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Tirzepatide versus Positive Airway Pressure for treatment of Obstructive Sleep Apnoea: A Randomised Comparative Effectiveness Trial

Short title

The TIRZE-PAP Study

Trial registration identifier	NCT07846865
Coordinating principal investigator	Associate Professor Craig Phillips
Signature	
Protocol authors	Associate Professor Craig Phillips and Dr Julia Chapman
Sponsor	Woolcock Institute of Medical Research
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STUDY SUMMARY

Trial registration identifier	TBD
Funding sources	Sleep and Circadian Research Group, Woolcock Institute of Medical Research
Primary sponsor	Woolcock Institute of Medical Research 2 Innovation Rd, Macquarie Park, NSW, 2113 +61 2 9805 3000
Contact for queries	A/Prof. Craig Phillips c.phillips@mq.edu.au
Public title	Weight loss compared to CPAP for treating obstructive sleep apnoea
Scientific title	Tirzepatide versus positive airway pressure for the treatment of obstructive sleep apnoea: a randomised comparative effectiveness trial
Country of recruitment	Australia
Health condition	Obstructive Sleep Apnoea
Intervention	Continuous Positive Airway Pressure (CPAP) (as prescribed) or Tirzepatide (15mg or maximum tolerable dose)
Study type	Randomised comparative effectiveness superiority trial
Expected first enrolment	1st October 2026
Target sample size	256
Primary outcomes	Breathing Disturbance Index (BDI) - breathing disturbances per hour of sleep measured every night over 4-weeks
Secondary outcomes	Oxygen Desaturation Index (ODI) – number of oxygen desaturations ≥3% per hour of time in bed measured over 7 to 14 nights PROMIS- Sleep Related Impairment Short Form 8a Questionnaire Epworth Sleepiness Scale (ESS) Sleep Systolic Blood Pressure (24-hr ambulatory blood pressure) Blood-based cardio-metabolic markers (Low Density Lipoprotein Cholesterol (LDL-C), Glycolated haemoglobin (HbA1c))
Tertiary Outcomes	Hypoxic burden[1] – measured over 7 to 14 nights. Short-form Functional Outcomes of Sleep Questionnaire (FOSQ-10) Blood-based cardio-metabolic markers (BG, TAG, HDL-C, T-C) Office Blood Pressure Anthropometry (BMI, waist circumference, neck circumference, body weight, BMI) Executive functioning and working memory - CANTAB battery Alertness - Psychomotor vigilance task (PVT) performance Blood based neurodegeneration biomarker panel – e.g. amyloid beta, phosphorylated tau, GFAP
Inclusion and exclusion criteria	Inclusion criteria ▪ Adults aged ≥18 years. ▪ Untreated moderate–severe obstructive sleep apnoea (AHI ≥15 per hour) diagnosed with type 1 or type 2 sleep study. ▪ Moderate overweight or obesity (BMI≥27kg/m^2) adjusted for ethnicity. ▪ No contraindication to tirzepatide use as per Australian Product Information ▪ Home or mobile phone-based internet access. ▪ Fluent English literacy. Exclusion criteria OSA or other respiratory related criteria: ▪ Respiratory failure including obesity hypoventilation syndrome (OHS) or daytime hypercapnia or moderate-severe chronic obstructive pulmonary disease (COPD) with FEV1/FVC ratio<0.7 and FEV1<80% predicted (GOLD criteria). ▪ Driver occupation with excessive sleepiness (Epworth Sleepiness Scale >=16) or sleepiness-related motor vehicle accident or near accident within 12 months prior to enrolment ▪ Current or prior OSA treatment with mechanical therapy (CPAP, MAS, Positional) ▪ >50% respiratory events with Cheyne-Stokes Respiration (CSR) or Central Sleep

	Apnoea (CSA) ▪ Relative or absolute contraindication to CPAP including chronic cranial injury; recurrent pneumothorax; indication for oral-pharyngeal surgery, significant craniofacial abnormalities that may affect breathing, or are unwilling to use CPAP ▪ Any previous or planned surgery for OSA or major ear, nose or throat surgery, including tonsillectomy and adenoidectomy that still may affect breathing ▪ Inclusion of a participant with more minor ear, nose or throat surgery (for example, deviated septum) will be at the investigator's discretion Glycaemia related criteria: ▪ HbA1c ≥ 48 mmol/mol (6.5%) at screening ▪ Type 1 or type 2 diabetes mellitus ▪ Treatment with glucose-lowering agent(s) within 90 days before screening ▪ Treatment with a GLP-1 receptor agonist within 90 days before screening Obesity related criteria: ▪ A self-reported change in body weight >5 kg or >5% within 90 days before screening ▪ Treatment with medication for the indication of obesity within 90 days before screening Other criteria: ▪ Pregnancy/breast feeding or planning a pregnancy during the trial period ▪ Relative or absolute contraindication to tirzepatide including needle phobia

APPROVAL AND ETHICS STATEMENT

Part or all the information in this protocol may be unpublished material. Accordingly, this protocol is to be treated as confidential and restricted to its intended use. The study will be conducted in accordance with the protocol, Good Clinical Practice, and all other applicable regulatory requirements, including the archiving of essential documents; and the National Statement on Ethical Conduct in Human Research (2007 – incorporating all updates) (Link to National Statement), the CPMP/ICH Note for Guidance on Good Clinical Practice (Link to CPMP/ICH) and consistent with the principles that have their origin in the Declaration of Helsinki (2024). Compliance with these standards provides assurance that the rights, safety, and well-being of trial participants are respected. See Section 6. ETHICS AND DISSEMINATION for more information.

VERSION CONTROL

Protocol version	Date	Changes
1.0	12th Dec 2025	Initial approved protocol
2.0	6th Aug 2026	Amendments to rank order of objectives/outcomes, removal of waist and neck circumference measuring at home, and aspect of risk to health in Trizepatide dosing for participant safety.

PROJECT TEAM ROLES AND RESPONSIBILITIES

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Study Funders

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Staff and research sites

In addition to the team members, the study is executed with help from a team of research assistants, undergraduate or higher-degree research students, post-doctoral researchers, and clinicians/physicians; all affiliated with the Woolcock Institute of Medical Research. This team is embedded in the management structure of the Sleep and Circadian Research group and will be overseen by PI Phillips who is a Research Leader in the group. The delegation and training log provides documentation about who is part of the team, at what dates they joined or left the team, and that they fulfilled training requirements. Other than the Woolcock Institute of Medical Research, there are currently no other research sites.

Study Governance

In this comparative effectiveness trial, we will not establish a formal steering committee. Instead, an operation committee comprising (CP, JC, CH, RG, BY and NM) will convene as necessary to manage day-to-day responsibilities. Feedback from investigators and members of our established Woolcock consumer panel will be sought at predetermined timepoints. The operation committee will oversee data management roles.

1. INTRODUCTION

1.1. Background and rationale for performing the study

Currently, the need for an effective treatment for obstructive sleep apnoea (OSA) is not being met by the one-size-fits-all "gold-standard" mechanical therapy of continuous positive airway pressure (CPAP). This device-based therapy fails to treat overweight and obesity - the primary reversible cause for most OSA and, has not been shown to provide long-term meaningful improvements in health outcomes.[2] The ineffectiveness of CPAP therapy is underpinned by low uptake, sub-optimal adherence, and unacceptably high rates of attrition. Newly available medication to reduce obesity could now provide a critical alternative to CPAP as a more effective treatment for OSA. In the recent global SURMOUNT-OSA trial[3], effective (~20%) weight loss using tirzepatide (a dual agonist of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors) reduced OSA severity (determined by the number of breathing disturbances per hour of sleep - the Apnoea Hypopnea Index or AHI) by up to 63% in patients who had severe OSA (AHI 51.5/hr) and severe obesity (BMI 39kg/m2). These data signal a clinical revolution in weight loss management that will have a major impact on how we treat OSA.[4] However, the eventual replacement of CPAP with weight loss in clinical practice must be evidence based. This proposed comparative effectiveness trial aims to demonstrate superiority of weight loss over CPAP for reducing OSA severity and improving OSA specific health outcomes.

1.2. Objectives

1.2.1. Primary objectives

To investigate whether OSA severity at 12 months (assessed by mean nightly at-home breathing disturbance (BDI) over 28 nights) with tirzepatide is greater than with CPAP.

1.2.2. Secondary objectives

To investigate at 12 months, whether improvements in

- hypoxia (assessed by the Oxygen Desaturation Index [ODI 3%] over 7 to 14 nights)
- sleepiness (assessed by PROMIS [Sleep Related Impairment Questionnaire] and the Epworth Sleepiness Scale [ESS])
- sleep systolic blood pressure (assessed by 24-hour ambulatory blood pressure monitoring)
- cardiometabolic risk (assessed by fasting blood levels of LDL and HbA1c)

are greater with tirzepatide than with CPAP.

1.2.3. Tertiary and exploratory objectives

To investigate at 12 months, whether improvements in

- hypoxic burden ([%min/hr] assessed by oximetry over 7 to 14 nights)
- sleep-related quality of life (assessed by the short-form Functional Outcomes of Sleep Questionnaire [FOSQ-10])
- cardiometabolic risk (assessed by fasting blood levels of glucose, triglycerides, HDL, tot cholesterol)
- blood pressure (sleep diastolic, wake systolic and diastolic, 24hr MAP, office systolic and diastolic)
- excess adiposity (BMI, weight, % weight, waist circumference, neck circumference)
- executive function and working memory (assessed by the CAmbriidge Neuropsychological Test

Automated Battery [CANTAB] Spacial Working Memory Task

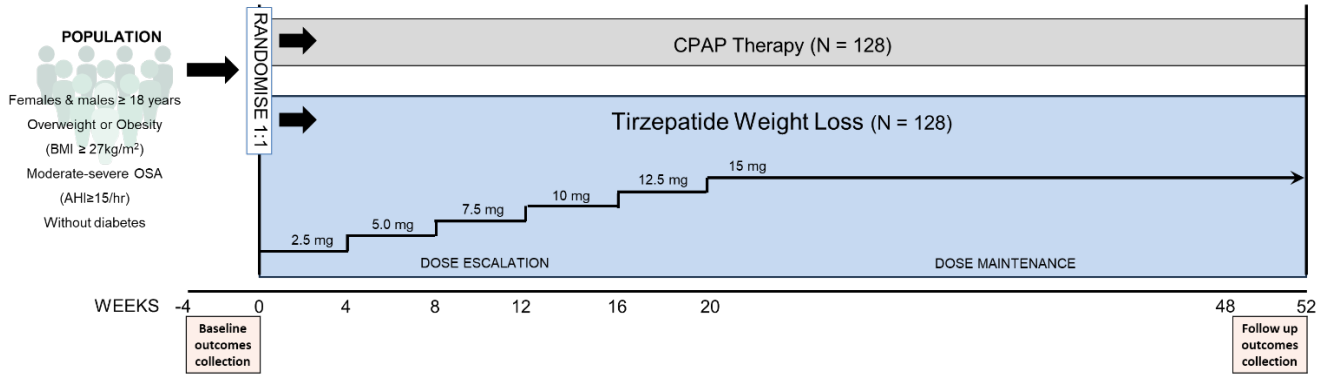
- alertness (assessed by the Psychomotor Vigilance Task [PVT])
- blood-based neurodegeneration biomarkers (amyloid beta, p-TAU and GFAP)
- hypoxia metrics (time spend with SpO2<88%, minimum SpO2 and average desaturation)

are greater with tirzepatide than with CPAP

1.3. Trial design

The TIRZE-PAP study (see Figure 1 below) is a parallel randomised superiority trial comparing weight loss with weekly tirzepatide (15mg or the maximum tolerated dose) versus CPAP, in 256 people with moderate-severe OSA (AHI≥15/hr) and overweight or obesity (BMI: ≥27kg/m^2). Participants allocated to CPAP will receive therapy as per usual care by their treating physician. Participants allocated to tirzepatide will undergo a 20-week stepped titration with a monthly increase of dose to a maximum 15mg (or maximum tolerated) by week 20. Outcomes will be collected over two 28-day periods commencing at baseline (pre-intervention weeks -4 to 0) and at follow-up (post-intervention weeks 48 to 52).

Figure 1. *Study flow diagram.*



OUTCOMES: See Section 2.4

2. METHODS: PARTICIPANTS, INTERVENTION, OUTCOMES

2.1. Study setting

The study will be conducted at the Woolcock Institute of Medical Research which is a specialised respiratory and sleep medicine research institute and clinic, located at 2 Innovation Rd, Macquarie Park, NSW, Australia. Participants may reside in any location and will be required to attend the Woolcock for any required face-to-face visits. Expansion of this trial to other sites may occur any time after the first 10 patients are randomised after necessary ethical and governance approvals.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

- Females and Males aged ≥ 18 years at the time of signing informed consent
- Moderate-severe OSA defined as an AHI ≥ 15/hr determined from a Type 1 or 2 sleep study conducted within the previous 12 months with a clinician recommendation for CPAP therapy.
- Moderate overweight or obesity defined as BMI ≥ 27 kg/m^2. (Adjusted to BMI ≥ 25 kg/m^2 for Asian populations as per WHO guidelines)
- No contraindication to tirzepatide use as per Australian Product Information
- Home internet access to enable cloud storage of SleepTracker-AI in-home BDI.
- Fluent English literacy and able to provide informed consent.

2.2.2. Exclusion criteria

OSA or other respiratory related criteria:

- Respiratory failure including obesity hypoventilation syndrome (OHS) or daytime hypercapnia or moderate-severe chronic obstructive pulmonary disease (COPD) with FEV1/FVC ratio<0.7 and FEV1<80% predicted (GOLD criteria).
- Driver occupation with excessive sleepiness (Epworth Sleepiness Scale >=16) or sleepiness-related motor vehicle accident or near accident within 12 months prior to enrolment
- Current or prior (≤3 months) OSA treatment with mechanical therapy (CPAP, MAS, Positional)
- >50% respiratory events with Cheyne-Stokes Respiration (CSR) or Central Sleep Apnoea (CSA)
- Relative or absolute contraindication to CPAP including chronic cranial injury; recurrent pneumothorax; indication for oral-pharyngeal surgery, significant craniofacial abnormalities that may affect breathing, or are unwilling to use CPAP
- Any previous or planned surgery for OSA or major ear, nose or throat surgery, including tonsillectomy and adenoidectomy that still may affect breathing

  (NB: Inclusion of a participant with more minor ear, nose or throat surgery (for example, deviated septum) will be at the investigator's discretion)

Glycaemia related criteria:

- HbA1c ≥ 48 mmol/mol (6.5%) at screening
- Type 1 or type 2 diabetes mellitus
- Treatment with glucose-lowering agent(s) within 90 days before screening
- Treatment with a GLP-1 receptor agonist within 90 days before screening

Obesity related criteria:

- A self-reported change in body weight >5 kg or >5% within 90 days before baseline
- Treatment with medication for the indication of obesity within 90 days before baseline and/or currently enrolled in a weight loss program

Other criteria:

- Pregnancy/breast feeding or planning a pregnancy during the trial period
- Relative or absolute contraindication to tirzepatide including needle phobia

2.3. Interventions

2.3.1. Baseline Outcomes Collection

After screening and informed consent and before randomisation, each participant will undergo baseline outcomes collection encompassing the measurement of the primary, secondary and tertiary outcomes. Following baseline outcomes collection, participants will be randomised to CPAP or tirzepatide.

2.3.2. Continuous Positive Airway Pressure (CPAP)

2.3.2.1. Overview

The gold standard treatment for OSA which delivers air from a pump device at a fixed or variable pressure via a flexible hose and custom-fitted nasal or face mask. As this is a pragmatic trial, patients allocated to CPAP will be managed by their caring sleep physician as per their normal practice. Before initiating CPAP, a second in-laboratory study may be required to establish a therapeutic pressure. Alternatively, some physicians bypass this process using auto-CPAP at home. Patients may also be counselled on losing weight with diet and exercise as per usual practice. For participants in this trial, initiating CPAP will be fast-tracked to occur as quickly as possible after randomisation.

2.3.2.2. Dispensing of CPAP

The study medical officer will complete the prescription for supply of CPAP at the recommended pressure settings for the 12-months follow up. Patients starting CPAP will attend a clinic with a CPAP therapist who delivers CPAP education about use and management of side effects. Additional follow up visits will occur as required to monitor and optimise compliance. CPAP machines, masks and humidifiers will be provided to participants free of charge for the duration of the trial.

2.3.2.3. Adherence to CPAP

CPAP adherence data will be downloaded from each participant's machine during scheduled visits or via online cloud-based storage.

2.3.3. Tirzepatide

2.3.3.1. Overview

Patients allocated to weight loss with tirzepatide will be managed by the study dietitian. The tirzepatide formulation is self-administered subcutaneously once weekly using single-use injection pens. The dietitian will manage all aspects including education on self-injection techniques, side-effects and diet and lifestyle advice. Tirzepatide will require a prescription from the study doctor. Participants will undergo a 20-week dose escalation

phase followed by a dose maintenance phase for the remainder of the 12-month study period.

2.3.3.2. Dispensing Accountability and Reconciliation of Tirzepatide

The study medical officer will complete each prescription for a supply of tirzepatide to last no longer than 3 months (12 injection pens). The prescription will be sent to a retail pharmacy who will dispense and courier directly to the study participant under their normal operating procedures and within their pharmaceutical scope of practice. The participants will be provided with storage instructions.

Study staff will contact the participant to confirm receipt. Participants will be provided with a link to an electronic Dosing Diary to record each week if they have taken or missed a dose. All diaries will be monitored daily by trial staff and participants will be encouraged to give a reason if a dose is missed.

At the end of the treatment period participants will return all unused tirzepatide pens to the Woolcock Institute of Medical Research at their final scheduled visit or their local pharmacy for destruction.

2.3.3.3. Modifications of Tirzepatide Dose

The aim is to escalate the dose of tirzepatide up to a weekly maintenance level of 15mg by 20 weeks. Participants unable to tolerate this dose due to side effects will be stabilised on their maximum tolerable dose. A medical investigator may stop the drug in response to an adverse event (see section 5), or risk to health, if they see fit after consultation with the Medical Principal Investigator and the participant.

2.3.3.4. Adherence to Tirzepatide

A consumer representative who has previously been treated with both tirzepatide and CPAP, was involved in the study design process and protocol development to ensure feasibility and practicality for participants. To enhance adherence to the intervention protocols, participants will be provided with clear instructions on the study drug regime. Participants will also be provided with access to the above-mentioned electronic Dosing Diary to record each instance of drug administration accurately.. In the case where a dose entry is missed, an email and/or text message will be automatically sent to the participant. A study member will follow up with a phone call if required.

2.3.4. Concomitant care

The study medical officer/s including sleep and obesity specialists should be contacted if there are any questions regarding concomitant or prior therapy. The use of concomitant medications by the participant will be taken into consideration prior to enrolment. Any medication considered necessary for the participant's welfare, and which does not interfere with the study objectives, assessment or treatment may be permitted at the discretion of the trial physician. Allowed medications must be maintained at consistent dose as far as possible as deemed appropriate by study medical officers.

Dose changes of existing concomitant medication or the use of additional prescribed or non-prescribed medication should be recorded on the Concomitant Medication Form noting drug, dosage, duration and reasons for use or dose change. Any additional diagnostic, therapeutic or surgical procedures performed during the study period will also be recorded, including date, reason for and description of procedure and its outcome.

2.4. Outcomes

All outcomes will be acquired during baseline (weeks -4 to 0) and follow-up (weeks 48-52) periods.

2.4.1. Primary outcome

Breathing Disturbance Index (BDI) (/hr) This is the primary severity metric of OSA which will be measured by the number of breathing disturbances per hour of sleep. This will be determined as a mean of 28 nights of data acquired at baseline (weeks -4 to 0) and follow-up (weeks 48-52) using contactless mattress-based OSA monitors (SleepTracker-AI)[5]. These monitors measure nightly OSA severity for the entire sleep periods.

2.4.2. Secondary outcomes

- Oxygen desaturation index (ODI 3%) (/hr) The mean number of oxygen desaturation events ≥3% per hour of time in bed. This will be determined as a mean of 7-10 nights of data acquired during baseline and follow-up assessments using an oximeter.
- Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep-related impairment short form 8a score. PROMIS-SRI consists of 8 items that assess self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours and perceived functional impairments associated with sleep problems. PROMIS-SRI has a recall period of "in the past 7 days", and each item is rated on a 5-point scale from "not at all" to "very much."
- Epworth Sleepiness Scale (ESS)[6] (score/24) Subjective sleepiness scored out of 24 measured using an 8-item questionnaire.
- Sleep Systolic Blood Pressure (mmHg) The mean sleep systolic BP determined using ambulatory blood pressure monitoring measured hourly during the self-reported sleep period. This is the most consistent cardiometabolic outcome that is (modestly) lowered with CPAP treatment.[9]
- Low Density Lipoprotein Cholesterol (mg/dL) Cardiovascular risk marker measured from a fasted blood sample.
- Glycolated haemoglobin (HbA1c) (%) Diabetic risk measured from a fasted blood sample.

2.4.3. Tertiary and exploratory outcomes – measured as per Table 1 Schedule of Assessments

- Hypoxic burden (%min/hr) This is a novel oximetry-derived measurement using established algorithms.[1] Measures will be quantified from nightly at-home oximetry acquired using an oximeter[10,11], over a minimum 7-10 night monitoring period.
- Short form Functional Outcomes of Sleep Questionnaire (FOSQ-10):[7,8] (score/20)The most reliable measure of sleep-related quality of life - assessing the impact of daytime sleepiness on activities of daily living.
- Blood Glucose [BG] (mmol/L) measured from a fasted blood sample
- Triglycerides [TAG] (mg/dL) measured from a fasted blood sample.
- High Density Lipoprotein Cholesterol [HDL] (mmol/L) measured from a fasted blood sample.
- Total Cholesterol (T-C) (mmol/L) measured from a fasted blood sample.
- Sleep diastolic BP (mmHg) measured from hourly ambulatory BP monitoring.
- Wake Systolic BP (mmHg) measured from hourly ambulatory BP monitoring.
- Wake Diastolic BP (mmHg) measured from hourly ambulatory BP monitoring.
- 24hour Mean BP (mmHg) measured from hourly ambulatory BP monitoring.

- Office Systolic BP (mmHg)
- Office Diastolic BP (mmHg)
- Body Mass Index (kg/m^2)
- Weight (kg)
- Weight (%)
- Waist Circumference (cm)
- Neck Circumference (cm)
- Executive Function measured using the CAmbridge Neuropsychological Test Automated Battery (CANTAB) Multitasking Test
- Working Memory measured using the CAmbridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory Task
- Alertness (msec) measured using the Psychomotor Vigilance Task (PVT) reciprocal mean reaction time
- Amyloid beta [Aβ] measured from blood plasma
- Phosphorylated tau [p-Tau-217] measured from blood plasma
- Glial fibrillary acidic protein [GFAP] from baseline to follow-up
- Time spent with SpO2<88% (sec)
- Minimum SpO2 (%)
- Average SpO2 desaturation (%)
- 12-month Breathing Disturbance Index measured nightly for 12-month treatment duration
- FOSQ measured at 3, 6, and 9 months
- Weight measured at home at 3, 6, and 9 months

2.5. METHODS: Description of Visits

2.5.1. Pre-screening

All potential participants will be contacted by a member of the study team and asked some basic pre-screening questions and given a brief overview of the study. If they are interested in participating, they will be emailed the Participant Information Sheet (PIS) and a follow up call/email from the research team will be arranged to confirm their continued interest in the study and to book in a face-to-face screening visit as applicable. At the screening visit, participants will be assigned a unique clinical screening number by the EDC which will comprise a three-digit number prefixed by “S” (e.g. S001, S002 etc).

2.5.2. Screening visit (Visit 1)

This visit will be conducted at the Woolcock Institute of Medical Research. To comply with the National Standard Operating Procedures for Clinical Trials Guidelines (Health Department, 2021), all persons who are not known to each other must produce identification to the other person to ensure verification of each person’s identity and to confirm the identity of the participant who is giving valid consent. The study team will explain the study to each participant and ensure they have had ample time prior to the visit to read and understand the PIS and have had the opportunity to ask any questions. The study personnel and medical officer will also be available for any further questions as appropriate. The consent form will be signed by both the participant and a medical officer who has been delegated this responsibility by the Principal Investigator. A copy of the completed consent form will be given to the participant for their records.

As part of the consent process, trial staff will explain that participants can withdraw their consent at any time

through verbal, written, telephone, or email communication, without the need to disclose a reason for withdrawal. Any data collected up to the point of withdrawal of consent will be kept as digital records with participant permission. Once consent is gained, the screening procedures shown in Table 1 will be undertaken to determine the eligibility of the participants (outlined in section 2).

2.5.3. Baseline Visit including 4-week OSA monitoring

After the screening visit and confirmation of eligibility, trial staff will provide participants with detailed instructions on setting up the SleepTracker-AI mattress monitor and an oximeter for use at home. A visit will be scheduled to complete to set-up 24-hour ambulatory blood pressure monitoring to be returned the next day at the Baseline Visit (See Table 1 Schedule of Assessments). Completion of baseline monitoring of OSA with SleepTracker-AI for 28 days and oximetry over a minimum period of 1 week will be confirmed with successful data acquisition. This will be confirmed by trial staff examining acquired data through a cloud-based database. Concomitant medication use, and adverse event records will be updated. Participants will complete questionnaires, CANTAB assessments, PVT. Participants will then be randomised. The allocated treatment will then be arranged. See Section 3 for Methods: Assignment of Intervention.

2.5.4. Treatment Initiation and Follow Up

2.5.4.1. Initiating CPAP

Participants randomised to the CPAP treatment arm will be managed by their caring sleep physician as per their normal practice. This could involve a formal in-lab titration study and a consultation with a CPAP therapist for education and mask fitting. This process will be expedited for trial participants. The date of commencing CPAP treatment at home will be recorded in the study data base as the start of the 12-month treatment period. During follow-up, any participant visits to their sleep physician or CPAP therapist to rectify CPAP problems (including equipment and pressure changes) will be recorded in the trial data base. In addition, CPAP compliance data will be downloaded for the entire follow-up period and stored in the trial data base.

2.5.4.2. Initiating weight loss with tirzepatide

Prior to commencing treatment, participants randomised to the weight loss with tirzepatide treatment arm will meet with the study dietitian for a detailed education session on self-injection techniques and potential side-effects from tirzepatide. The formulation is administered subcutaneously once weekly using single-use injection pens. Monthly dispensing from the Woolcock pharmacy will be established. Pens for patients will require a prescription from the study doctor. Participants will be started on a once-weekly dose of 2.5 mg for 4 weeks increasing to 5, 7.5, 10, and 12.5 mg/week for 4 weeks each and peaking at a 15mg maintenance dose by 20 weeks. Participants unable to tolerate 15mg will be maintained on their maximum tolerable dose (determined by the dietitian and study doctor). In addition to the routine trial activities outlined in Table 1, monthly telehealth consultations will be conducted during dose escalation and then as needed until trial completion at week 52. These are required for providing guidance about adjunctive diet and exercise, and for monitoring and management of any side-effects with tirzepatide, gastrointestinal being the commonest.

2.5.4.3. Follow-up and End-point Assessments

After randomisation, routine collection of trial data at prespecified time-points during follow-up will be similar for all randomised participants according to the schedule in Table 1 (section 4 below). Collection of trial data at 3,

6, and 9 month visits will be done using Telehealth and will include SleepTracker-AI data, concomitant medication use, adverse and serious adverse events. Participants will complete questionnaires online and will measure anthropometry at home as per instructions provided to them.

At 12 months, all participants will be asked to return with all equipment to the study site for a face-to-face visit that includes trial and outcomes data collection similar to Baseline as per Table 1 Schedule of Assessments (questionnaires, blood sample, cognitive tasks, anthropometry, office and 24-hour BP, oximetry).

2.6. Sample size and Power Calculations

128 patients in each group (256 in total), which includes an allowance for a dropout of 19 patients per group (15% loss from randomised) will give us 218 completers and 90% power to detect an f=0.18 difference in effect in the BDI (α=5%). This was calculated in G*Power (v.3.1.9.7) using a repeated measures ANOVA (between factors) option with 28 repeated measurements (28 nights each at baseline and follow-up) and the previously observed correlation between repeated measures of 0.65 calculated from AHI data in people with moderate-severe OSA.

3. METHODS: ASSIGNMENT OF INTERVENTION

3.1. Sequence Generation

The randomisation list with random treatment block sizes of 4 or 6 will be computer generated by a statistician who will not be involved in the recruitment or management of study participants or have any other involvement in the study.

3.2. Recruitment

Recruitment will continue until the target sample is achieved or funding is exhausted. The recruitment strategy (developed with input from a consumer representative to ensure a participant-centred focus), will encompass several sources including sleep clinics and the Woolcock Volunteers' database.

Patients who have had OSA diagnosed from Type 1 or 2 diagnostic sleep studies at the Woolcock Institute and affiliated clinics and who have consented to be contacted for potential participation in research will be contacted by the study team. A member of the team will contact them to provide further details about the study and to proceed to pre-screening to determine potential eligibility.

3.3. Allocation Concealment Mechanism and Implementation

Allocation concealment will be maintained by embedding the randomisation lists into the secure online REDCap study database using an electronic data capture interface. Access to the lists will be blocked to all study personnel except for the statistician who created the sequence. Upon obtaining written informed consent from each participant and confirmation of them meeting all eligibility criteria, the medical principal investigator or delegate will be required to irrevocably enter 3 unique participant eligibility identifiers (month/year of birth, AHI and screening number) into the database before the randomisation code is permanently recorded against that participant's online record. All documents will use the participant's unique participant screening and randomisation numbers to ensure participant anonymity.

3.4. Randomisation

Randomisation to Tirzepatide or CPAP (1:1) will occur after the baseline data collection. Participants will be sequentially assigned a unique randomisation number comprising 3 digits prefixed by “R” (e.g. R001, R002 etc).

4. METHODS: DATA COLLECTION, MANAGEMENT, ANALYSIS

4.1. Schedule of Assessment

Table 1. *Schedule of assessment.*

Visit number	1[F]	2[F]	3[F]	4[T]	5[T]	6[T]	7[T]	8[T]	9[T]	10[T]	11[F]	12[F]
Visit name	Screening	Pre-baseline	Baseline	DE1	DE2	3 months (DE3)	DE4	DE5	6 months	9 months	Pre-12 months	12 months
Timeframe/visit windows	-8 to -4 weeks	Day -1	Day 0	1 month	2 months	3 months *	4 months	5 months	6 months *	9 months *	Pre-12 months	12 months *
Study consent	X											
Eligibility check	X		X									
Demographics	X											
Medical History	X											
Lifestyle Factors	X											
Randomisation			X									
FOSQ-10 Questionnaire[7,8]			X			X			X	X		X
Epworth Sleepiness Scale (ESS)[6]	X		X			X			X	X		X
PROMIS-Sleep Related Impairment Questionnaire			X			X			X	X		X
CANTAB testing battery			X									X
Psychomotor Vigilance Task			X									X
Provide 24-hour Ambulatory Blood Pressure Monitor		X									X[a]	
Download 24-hour Ambulatory Blood Pressure Monitor			X									X
Anthropometry	X		X			[d]			[d]	[d]		X
Office blood pressure	X		X									X
Lipids, Glucose, HbA1c	X											X
Blood collection for storage			X									X
Provision and training of SleepTracker AI	X											
SleepTracker-AI Data Extraction[#]			X			X			X	X		X

Provision and training of oximeter§	X										X[b]	
Download oximeter			X									X
Concomitant Medication Use	X		X	X	X	X	X	X	X	X		X
AE and SAE monitoring†			X	X	X	X	X	X	X	X		X
Referral for CPAP therapy (CPAP group only)+			X									
CPAP data download (CPAP group only)						X			X	X		X
Dispensation of Tirzepatide (Tirz group only)^			X[c]	X	X	X	X	X	X	X		
Dose escalation (Tirz group only)				X	X	X	X	X				
Return of medication (Tirz group only)												X
Return study equipment												X

[F] Denotes this is a face-to-face visit. [T] Denotes this is a telehealth visit

DE=Dose Escalation visit. This will include a telephone consultation as required clinically. FOSQ= Functional Outcomes of Sleep Questionnaire. PROMIS= Patient-Reported Outcome Measures Information System. CANTAB= CAmbridge Neuropsychological Test Automated Battery.

d – Self-measured Weight

 # SleepTracker-AI[5] - data will be collected continuously across the study period. Data including nightly BDI will be extracted every 3 months from a cloud-based data store.

§ RingConn – Gen 2 – oximetry data including ODI, min SpO2, T90 and hypoxic burden variables.

†AE (Adverse Event) and SAE (Serious AE) monitoring every month for 6 months and every 3 months after that unless directly reported by participants outside of these times.

+ Note that Referral for CPAP therapy will require additional visits as per usual care under the guidance of the participant's sleep physician. See Section 2.5.4 for more information

**The follow-up visits will be performed this many months after treatment initiation.*

^ Tirzepatide will be dispensed monthly for the 20-week dose titration period, then 3-monthly thereafter

a 24 hours prior to the visit
b 7 days prior to the visit
c Includes detailed education session on self-injection techniques, side effects, diet and lifestyle conducted by dietitian

4.2. Data Collection

4.2.1. Demographics

Demographic data will be collected for all enrolled participants at screening. This will include age, sex at birth, gender identity (where applicable) and ethnicity.

Demographic variables will be summarized descriptively and used to characterize the study population and assess comparability between study groups.

4.2.2. Medical History

A comprehensive medical history will be obtained at screening, including past and current medical conditions, Relevant medical history will be documented in the case report form (CRF) and reviewed to confirm participant eligibility and to support safety evaluations throughout the study.

4.2.3. Lifestyle Factors

Information on lifestyle factors will be collected at screening, including tobacco use (current and past smoking status), alcohol consumption, and caffeine intake. Data will include frequency, quantity, and duration of use where applicable.

4.2.4. SleepTracker-AI (390 to 400 nights)

Nightly BDI, heart rate and sleep macro-architecture will be collected every night during the four weeks leading up to the baseline visit and during the 12 months follow up using the under-mattress SleepTracker-AI monitor. Data will be downloaded every 3 months from a secure password protected cloud-based server database owned and operated by FullPower Inc. Note: The primary outcome (at home BDI) analysis will be performed from data acquired over 28 successive nights during baseline prior to randomisation and during the final month of follow-up (weeks 48-52).

4.2.5. Questionnaires

4.2.5.1. Epworth Sleepiness Scale (ESS) (2 minutes)

The Epworth Sleepiness Scale will be included to assess improvements in subjective excessive daytime sleepiness. The ESS is an 8-question participant-completed subjective sleepiness questionnaire completed online. It asks the participant to rate on a scale from 0 (would never doze) to 3 (high chance of dozing) their usual chances of dozing in 8 different situations. In this study we will ask for a recall period to align with the primary outcome collection time of “in the past 4 weeks”. The total score summates the 8 responses, resulting in a total from 0-24 with higher scores indicating greater daytime sleepiness.

4.2.5.2. Functional Outcomes of Sleep Questionnaire (FOSQ) (4 minutes)

This is a 10-question participant-completed sleep-related quality of life questionnaire completed online. It assesses the impact of sleep disorders/excessive sleepiness on daily functioning. Participants are asked to rate

the impact of their sleep disorder/excessive sleepiness on several activities, with 1 indicating the highest/extreme impact and 4 indicating the lowest level of impact. The average score for each subscale is summed to produce a total score. Total scores range from 5-20, with lower scores indicating greater impact of sleepiness on activities of daily living. The short form FOSQ-10 will be used to minimise participant burden.

4.2.5.3. PROMIS Short Form v1.0 Sleep-related Impairment 8a

This questionnaire assesses participant-reported levels of alertness, sleepiness and tiredness and the functional impairments associated with sleep problems or reduced alertness over the past 7 days. It consists of 8 questions with responses rated on a 5-point scale from “not at all” to “very much”. Individual item scores are summated to obtain a raw score, with higher scores indicating more sleep-related impairment. Raw scores can be converted to a T-score, which is standardized with a mean of 50 and a SD of 10.

4.2.6. Blood Pressure Measurements

4.2.6.1. 24-hour Ambulatory Blood Pressure (24ABPM) (25 hours including setup and removal)

Requires setup of the device on the participant on the first day and return of the device with data download on the second day – encompassing a 24-hour recording period. Participants will be given the option to post the device back to the clinic using a supplied, pre-paid envelope.

4.2.6.2. Office Blood Pressure and Heart Rate

Blood pressure and heart rate will be taken using an automated blood pressure machine after sitting quietly for 5 minutes. Preferably on the non-dominant arm and on the same arm at each visit.

4.2.7. Anthropometry (2 minutes)

Height, weight, waist and neck circumference will be collected in the clinic as per the Schedule of Assessments. BMI will be calculated using the height collected at screening and will not need to be re-measured at subsequent visits. Weight will be self-measured by the participant at home at baseline, 3, 6 and 9 months.

4.2.8. Fasting Blood Sample (5 minutes)

A single fasted sample will be collected during the screening period and at 12 months to measure lipids, glucose and HbA1c. A small additional amount of blood will be collected and pre-processed using standardised procedures to enable storage (at -80 degrees Celsius) for analysis of neurodegenerative biomarkers.

4.2.9. Oximetry (7 to 14 nights)

Overnight oximetry will be collected for at least 7 nights (maximum 14 nights) during baseline and at 12 months (weeks 48-52) using the RingConn Gen 2 smart ring. Data will be downloaded from a database on a secure password protected cloud-based server owned and operated by RingConn Inc.

4.2.10. Cognitive testing battery

4.2.10.1. Alertness measurement – Psychomotor Vigilance Task (10minutes)

A 10-minute psychomotor vigilance task (PVT) will be performed to assess a participant’s level of alertness. This test requires a participant to sit in a quiet room while performing the task. They will be asked to respond

by pressing a button as quickly as possible to the appearance of a stimulus (numbers appearing on a screen). The PVT response variables to be analysed are: a) mean reciprocal reaction time (RT); b) mean of the fastest 10% of RTs; c) mean reciprocal of slowest 10% of RTs; and, d) number of lapses (response time >500ms).

4.2.10.2. Executive functioning and working memory – measured using the CAmbridge Neuropsychological Test Automated Battery (CANTAB)

The CANTAB battery will be used to assess cognitive domains associated with obstructive sleep apnoea. These will include assessments of executive functioning and working memory.

The Spatial Working Memory Task (SWM) assesses working memory and strategy and is applicable in the assessment of general cognitive function. In this task, participants are asked to locate a 'token' by touching a box. In each trial, each box contains only one token (i.e. a token will never be found in the same box again). Across trials, the number of tokens and boxes increases from 3 to 6 to 9 to 12. Outcomes are the number of times the participant touches a box that previously contained a token in trials with 4, 6, and 8 boxes.

The Multitasking Test (MTT) tests executive functioning and cued attentional set shifting. An arrow, pointing either left or right, appears on the right or left side (independent of arrow direction) of the screen. Additionally, the words 'direction' or 'side' appear at the top of the screen. In the first two trials, participants decide the direction in which the arrow is pointing or the side on which the arrow is located by pressing the left or right buttons on the bottom of the touchscreen. In the final trial, the two rulesets are mixed, and participants are required to adjust to changing 'direction' and 'side' rules. All the trials are preceded by a practice trial, which provides verbal feedback regarding their answers to ensure the participants understand the rules. The response latency for same-rule set and switching-rule set tasks are the outcome measures.

4.3. Retention

4.3.1. Participant retention

Once a participant is enrolled, the study staff members will make every reasonable effort to follow the participant for the entire study period. They are responsible for developing and implementing local standard operating procedures to achieve this level of follow-up. Retention methods include:

- Regular contact with participants (by phone calls) will occur monthly for the first 6 months and every 3 months after that to record adverse/serious adverse events and concomitant medications and to ensure no protocol deviations.
- At the end of the study, participants may be notified of routine clinical care pathways, potential clinical trials, and research studies to further help with their OSA where needed.

As this is a comparative effectiveness trial testing commercially available treatments, there may be instances during the trial where a participant chooses to use CPAP despite being randomised to the tirzepatide group or chooses to use tirzepatide or another weight loss agent despite being randomised to the CPAP group. Some participants may use both therapies. These "drop-ins" or crossovers will be documented in the participant's file and collated for the final study report if applicable. The participants will remain in the trial and will be analysed as per the allocation to which they were randomised as per the intention to treat principle. Sensitivity analyses may be performed to assess the impact of removing these participants from the primary analyses.

4.3.2. Participant withdrawal

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.
A participant may choose if they choose to withdraw from the study intervention but remain in the trial for data collection purposes. In this case all attempts will be made to collect as many outcomes from the 12 month visit as possible. If required, this visit may be brought forward to accommodate an early termination visit for a participant wishing to cease study participation early.
A participant may choose to withdraw their consent from the trial without giving a reason and will not consent to any further follow-up assessments. 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 their reasons). Any post-randomisation data collected from that participant will be used in study analyses as much as possible as per the intention to treat principle.

Additionally, the investigator may withdraw a participant at any time for the following reasons:

- If any of the study exclusion criteria are met.
- Protocol violations.
- Adverse or serious adverse events.

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

4.4. Statistical methods

Statistical analyses will be completed using a commercial statistical package (e.g. SPSS, SAS etc). Outcome data will be analysed using linear Mixed Models due to expected inter-participant variability repeated measures and to deal with data missing at random. Baseline (i.e. 'pre-treatment') data (BMI, AHI) for the primary outcome being analysed will be included in the model as a covariate. Participants will be random factors. Fixed factors will be Treatment (CPAP and Weight Loss with tirzepatide) and baseline value (if available). The critical p-values will be set at 0.05 (two tailed). Effect sizes will be calculated as partial eta squared (η_p^2), Cohen's d, and Hedges' g, where appropriate. A statistical analysis plan will be written and published on a publicly available website before the completion of data collection.[12]

4.5. Data management

4.5.1. Data entry, security, and storage

To ensure data integrity is achieved the principles of ALOCOA-C will be adhered to throughout.

Source documents pertaining to the trial must be securely maintained by the investigational site. Source documents may include a participant's medical records, hospital charts, clinical charts, the investigator's participant study files, as well as the results of diagnostic tests such as sleep studies and laboratory tests. The

following information will be captured by the paper-based visit template:

a. The participant's protocol identification
b. The date that the participant entered the trial, and participant number
c. A statement that informed consent was obtained (including the date)
d. Relevant medical history
e. Dates of all participant visits and results of key trial parameters
f. The date the participant exited the trial, and a notion as to whether the participant completed the trial or reason (if given) for discontinuation.

Storage of the data collected will adhere to the Macquarie University regulations and the Australian Code for the Responsible Conduct of Research. De-identified data may also be made available to the public. In any publication and/or presentation, information will be provided in such a way that participants cannot be identified, except with their written, informed permission. Any information obtained for the purpose of this research that could identify participants will be treated as confidential and securely stored.

All data will be collected onsite at the Woolcock Institute of Medical Research in written and computerised formats. Overnight diagnostic sleep study recordings will also be securely stored on a cloud-based Compumedics 360 Nexus system (Silverwater, NSW). Paper records will be securely stored in locked cabinets for a minimum of 15 years following the end of the study. Computerised data will be stored and backed-up on a secure cloud-based, individual password-protected database system (REDcap) and the Macquarie University endorsed and secure on-campus data management infrastructure (Amazon FSx File Server, Amazon Web Services [AWS]). REDcap logs all access or changes to data back to individual users who will be given only access or change privileges to data which they require for their role. The Macquarie University endorsed and secure on-campus data management infrastructure, AWS, is a central location where approved projects, once registered, can store digital research data. Storage of the data collected will adhere to the Woolcock Institute of Medical Research's policies and regulations and the Australian Code for the Responsible Conduct of Research. Only approved members of the research team have access to the data pertaining to the individual research studies they are assigned to.

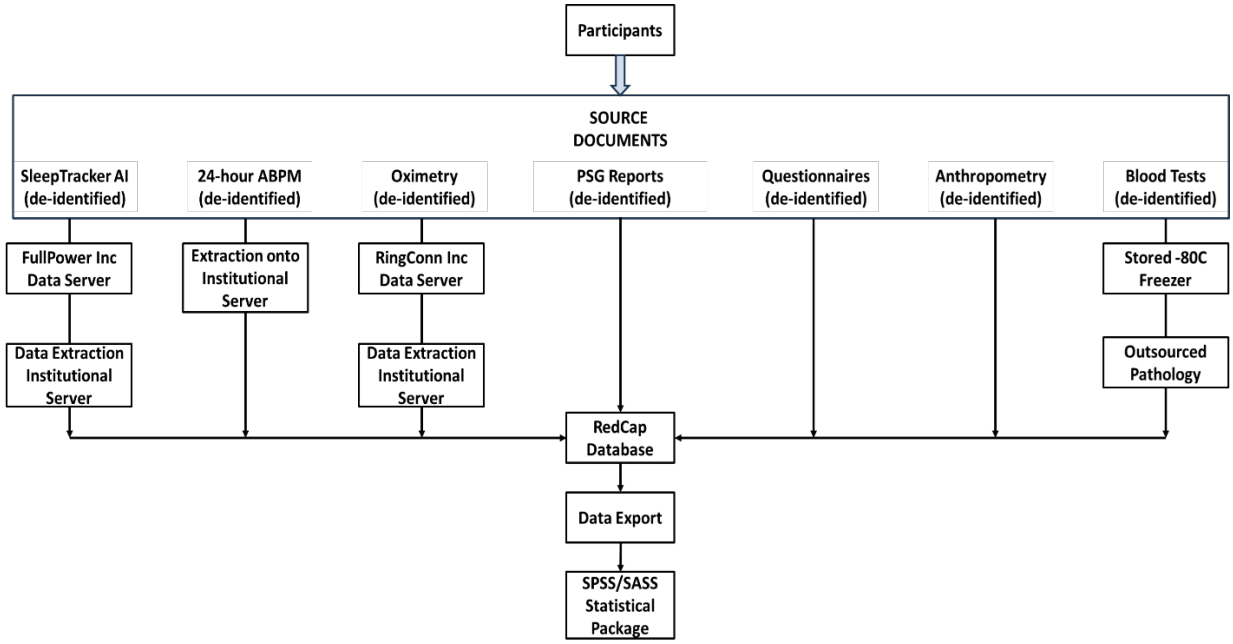
To prevent the disclosure of sensitive information all data stored will be deidentified but can be reidentified using a unique study ID (see below). Identification will only be known by the research team at the Woolcock Institute. Only researchers permitted to view and/or use this data will have access to Macquarie University endorsed and secure on-campus data management infrastructure.

All data will be re-identifiable as participants will be allocated an individual study code number. The master coding sheet that allows re-identification of participants will be kept in a password-encrypted file, and only investigators and research staff will have access to it. However, if needed, each participant will be able to be re-identified. After study completion, only investigators named at the front of this protocol will be allowed access to the study data under the supervision of the Principal Investigators. Details regarding data access after database lock and study completion are explained in section 6.7.

Data integrity will be enforced through a variety of mechanisms including data rules, range checks, and consistency checks against data already stored in the database. A list of valid codes and a description of what each code means will be available where applicable. Modifications to data in the database will be documented through the online data change system or by a physical signature and date for case report forms. Data entered in the online platform will be retrievable by running a query. The type of activity that an individual user may undertake is regulated by the privileges associated with the user identification code and password. Written documentation of changes will be available through electronic logs and audit trails. The investigators will periodically check captured data during the study and if a data discrepancy is noted the investigators will check original forms and source notes for inconsistency and will determine the correction, modifying the original response as required.

All blood samples will be stored on site in a safe, secure storage facility at the Woolcock, Macquarie University. Samples will be analysed at local commercial pathology labs. Samples will only be used for the purposes within the scope of this study.

Figure 3. *Data flow*



5. METHODS: MONITORING

5.1. Data Monitoring

The investigators will form the data monitoring committee. Data monitoring will occur on a regular basis. Primarily, investigators will implement visual cross-validation of the data for complex errors, and regular monitoring of the quality and completeness of the data. Investigators will review the source documents when required, to determine if data reported in the RedCap web-based system are complete and accurate. Investigators will also verify that all adverse events were documented in the correct format and are consistent with protocol definition.

5.2. Data Safety Monitoring

Both treatments are approved for treatment of OSA by the Therapeutic Goods Administration of Australia. Accordingly, there will not be any formal independent Data Safety Monitoring Committee. Instead, participant safety will be managed by 3 key members of the research team (CI Hocking - an endocrinologist, CI Yee – a sleep physician and CI Marshall – a clinical trialist). These CI members have experience managing weight loss with tirzepatide, OSA, clinical trial conduct and statistical interpretation.

5.3. Harms

5.3.1. Definitions

Adverse Event

Any untoward medical occurrence in a study participant administered an intervention and that does not necessarily have a causal relationship with this intervention. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an intervention device, drug (or protocol procedures), whether it is related to that device, drug or procedures or not.

Collection of adverse events will commence from the time that the participant signs the consent to participate in the study. Adverse events will be reviewed routinely at each visit, documented in source notes as they occur and entered in an electronic case report form (eCRF) until completion or withdrawal from the study. All adverse events reports will be reviewed, assessed and signed off by a study medical officer.

If the investigator believes that the adverse event is causally related to the investigational device or treatment, then withdrawal should be considered. This will be assessed by the investigators, study doctors and other members of the study team. Participants will have access to a 24-hour emergency study contact who can advise at the time of an emergency. Participants will be advised to contact emergency services in case of medical emergencies.

Serious Adverse Event

A Serious Adverse Event (SAE) is an event that meets any of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent of significant disability/incapacity
- Is a congenital anomaly/birth defect, or
- Other important medical events that based upon appropriate medical judgement are thought to jeopardise the participant or subject and/or require medical or surgical intervention to prevent one of the outcomes defining a serious adverse event

Planned hospitalisations or surgical interventions for a condition that existed before the participant signed the Informed Consent Form and that did not change in intensity are not SAEs. Emergency room visits that do not result in admission to the hospital are not necessarily SAEs; however, they must be evaluated to determine whether they meet any SAE definitions (e.g. life-threatening or other serious [medically important] event).

Urgent Safety Measures

An urgent safety measure (USM) is a measure required to be taken to eliminate an immediate hazard to a participant's health or safety. This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions. The site will be responsible for reporting the reason for the USM, the measures taken and further action plans.

The PI will be required to report the USM to the sponsor without undue delay and within 24 hours.

Significant Safety Issue

A Significant safety Issue (SSI) is a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the study.

An SSI can be a SAE that is associated with the study (either definitely related, probably related, or possibly related); a SAE that could be associated with the trial procedures and that requires modification of the conduct of the trial.

An SSI that meets the definition of an USM requires reporting by the sponsor to the TGA (using the Clinical trial Significant Safety Issue/Urgent Safety Measure [SSI/USM] safety reporting form), the HREC and the investigators. This should be done within 72 hours.

All SSIs (not meeting the USM definition) require notification to the TGA (using the above mentioned form), ethics and investigators by the sponsor within 15 calendar days of the sponsor instigating or being made aware of the issue.

5.3.2. Assessment of Adverse Events

5.3.2.1. Assessment of AE Intensity

Each AE will be assigned a category by the principal medical investigator or medically-qualified delegate as follows:

Mild:	An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities.
Moderate:	An AE that is sufficiently discomforting to intervene with normal everyday activities; intervention may be needed.
Severe:	an AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

5.3.2.2. Assessment of AE Causality

For each recorded AE or SAE, the investigator or designee must make an assessment for causality based on the following criteria to determine the relationship between the AE and treatment intervention or procedure:

Unrelated – the event is produced by the participant's clinical state (basic disease, pre-existing condition, concurrent disease, other) or other therapy administered.

Unlikely – the event does not follow a reasonable temporal sequence from treatment with the intervention or study procedures. The event could have been produced by documented pre-existing conditions, concomitant medication or the participant's clinical state.

Possible – the event follows a reasonable temporal sequence from treatment with the intervention or study procedures. The event follows a known response pattern to the intervention or study procedures, but the event could have been produced by the participant's clinical state or other therapy administered.

Probable – the event follows a reasonable temporal sequence from treatment intervention or study procedures. The event abates upon discontinuation of treatment. The event cannot reasonably be explained by the known characteristics of the participant's clinical state, or by other therapy administered.

Definite – the event follows a reasonable temporal sequence from the treatment intervention or study procedures. The event abates upon discontinuation of treatment. The event confirmed by reappearance of the AE on repeat exposure (re-challenge).

For pre-treatment adverse events, a causality assessment is not relevant.

5.3.2.3. Assessment of AE Outcomes

The Principal Investigator or medically-qualified delegate will assess the outcomes of all AEs (including SAEs) recorded during the study as:

- Resolved without sequelae
- Resolved with sequelae
- Ongoing
- Not resolved
- Fatal
- Unknown

5.3.3. Adverse event reporting

Any adverse events will be logged in the hard copy source document and reviewed by a study clinician/physician in the context of known information on the intervention to determine whether the event was intervention-related (i.e., an adverse reaction) or not.

Serious adverse events are reported immediately to the sponsor. This report is followed by a detailed written report, identifying the participant/s by their assigned participant identifier (rather than by name). A study clinician/physician reviews any serious adverse events in the context of known information on the intervention

and decides whether the event was intervention-related (i.e. a serious adverse reaction). All serious adverse events will be reported to the sponsor within 72 hours of learning of the event. Serious adverse events will be included in the annual reports to the ethics committee as required. If deemed a serious adverse reaction these will be reported to the requisite bodies (e.g., the ethics committee) within 72 hours.

5.3.4. Early termination

The study may be discontinued at any time on the advice of the responsible principal investigators based on new information regarding safety. Additionally, the study may be terminated if progress is unsatisfactory. In case of premature termination or suspension of the study, the principal investigator will inform the study participants and ensure appropriate follow up in the event this is clinically required. In addition, the appropriate ethics committee will be informed. See also Section 4.3.2 Participant Withdrawal.

5.3.5. Risk assessment

The study activities involved may cause some side effects. Participants may have none, some or all the effects (listed below) and they may be mild, moderate or severe.

5.3.5.1. Treatment Side Effects

Side effects of Tirzepatide are outlined in the *Australian Public Assessment Report for Mounjaro* and the Australian Product Information. Side effects include nausea and diarrhoea (≥10%), abdominal pain, dyspepsia, vomiting and fatigue (≥1% to <10%).

5.3.5.2. Blood Draws

Some known risks, although rare, are associated with placing a needle into a vein under the skin. Participants may have pain, swelling, or bruising at the site. There may also be risk of infection, dizziness or fainting.

5.3.5.3. Ambulatory Blood Pressure Monitoring (ABPM)

ABPM is non-invasive, with minimal discomfort involved. The inflatable blood pressure cuff that is fitted to the participants' arm may cause discomfort during inflation and may be associated with mild pain, numbness or a tingling sensation in the extremity (fingers). The research team will do everything possible to ensure that the experience is as comfortable for participants as possible. This will be done by familiarising participants with the cuff during their visit and ensuring that the cuff is the correct size to reduce over-inflation.

5.3.5.4. Oximetry

The ring-based oximetry is non-invasive. The ring may cause minimal discomfort for participants who are not accustomed to wearing a ring on their finger. The research team will do everything possible to ensure that the experience is as comfortable for participants as possible. This will be done by ensuring the ring size is appropriate for the size of the finger. Participants only need to wear the ring during sleep.

5.3.6. Minimization, management, and justification of risk

All costs and burdens are negated, minimised, or managed through close monitoring of participants by the clinical dietitian, study doctors, and trained research staff. Participants are routinely monitored for adverse events, discomfort, and harm at regular time points as described in this protocol. The different risks associated with the burden of participating in this study are explained clearly and repeatedly. Furthermore, participation is

voluntary, and participants are given the opportunity to skip or stop a certain research activity without penalty. Moreover, crisis support hotlines (i.e., Lifeline, Beyond Blue) and contact details for the Principal Investigator and delegated medical officers are provided where appropriate.

If any of the risks result in harm to the participants, the event is recorded through the Woolcock Institute of Medical Research's standard procedures for adverse event documentation and reporting, and the sponsor will perform an analysis of these adverse events as per their standard procedures. Serious adverse events will also be reported to regulatory agencies as required.

As per the 2023 National Statement, risks are justified by the gains in knowledge, insight and understanding of the complex interplay between OSA and excess weight, and how weight loss can impact and modulate the severity of OSA and associated health outcomes relative to CPAP.

5.4. Audits

The study will not be externally audited. However, internal audits and quality control processes in accordance with the 'Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA Comments' are adhered to.

6. ETHICS AND DISSEMINATION

6.1. Research ethics approval

This protocol and informed consent forms will be reviewed and approved by the sponsor and the applicable ethical review bodies with respect to scientific content and compliance with applicable research and human subject regulations. Authorisation will be granted to commence recruiting to the study only when ethics approval, approved versions of the participant information and consent form, clinical trial registration and any clinical trial notification have been obtained.

6.2. Protocol amendments

If any important/significant protocol modifications or amendments are made, standard steps will be taken to gain approval from ethics for relevant documents and to re-consent affected participants with the new participant information form as applicable.

6.3. Patient protection

The responsible investigator/s will ensure that the study is completed in accordance with the guidelines set out in the National Statement on Ethical Conduct in Human Research (2007 – incorporating all updates) (the National Statement) and the CPMP/ICH Note for Guidance on Good Clinical Practice and any other relevant legislation/guidelines.

6.4. Consent

Delegated research staff will collect written informed consent from each participant before their participation in the study. Prior to this, research staff will contact interested and provisionally eligible participants to go through details of the study, i.e. objectives, benefits, risks and requirements of the study, with the participant. The participant will be provided with an information sheet and consent form prior to their first study appointment and

have ample time to discuss the details of the study with researchers and to decide whether to participate.

Only eligible adults providing written informed consent, according to the protocol approved by the local ethics committee, will be enrolled in the trial. Eligibility will be determined by the medical PI or delegate as per inclusion/exclusion criteria.

6.5. Post-study care

At the end of the study, participants may be notified of routine clinical care pathways, potential clinical trials, and research studies to further help with OSA management where needed. If, however, any harm is caused during this protocol or a medical condition becomes apparent, then medical follow-up will be arranged with either a member of the clinical research team or the participant's usual medical practitioner.

6.6. Confidentiality

Participant data will be identified by a code number that will be allocated after the participant gives consent to participate in the study. The key linking the participant's identity to the relevant code will be stored in a password encrypted file that will not be accessible from the internet. Storage of the data collected will adhere to the University regulations and the Australian Code for the Responsible Conduct of Research. De-identified data may also be available for the public. In any publication any/or presentation, information will be provided in such a way that participants cannot be identified, except with their written, informed permission. Any information obtained for the purpose of this research that could identify participants will be treated as confidential and securely stored.

6.7. Access to the data

The medical and scientific PI's will be the data custodians for this study. Only investigators and members of the study team will have access and control to any data collected from participants during this study. There are no contractual agreements that would limit access or control of the study to the investigators. Other WIMR-affiliated staff may also request access to the non-identifiable dataset, which will be considered by the principal investigator and co-investigators. A copy of the non-identifiable dataset may be requested by academic collaborators not affiliated with the WIMR through a data request form which outlines the investigators, aims and hypotheses, data to be included, a statistical analysis plan, ethics approval, and security measures. Data can be shared with the participant or their personal health care providers regarding any potential incidental findings upon request. However, all other experimental data cannot be shared with the participant.

6.8. Dissemination policy

Findings will be disseminated via conferences, publications and media, as applicable. In any publication or presentation, information will be provided in such a way that participants cannot be identified, except with their written, informed permission. Participants will be informed of the results of the study at the conclusion of the trial. Eligible authors of publications will follow the ICMJE Authorship Guidelines and will include investigators who provided substantial contribution to the conception and design of the study, or the acquisition, analysis, or interpretation of data for the work; AND drafting the work or revising it critically for important intellectual content; AND final approval of the version to be published. It is anticipated that there may be multiple publications stemming from this study, and primary and secondary outcomes may be published separately from exploratory

outcomes. The analysis of exploratory outcomes is expected to require more time due to their complexity. A formal publication plan will be developed and approved by the predefined investigators. Additionally, a consumer representative involved in the planning of the study will also contribute to the dissemination process to ensure that findings are communicated effectively to the broader community and that the perspectives of participants are considered in the dissemination strategy.

7. REFERENCES

1. Martinez-Garcia MA, Sanchez-de-la-Torre M, White DP, et al. Hypoxic Burden in Obstructive Sleep Apnea: Present and Future. Arch Bronconeumol. 2023;59(1):36-43.
2. Balk EM, Adam GP, Cao W, et al. Long-term effects on clinical event, mental health, and related outcomes of CPAP for obstructive sleep apnea: a systematic review. J Clin Sleep Med. 2024;20(6):895-909.
3. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. N Engl J Med. 2024;0(0).
4. Grunstein RR, Wadden TA, Chapman JL, et al. Giving weight to incretin-based pharmacotherapy for obesity-related sleep apnea: a revolution or a pipe dream? Sleep. 2023;46(10).
5. Ding F, Cotton-Clay A, Fava L, et al. Polysomnographic validation of an under-mattress monitoring device in estimating sleep architecture and obstructive sleep apnea in adults. Sleep Med. 2022;96:20-7.
6. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.
7. Weaver TE, Menno DM, Bron M, et al. Determination of thresholds for minimally important difference and clinically important response on the functional outcomes of sleep questionnaire short version in adults with narcolepsy or obstructive sleep apnea. Sleep & breathing = Schlaf & Atmung. 2021;25(3):1707-15.
8. Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the Functional Outcomes of Sleep Questionnaire. Sleep. 2009;32(7):915-9.
9. Pengo MF, Schwarz EI, Barbe F, et al. Effect of CPAP therapy on blood pressure in patients with obstructive sleep apnoea: a worldwide individual patient data meta-analysis. Eur Respir J. 2025;65(1):2400837.
10. Gamble C, Krishan A, Stocken D, et al. Guidelines for the content of statistical analysis plans in clinical trials. Jama. 2017;318(23):2337-43.