in My Vitality Club Pro which is a website developed by Air Liquide Healthcare and gives researchers and sleep physicians the possibility to access patient's clinical data and monitor their progress with CPAP therapy. The data extracted from CPAP machines will be accessible by both sleep physicians and researchers in this study. During each visit to Air Liquide CPAP clinics, you will also be asked to undergo weight measurement, using a stand on digital scale.

Lifestyle intervention program:

This is a 6 month program where we will assist you to manage your weight. The first and last (6th) session of this program will be run at the Be Active Sleep Eat (BASE) facility at Notting Hill. Before attending your first and last session of the lifestyle intervention program, you will be asked to fast overnight (for 10-12 hours). When attending these two sessions, you will need to undergo weight measurement by using a calibrated digital scale. Then you will be required to undergo blood pressure measurement, followed by body measurements (i.e. waist and neck circumference). After obtaining a verbal consent, a qualified phlebotomist will collect a 17 ml blood sample. You will then be asked to provide a written consent for undergoing dual-energy x-ray absorptiometry (iDXA) scan. You will not be eligible for this test if you are pregnant. An iDXA machine will be used in this study to provide iDXA scans. An iDXA scan evaluates how much fat and muscle you have in your body. To undergo an iDXA scan, you will be required to change into a gown and remove any artefacts (e.g. jewellery, piercings, and watches). It will involve lying on a padded table for approximately 10 minutes while the scan is performed. For this study you will need to undergo two iDXA scans at two different timepoints (first and last session of the lifestyle intervention program) which both will operate by a qualified radiographer. Once the

scan is completed, a copy of the iDXA scan will be provided for the study dietitian. You may also ask for a copy of your iDXA scan to keep it for your own records. After all the measurements are completed, you will be provided with a light breakfast (cereal, fruit, milk, coffee or tea). Ultimately, you will be asked to complete the same questionnaires as the screening session. The first and last session of the lifestyle intervention program will follow the same procedure which has been explained above.

Meeting with the study dietitian: During 6 months of the lifestyle intervention program, you will have monthly counselling sessions with an Accredited Practising Dietitian (APD). During the first session, the dietitian will ask you about your eating habits and describe what you will be required to do during this program which involves an active weight loss phase (initial 3 months) and maintenance phase (the second 3 months). The active weight loss phase includes diet and exercise. The diet comprises a combination of an intermittent fasting diet and a reduced energy diet (modified 5:2 fasting regimen). For the structured low energy diet days, you will be provided with a nutrition pack, which each will last for a month. The nutrition pack consists of proportioned skim milk powder (which you will be asked to mix with skim milk/reduced fat milk at home), multivitamins with fish oil and fibre supplements. For each day of the structured low energy diet, you will be asked to use the skim milk powder with milk, multivitamin, and fish oil and fibre supplements for two meals and for the other meal you will be asked to eat a low energy meal (suitable options will be discussed with you by the dietitian). If you have not used up your allocated one-month supply of the nutrition pack, you are required to return them to the study dietitian when you come in for your next visit. You will be encouraged to schedule at least three 30 minute sessions of light physical activity (e.g. walking or jogging) each week during the 3 months of active weight loss phase. You are strongly advised to seek professional medical advice if you intend to pursue more intense physical activity. The dietitian will have access to your personal online account in Fitbit website which had been created in the beginning of the study.

You will also be asked to install the myPace App on your smartphone or tablet device to use in between consultations with the dietitian. MyPace is an app that has been developed by psychologists and its use has been shown to help people when they are trying to lose weight. It is available on the Apple App Store and Android Google Play. It will require an internet connection (Wi-Fi or mobile data) and permits communication with your dietitian. You will receive individualised 'small steps' through the app, which are simple action-based goals (e.g. eating, behaviour and physical activity oriented) that you can complete each day to help you with your weight management goals. If you do not have access to smartphone or tablet device, you will receive regular text messages or phone calls from the study dietitian.

The study dietitian will be focused on assisting you with adhering to this program. Previous participants that have completed a similar program have lost about 6kg over 3 months. Depending on your body weight after 3 months, tailored dietary advice will be provided either to help you maintain your weight lost or to lose more weight.

The first appointment will last 60 minutes, other monthly visits with dietitian last for 30 minutes and can be organised to be held either at BASE facility, or dietitian's rooms in North Fitzroy or Box Hill Hospital via the dietitian directly.

Monthly visits:

As part of your involvement in this study, you are expected to let us measure your weight every month (using a calibrated digital scale). Each visit for weight measurement may take ~5-10 minutes.

Options for weight measurement are as follows:

- At Air Liquide CPAP clinics (one month, 6 month, 12 month)
- At BASE, Box Hill Hospital, or Monash Medical Centre or Alfred Health sleep clinics
- At the dietitians rooms located in North Fitzroy or Box Hill
- If none of the venues above are suitable, a home visit may be arranged by one of the

Overnight sleep study:

After 12 months of CPAP treatment, you will be scheduled for a sleep study. This visit will take about 13 hours and will allow us to see if there have been any changes in your health status and OSA severity. You will be asked to arrive at either BASE facility or your referring hospital (i.e. Monash/Eastern Health) at about 7:00 pm. We will provide you with a transportation voucher for attending the overnight sleep study. During this visit, the same questionnaires as previous visits will be completed. In addition your weight and body measurements will be assessed using a calibrated digital scale.

Your set-up for the sleep study will then start with placing leads on your body and head for measurement of heart beat, blood pressure, muscle activity, eye movements, brain activity and the level of oxygen level in the blood. Two stretchy belts will be also placed around your stomach and your chest to monitor your breathing. Two sensors will also be put under your nose (above your top lip) to measure the air that you are breathing in and out. Once all of this equipment is placed on you and you are comfortable, you will be asked to look in several directions, blink, wriggle your feet, and make chewing movements so that we can check that all of our equipment is working. We will then turn off the lights and let you go to sleep. Your breathing and sleep will be recorded until approximately 6:00 am when you will be waken up and all the study equipment, electrodes, and sensors will be removed. In morning, when you have fasted overnight for 10-12 hours, your blood pressure will be measured and subsequently, a certified phlebotomist will obtain a 17 ml sample of your blood so that we can examine your total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, insulin, leptin, cytokines, adipokines, and gene expression. Ultimately, you will be provided with a light breakfast (cereal, fruit, milk, coffee or tea).

After successfully completing the study procedure, you will be offered with a discount letter for purchasing the CPAP machine from Air Liquide and you will be able to keep the Fitbit tracker free of charge.

4 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine care, your relationship with professional staff or researchers.

5 What are the possible benefits of taking part?

Currently CPAP is considered the gold standard treatment for OSA as it improves the many symptoms of the disorder and may reduce the chances of cardiovascular-related deaths. Weight loss also helps manage OSA and 5-10% body weight loss can also reduce cardiovascular risk.

A CPAP machine and mask will be provided free of charge for all participants for use during this study by the company called *Air Liquide* (with approximate value of \$1,600-\$2500). Air Liquide will also provide free support to help establish you on CPAP therapy. At the end of the study the equipment needs to be returned, however you will receive a 30% discount voucher (with approximate value of \$480-750) if you wish to purchase CPAP equipment from Air Liquide at the completion of the trial. If you choose to take advantage of this special offer, Air Liquide will allow you to keep the mask that you have had used during the study free of charge (with approximate value of \$300). In this study, along with CPAP treatment, you will be provided with

a 6-months lifestyle intervention. For your every visit to BASE facility, free parking will be provided. You will attend six monthly sessions with a dietitian (with approximate value of \$600) and receive a Fitbit activity and sleep tracker (with approximate value of \$100) and some liquid replacement meals and supplements for 3 months. These interventions are expected to improve your health status and OSA severity. However, we cannot guarantee that you will receive benefits from this research. You will also be provided with an overnight sleep study at no charge. Possible benefits may include improving your general health and helping others with OSA to explore more effective interventions.

6 What are the possible risks and disadvantages of taking part?

DXA: This is a X-ray and is not painful or invasive and involves a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2.0 millisieverts (mSv) each year. The effective dose from this study is approximately 0.06 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure.

Questionnaires and body measurements: You may feel tired after answering questionnaires and undergoing body measurements. If you do not feel ready to continue assessments, you may ask our researcher to take short breaks. You may feel that some of the questions we ask are stressful or upsetting. If you do not wish to answer a question, you may skip it and go to the next question, or you may stop immediately. If you become upset or distressed as a result of your participation in the research project, the research team will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research team. This counselling will be provided free of charge.

CPAP: CPAP is considered extremely effective at resolving OSA and is completely safe. However, some individuals may experience difficulties using the machine in the beginning; in particular some individuals may experience some level of discomfort caused by the mask that they are using. If this feeling of discomfort continues for longer than 2-3 weeks, you need to inform our researchers. You may find it difficult to use your device regularly for 12 months, but you should know that your compliance to CPAP therapy is very important and the more you use it the more benefit you gain.

Lifestyle intervention: Participants may experience tiredness or hunger after undergoing diet as a part of lifestyle intervention. This may occur due to a lower energy intake or a higher level of physical activity, compared to your usual daily lifestyle. It will take some time for your body to get used to this program, but it is expected that those who are actively engaged in lifestyle intervention will potentially benefit from improvements in OSA severity and their general health.

Overnight sleep study: some of our patients have trouble sleeping in the sleep laboratory as it is a different environment to their usual routine. Every effort will be made to ensure patient comfort during the sleep study, but it is crucial for participants to undergo sleep study in the sleep laboratory which is a carefully controlled environment.

7 What if I withdraw from this research project?

If you do consent to participate, you may withdraw at any time. If you decide to withdraw from the project, you need to return the CPAP machine and notify a member of the research team before you withdraw. If you do withdraw, you will be asked to complete and sign a 'Withdrawal of Consent' form; this will be provided to you by the research team.

If you decide to leave the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research

project results. If you do not want your data to be included, you must tell the researchers when you withdraw from the research project.

8 What happens when the research project ends?

When the research project is completed, your data will be analysed and the results will be prepared for publication in a scientific journal. If you wish to see a copy of the results of the study please contact one of the research team listed on this form. *You will be asked to fill in a short evaluation questionnaire which will assist us in planning other studies*

Part 2 How is the research project being conducted?

9 What will happen to information about me?

By signing the consent form you consent to the research team collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. The data collected will be stored on password protected computers and in locked offices and accessed only by the research team. All information will be retained for 7 years following the completion of the study. The data collected in this study will only be used for the purpose of this research project and other future studies where the appropriate ethical approval has been obtained and it will only be disclosed with your permission, except as required by law.

The personal information that the research team collect and use is data collected through questionnaires, Fitbit trackers, physical measurements (e.g. weight and height), iDXA scans, blood samples, and sleep studies and will be stored using data storage software called LabArchives.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your express permission. Your data may be presented in de-identified format or analysed as a group.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information about you that is collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please inform the research team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for the future research that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

10 Complaints and compensation

If you suffer any distress or psychological injury as a result of this research project, you should contact the research team as soon as possible. You will be assisted with arranging appropriate treatment and support.

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with 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.

11 Who is organising and funding the research?

This research project is being conducted by Professor Helen Truby and her team from Monash University. It is funded partly by the department of Nutrition and Dietetics (School of Clinical Sciences) and by Dr Bradley Edwards at the Sleep and Circadian Medicine laboratory (School of psychological sciences). Air Liquide are providing the CPAP machines for 12 months.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

12 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC).

The ethical aspects of this research project have been approved by the HREC of Monash Health. This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

15 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the researcher on 9905 0187 or any of the following people:

Research contact person

Name	Professor Helen Truby
Position	Chief Investigator
Telephone	03 9902 4261
Email	Helen.Truby@monash.edu

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Monash Health
HREC Executive Officer	Deborah Dell
Telephone	03 9594 4611
Email	Deborah.Dell@monashhealth.org

Summary of Study Requirements

Visit	Location Options	Time and Details	What will happen
Screening visit for eligibility	Be Active Sleep & Eat (BASE) facility in Notting Hill * Free parking	~60-90 mins Appointments available between 7 and 11am appointment * Breakfast will be provided	- Blood pressure, weight, height, neck, and waist measurement - Blood test (17ml) for cardiovascular risk markers and metabolites related to OSA and changes in gene expression - Questionnaires - Collect free Fitbit activity tracker
Fitting of CPAP mask and setup CPAP machine and support sessions	Air Liquide CPAP clinic: Richmond Mon-Fri 9am-5pm Or Dandenong Mon-Fri 9:30am-4pm Sat 9:30am-2pm Or Eltham Mon – Fri 9:30am-4:00pm Sat 9:30am-2:00pm	Initial setup ~60 mins Support sessions ~30 mins	- Initial setup visit: Collect a free CPAP machine and help you to get started on CPAP - Support sessions after 7 days, 1, 6 and 12 months - Receive phone calls from CPAP support team
Monthly	BASE facility * Free parking or Or Eastern, Monash or Alfred health Or Home visit by researcher	~10-15 mins	Weight measurement with a calibrated digital scale
Lifestyle intervention Period (6 month duration) Timing to start will be determined by random selection	BASE facility on Mon 10am-1pm * Free parking or Dietitians rooms: in North Fitzroy on Wed 1am-5pm or Box Hill hospital on Tue 2pm-5pm	Appointments are available at different places and times as follows: Initial meeting ~60-90 mins * Breakfast provided Follow-up meetings ~30 mins The myPace App is available on your smartphone which has been designed to help you meet your goals. If you do not have a smart phone the dietitian will phone you instead	At baseline and after 6 months: - A DXA will be performed to give you an accurate picture of your body composition - Blood pressure, weight, neck, and waist measurement - Blood test (17ml) for cardiovascular risk markers and metabolites related to OSA and changes in gene expression - Questionnaires At every 6 monthly sessions: - Meet with the dietitian who is available to support you to lose weight. See details of the intervention (page 4)

Overnight sleep study At the end of the study (12 months)	BASE facility sleep laboratory or referring hospital (Monash/Eastern health) * Free parking * Transport Vouchers	~13 hours * Breakfast provided * Collect your discount letter to purchase CPAP machine	As per screening visit plus an overnight - sleep study
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Consent Form - Adult providing own consent

Title *The Sleeping Well Trial: enhancing the effectiveness of continuous positive airway pressure (CPAP) treatment with a weight management program for overweight adults*

Short Title *The Sleeping Well Trial*

Protocol Number *HREC/15/MonH/93*

Principal Investigator *Prof Helen Truby*

Associate Investigator(s) *Assoc. Prof Garun Hamilton, Ms Ladan Ghazi, Dr Alan Young, Prof Matthew Naughton, Dr Bradley Edwards, Dr Denise O'Driscoll, Dr Maxine Bonham, Prof Terry Haines, Dr Simon Joosten, Ms Teanau Roebuck, Ms Kirsty Yull, Ms Kaitlin Day, Dr Chiara Murgia, Mrs Kerry Roem, Miss Kellie Hamill, Miss Claire Bristow.*

Location *Be Active Sleep & Eat (BASE) facility in Notting Hill (adjacent to Clayton campus) / Monash University*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I accept that de-identified data collected in this research project can be followed up or used for other studies in the future, where the appropriate ethical approval has been obtained.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher[†] (please print) _____

Signature _____ Date _____

[†] An appropriately qualified member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - Adult providing own consent

It is recommended that this form NOT be included as part of the PICF itself, but that it be developed at the same time and made available to researchers for later use, if necessary.

Title *The Sleeping Well Trial: enhancing the effectiveness of continuous positive airway pressure (CPAP) treatment with a weight management program for overweight adults*

Short Title *The Sleeping Well Trial*

Protocol Number *HREC/15/MonH/93*

Principal Investigator *Prof Helen Truby*

Associate Investigator(s) *Assoc. Prof Garun Hamilton, Dr Alan Young, Prof Matthew Naughton, Dr Bradley Edwards, Dr Denise O'Driscoll, Dr Maxine Bonham, Prof Terry Haines, Dr Simon Joosten, Ms Ladan Ghazi, Ms Teanau Roesbuck, Ms Kirsty Yull, Ms Kaitlin Day, Dr Chiara Murgia, Mrs Kerry Roem, Miss Kellie Hamill, Miss Claire Bristow.*

Location *Be Active Sleep & Eat (BASE) facility in Notting Hill (adjacent to Clayton campus) / Monash University*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine care, or my relationships with the researchers.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Senior Researcher must provide a description of the circumstances below.

Declaration by Researcher[†]

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Researcher (please print) _____

Signature _____ Date _____

[†] An appropriately qualified member of the research team must provide information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

The Sleeping Well Trial: Increasing the effectiveness of treatment with continuous positive airway pressure (CPAP) using a weight management program in overweight adults with obstructive sleep apnoea: A stepped wedge randomised trial protocol

Figures and tables document.

Figure 1 Trial design using a 6 stepped wedge.

Figure 2 Recruitment flowchart.

Table 1 The Sleeping Well Trial lifestyle intervention outline.

Session	Content covered
One	Review dietary pattern (24 hour recall), take weight measurements, identify key targets for dietary modification based on dietary history, introduce 5:2 modified fast, establish goal weight and physical activity recommendations, set up MyPace™ and communication strategy
Two	Review progress, record weight measurement, monitor adherence to fasting days, review goals from last appointment and discuss barriers/enablers to achieving these
Three	Review progress, record weight measurement, monitor adherence to fasting days, review goals from last appointment and discuss barriers/enablers to achieving these, discuss strategy moving into maintenance phase and cessation of fast days take weight measurements
Four	Review progress, record weight measurement, review goals from last appointment and discuss barriers/enablers to achieving these
Five	Review progress, record weight measurement, review goals from last appointment and discuss barriers/enablers to achieving these, prepare participant to end relationship with dietitian after the next visit, start to think about discharge strategy
Six	Review progress, record weight measurement, review goals from last appointment and discuss barriers/enablers to achieving these, provide follow up options and ensure that a strategy for maintenance/ further weight loss is in place.

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Author/s:

Truby, H;Edwards, BA;O'Driscoll, DM;Young, A;Ghazi, L;Bristow, C;Roem, K;Bonham, MP;Murgia, C;Day, K;Haines, TP;Hamilton, GS

Title:

Sleeping Well Trial: Increasing the effectiveness of treatment with continuous positive airway pressure using a weight management program in overweight adults with obstructive sleep apnoea-A stepped wedge randomised trial protocol

Date:

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