Study Title: Continuous Glucose Monitoring in OSA; A Randomised Continuous Positive Airway Pressure Withdrawal Trial

Internal Reference Number / Short title: Glucose Monitoring in OSA (GLUCOMOSA)

Ethics Ref: TBC

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Dexcom (IIS award)

Oxford Charitable Fund 0189

Chief Investigator Signature: 

There are no conflicts of interest to declare

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

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Sponsor	University of Oxford
Funder(s)	NIHR Oxford Biomedical Research centre (BRC4PP-09) Dexcom (IIS award) Oxford Charitable Fund 0189
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2. LAY SUMMARY

Type 2 diabetes mellitus (T2DM) is a long-term health problem in which uncontrolled blood sugar (glucose) levels cause serious health problems. Patients with "prediabetes" have slightly raised blood sugar levels and are at risk of developing T2DM. Up to half of patients with T2DM and "prediabetes" have obstructive sleep apnoea (OSA). OSA is a breathing condition that causes loud snoring and pauses in breathing during sleep. Patients with OSA are often sleepy in the daytime, have reduced quality of life and are at risk of road traffic collisions. Patients with OSA and T2DM or "prediabetes" have worse blood sugar control. It is not known whether OSA causes this worse blood sugar control in T2DM and "prediabetes". We surveyed over 500 patients with OSA. 95% of respondents thought that understanding if OSA worsens diabetes is important. We aim to determine the effect of treating OSA with CPAP on overnight blood sugar levels in patients who have OSA and also have T2DM or "prediabetes".

Continuous positive airway pressure or CPAP, is the main treatment for OSA. CPAP is delivered by a snug-fitting face mask, worn by patients during sleep, which connects to a bedside machine which blows air into the lungs to restore normal breathing overnight. One way of proving that OSA worsens blood glucose control in T2DM and "prediabetes" is by showing that CPAP improves blood glucose control. Previous studies looking to use CPAP to improve blood sugar control in patients with both OSA and T2DM or "prediabetes" have been inconclusive. This could be because only average blood sugar levels were assessed by measuring HbA_{1c}, which would not detect changes in overnight sugar levels when OSA is occurring. It also could be because the amount of CPAP used by patients in these previous studies was low.

We will overcome the problem of low CPAP use by inviting patients who are already good users of CPAP to participate. We will ask participants to briefly stop their CPAP and use sham CPAP instead for one week. We will also record blood sugar levels for one week when patients are using real CPAP. Stopping CPAP is

not a major concern as many patients stop their CPAP for 1-2 weeks, such as when they have a cold or when they are on holiday. In our survey, over 60% of respondents would be willing to consider briefly stopping CPAP for research purposes.

We will be able to look specifically at overnight blood glucose levels by using continuous glucose monitoring (CGM). CGM can measure blood sugar levels throughout the night for up to ten nights. CGM can comfortably be worn at home and allow patients to measure blood sugar levels whilst going about their daily lives.

We aim to show definitively that OSA causes worse blood sugar control in T2DM and "prediabetes". This is an important step to understanding if treating OSA might improve the long-term health of patients with OSA who have diabetes or "prediabetes".

3. SYNOPSIS

Study Title	**Continuous Glucose Monitoring in OSA; A Randomised Cross-over Continuous Positive Airway Pressure Withdrawal Trial**		
Internal ref. no. / short title	Glucose Monitoring in OSA (GLUCOMOSA)		
Study registration	TBC		
Sponsor	University of Oxford		
Funder	NIHR Oxford Biomedical Research centre (BRC4PP-09) Dexcom (IIS award) Oxford Charitable Fund 0189		
Study Design	Phase 2		
Study Participants	Randomised crossover controlled trial		
Sample Size	25		
Planned Study Period	Adult participants with OSA of moderate to severe severity and, either T2DM not on insulin therapy, or "prediabetes" (HbA_{1c} ≥6.0% and <6.5%) who have been effectively treated with CPAP for over 3 months with good compliance with therapy (mean >6 hours/night).		
Planned Recruitment period	01/08/2021 to 31/07/2023		
	Objectives	Outcome Measures	Timepoint(s)
Primary	The effect of one week of CPAP withdrawal versus continued CPAP on continuous interstitial glucose levels overnight	Continuous interstitial glucose measurements from 12 midnight to 7am overnight for each treatment arm	Nights 5, 6 and 7 of each arm

Secondary	The effect of one week of CPAP withdrawal versus continued CPAP on other derivatives from continuous nocturnal and 24-hour interstitial glucose levels, such as the mean glycaemic excursions	Continuous interstitial glucose measurements during 24 hours for each treatment arm	Days and nights 5, 6, 7 of each arm.
Exploratory	The effect of CPAP withdrawal on average glucose levels The effect of CPAP on withdrawal on cortisol levels The effect of one week of CPAP withdrawal versus continued CPAP on the overnight oximetry	Blood fructosamine levels Morning blood cortisol levels Overnight pulse oximetry from during sleep for each treatment arm	Follow-up visit each arm (Visits 2 and 4) Baseline and follow-up clinic visits (Visits 1-4) Nights 5, 6 and 7 of each arm.
Intervention(s)	CPAP withdrawal for 7 nights		
Comparator	Continued CPAP for 7 nights		

4. ABBREVIATIONS

AE	Adverse event
AHI	Apnoea Hypopnoea Index
AR	Adverse reaction
CGM	Continuous Glucose Monitor
CI	Chief Investigator
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials

CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DMP	Data Monitoring Plan
DSUR	Development Safety Update Report
EEG	Electro-encephalography
GCP	Good Clinical Practice
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
HbA1c	Glycated haemoglobin
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
ODI	Oxygen Desaturation Index
OSA	Obstructive sleep apnoea
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PSG	Polysomnography
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
T2DM	Type 2 Diabetes Mellitus

TSG	Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group

5. BACKGROUND AND RATIONALE

Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition of relative insulin deficiency caused by reduced beta cell function, often exacerbated by insulin resistance that leads to progressive hyperglycaemia. (1, 2) Almost 4 million people in the UK have been diagnosed with diabetes mellitus, and 90% of these patients will have T2DM (3). T2DM causes significant complications including ischaemic heart disease, stroke, nephropathy, neuropathy and retinopathy, which are promoted by hyperglycaemia (4). Long-term glycaemic control can be measured by a blood test measuring the amount of glycated haemoglobin (HbA_{1c}) (5). HbA_{1c} reflects the average glycaemic state over approximately the last 8 to 12 weeks (6) but may not be sensitive to short-term rises that could occur during OSA. HbA_{1c} is used in the long-term monitoring of patients with T2DM (7).

Tighter glycaemic control reduces diabetic complications, with the UK Prospective Diabetes Study (UKPDS) showing a 21% relative risk reduction for a composite endpoint of any diabetic complications for each 1% reduction in the HbA_{1c} (8). Following on from this, large randomised control trials targeting stricter glycaemic control versus standard glycaemic control have shown a reduction in diabetic complications (9, 10). There may also be downsides to targeting strict glycaemic control, especially in frail patients. One large RCT was stopped early due to excess all-cause mortality in the stricter glucose control group, which remain unexplained. There was also no difference in the primary outcome of cardiovascular and cerebrovascular complications (11). Nevertheless, data from these studies shows that improving glycaemic control can lead to improvements in outcomes such as diabetic complications and cardiovascular disease.

"Prediabetes"

"Prediabetes" is a term that encompasses several different measures of dysglycaemia in which subjects at increased risk for T2DM either have elevated fasting blood glucose levels or impaired glucose tolerance, but do not meet the criteria for diabetes. *Figure 1* outlines the criteria for diagnosing "prediabetes" and diabetes. Patients with "prediabetes" have a 3 to 10 fold increased risk of developing diabetes and have features of diabetic complications (12). Identifying "prediabetes" is important as it presents an opportunity to reduce the risk of developing diabetes, primarily through lifestyle modification and weight loss (13).

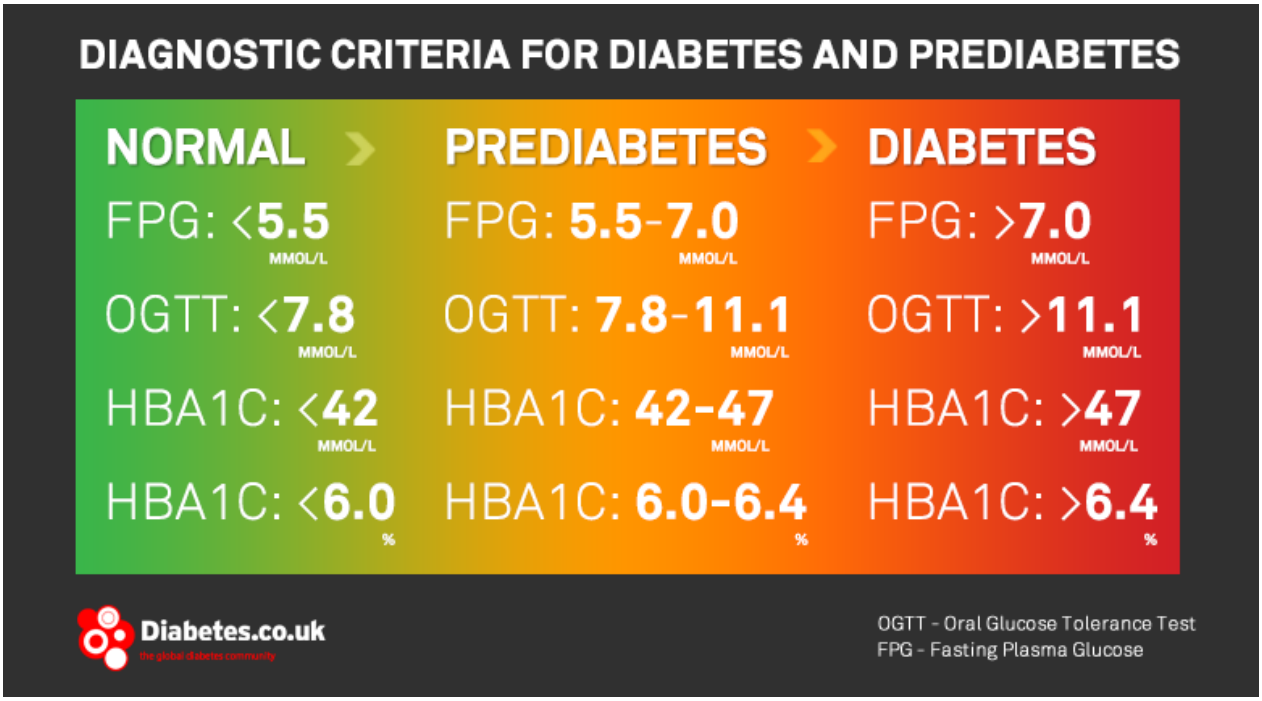


*Figure 1: Diagnostic criteria for normal, "prediabetes" and diabetes based on blood glucose levels. Diagnosis of diabetes either requires one of these criteria and diabetic symptoms or repeat elevated measurement on a separate occasion (*https://www.diabetes.co.uk/pre-diabetes.html*).*

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a common condition affecting 15-75% of the adult population, depending on the exact definition and population under study (14, 15). OSA is characterised by episodic upper airway occlusion during sleep, loud habitual snoring and awakenings during the night. Obstructive events in OSA lead on to intermittent hypoxia, increasing respiratory drive to breath causing large swings in intra-thoracic pressure, and recurrent arousals from sleep. OSA causes daytime sleepiness, reduces quality of life, and increases road traffic collisions (16-18). The presence of OSA on a sleep study, together with the typical symptoms of OSA, is often termed obstructive apnoea syndrome (OSAS). OSAS affects approximately 4% of the adult population (14).

In addition, OSA is associated with cardiovascular and metabolic complications (19, 20). The pathophysiological mechanisms underpinning this association between OSA and increased cardiovascular risk are not clear. Intermittent hypoxia, recurrent arousals, and intrathoracic pressure swings have downstream effects inducing sympathetic activation, sheer stress on blood vessels, and potentially inducing oxidative stress and pro-inflammatory changes which could lead to cardiovascular disease (21, 22).

OSA is usually diagnosed by an overnight sleep study. This involves either limited channel polygraphy, recording breathing and oxygen levels during sleep at home, or full polysomnography (PSG), typically requiring an overnight stay in hospital where sleep is also recorded using electro-encephalography (EEG). Polygraphy and polysomnography aim to record the number of obstructive events and the number of oxygen desaturations per hour in bed/asleep overnight. Commonly this gives two indices; the apnoea-

hypopnoea index (AHI) and the oxygen desaturation index (ODI). An AHI (or ODI) of <5/hour is considered normal, of 5-15/hour is consider to represent mild OSA, of 15-30/hour is considered to represent moderate OSA, and of >30/hour is considered to represent severe OSA (23). The additional presence of symptoms of daytime sleepiness, is required for the diagnosis of obstructive sleep apnoea syndrome (OSAS) (24).

OSA and T2DM

Epidemiological studies have shown a clear relationship between OSA and T2DM. Studies of GP databases estimate that T2DM almost doubles the incidence of OSA, the annualised incidence of OSA was 0.48% in non-diabetic and 0.88% in diabetic patients(25). The prevalence of OSA in patients with T2DM undergoing PSG are probably more helpful, with between 58-87% of patients with T2DM having an AHI of ≥5/hour on PSG (26-29). Using a slightly higher threshold for diagnosing OSA, an ODI >10 /hour, overnight oximetry estimated ~17% of patients with T2DM had OSA, compared to 6% of the general population (30). Conversely, 30% of newly diagnosed OSA patients also have T2DM (31), and non-diabetic patients with OSA have increased insulin resistance compared to healthy controls (32, 33). In non-diabetic patients the severity of OSA predicts HbA1c levels, after adjustments for likely confounders (34).

Given that the severity of OSA is predictive of HbA1c levels, it is important to understand whether OSA worsens glycaemic control, and perhaps more important to understand if treating OSA can improve glycaemic control.

Traditional clinical trials looking at OSA and glycaemic control

A systemic review of mainly uncontrolled longitudinal cohort studies has shown that compliance with CPAP therapy is associated with better glycaemic outcomes (35). However, these studies are susceptible to bias as patients who comply with CPAP therapy are likely to be inherently different to those who do not. Randomised control trials (RCTs) are helpful in potentially providing cause and effect data, not possible in uncontrolled cohort studies.

An early RCT of patients with OSA (ODI >10 and daytime sleepiness defined as an Epworth sleepiness score (ESS) of ≥9) assessed the effect of three months of CPAP versus sham CPAP on glycaemic control in 42 patients with T2DM and OSA (36). The primary outcome measure was the HbA1c and the study included a number of other outcome measures looking at insulin resistance and insulin sensitivity (HOMA and euglycaemic hyperinsulinaemic clamp). This study showed no significant between groups difference in HbA1c levels or any of its secondary outcome measures. However, the lack of any effect may have been due to low average hours of treatment usage, with 3.6 h/night usage in the CPAP group. Other early RCTs showed mixed results with CPAP not changing in insulin sensitivity or fasting glucose levels in non-diabetic patients with OSA (37, 38), improving insulin sensitivity only in non-diabetic patients with OSA (39), not changing fasting glucose levels in a mixture of diabetic and non-diabetic patients (40), not changing insulin sensitivity during 14 nights of CPAP withdrawal (41), and improving insulin sensitivity in pre-diabetic patients (42). Meta-analyses of the effect of CPAP showed improvements in HOMA, as a marker of insulin resistance, in non-diabetic patients (43), and improved insulin sensitivity, but not improved HbA1c in diabetic patients (44). Treating OSA has been shown to improve insulin resistance in non-diabetic and prediabetic patients (43, 45).

More recently two further RCTs have been published assessing the effects of CPAP therapy on HbA1c levels (46, 47). The larger GLYCOSA study looked at the effect of CPAP versus standard care on HbA1c levels in

298 patients with T2DM, HbA1c levels between 6.5-8.5% and OSA over 6 months of follow-up. They showed no difference in HbA1c levels between the groups. Again this study has been criticised for sub-optimal hours of usage of CPAP at 4.9 h/night. At the same time a smaller Spanish study was published which showed that 6 months of CPAP versus standard care improved HbA1c levels by 0.4% (95% confidence interval 0.04% to 0.7%). They included patients with an HbA1c of greater than 6.5% but, unlike the Australian study, did not exclude patients with particularly high HbA1c levels.

Continuous glucose monitoring

Continuous glucose monitoring (CGM) systems are now available as an adjunctive tool for patients to help with monitoring glycaemic control. They consist of a sensor with of a small needle, usually the width of a small hair attached to a patch that it inserted under the skin on the upper arm or the abdomen. Sensors measure interstitial glucose and not blood/plasma glucose levels, and can be worn for between 7-14 days, depending on the device. A transmitter is then connected to the sensor and this is connected wirelessly to a receiver or smart phone. This enables the user to have readouts of glucose levels normally every 5 minutes throughout the day and the night. Devices are either "flash" devices that require manual activation to send data to the receiver, and then only transmit the last 8 hours data such as the FreeStyle Libre™ , or true continuous glucose monitors such as the Dexcom G6 Platinum and Guardian REAL-Time devices.

A Cochrane review showed that the use of CGM can improve HbA_{1c} levels in patients with type 1 diabetes mellitus (T1DM) but leads to increased hypoglycaemia when used to direct insulin pump therapy, compared to standard glucose monitoring (48). This has led to NICE recommending their use for a limited number of patients with T1DM, including those with hypoglycaemic difficulties and those with an elevated HbA_{1c} despite frequent monitoring (49). CGM does have drawbacks, particularly with accuracy of their recordings. CGMs do not measure blood or plasma glucose levels, instead they measure interstitial fluid glucose levels. Whilst interstitial glucose levels are closely related to blood and plasma glucose levels they are probably less accurate than standard blood glucose monitoring and gold-standard laboratory glucose measurements, with mean absolute relative differences of between 10-12% for both "flash" and "true" CGM devices (50-53). The differences in measurement however, have little impact on clinical outcome with 85-87% of results leading to the same clinical management and 99% of results leading to the same clinical outcome with CGM, compared to standard glucose monitoring (50, 51). There is a lag-time of 4.5 ± 4.8 minutes for changes in blood glucose levels to be reflected in changes in interstitial CGM readings. Despite, CGM being slightly less accurate than blood glucose monitoring the ability to continuously monitor glucose levels overnight without admission to hospital means this is an ideal way to monitor the effects of OSA on glycaemic control. In addition, 98.6% of patients found the pain of CGM as acceptable or better than standard glucose monitoring (50). The device we intend to use – the Dexcom G6 – has a 10 day sensor life, with 87% of monitors surviving to 10 days (53).

Continuous glucose monitoring enables monitoring of the variability of glucose levels, in addition to assessing average overnight glucose levels. Glucose variability is predictive of macrovascular and microvascular complications of T2DM (54). The mean amplitude of glycaemic excursions (MAGE) is measure that captures the variability of glucose levels. MAGE is associated with secondary cardiovascular events, in those with endothelial dysfunction (55), and in diabetic and non-diabetic patients (56-58). MAGE predicts progression of atherosclerosis (59), vessel healing following coronary artery stenting (60) and is inversely related to baroreflex sensitivity (61). One theory as to why MAGE may be important is that

methylglyoxal, which is generated as a breakdown product of the glycolytic pathway, is correlated to glycaemic excursions and is thought to cause oxidative stress. The night-time mean amplitude of glycaemic excursions (NMAGE) is likely to be affected by OSA. In non-randomised studies OSA is associated with elevations in MAGE, NMAGE and the nocturnal coefficient of variation (CV) of glucose levels in diabetic and non-diabetic patients (62), elevations in MAGE in non-diabetic but not diabetic patients (63), and CPAP has been shown to improve MAGE in patients with DM and sleep-disordered breathing (64). To date the effect of OSA and CPAP on MAGE, NMAGE and CV of glucose levels has not been reported in randomised trials.

CPAP withdrawal as model to determine the physiological and metabolic effects of OSA

CPAP withdrawal is an experimental way of modelling the short-term consequences of OSA, pioneered by Professors Kohler and Stradling. CPAP withdrawal can be used to assess the physiological effects of OSA without the confounding effects seen in cohort studies or the issues of low CPAP usage in conventional RCTs. CPAP withdrawal trials with a cross-over design have even better control of confounders than parallel CPAP withdrawal studies and require a smaller sample size. Patients with known OSA who have been established on CPAP with high compliance, typically for at least 3 months, are randomised to 2 weeks of sham CPAP (with return of significant OSA) or continued therapeutic CPAP (control group). This model produces a significant return of OSA, with a between groups difference in AHI of +33.4/ hour (95% confidence interval +22.3 to +44.5), and with an associated return of sleepiness with a between groups rise of 2.6 points in ESS (95% confidence interval 1.1 to 4.3) (41). During CPAP withdrawal there is a 9 mmHg rise in systolic, and 7.8 mmHg rise in diastolic home morning blood pressure (65), increased sympathetic activity with increased urinary normetanephrine and impaired endothelial function (41). Using supplemental oxygen or sham during CPAP withdrawal has demonstrated that intermittent hypoxia is the dominant cause of increase morning blood pressure in OSA, rather than arousals (66). The impact of OSA on systemic oxidative stress during CPAP withdrawal is less clear. Traditional blood and urine biomarkers of oxidative stress are not increased by CPAP withdrawal (67, 68), but novel sophisticated analysis of exhaled breath shows an increase in compounds associated with oxidative stress with CPAP withdrawal (69). Physiological changes with CPAP withdrawal are also tissue specific as – in contrast to the deleterious effects on brachial artery endothelial function (41) – vascular effects have not been demonstrated elsewhere; with no change in measures of myocardial function, renal microvasculature function and dermal microvascular function (70), and no change in measures cerebrovascular endothelial function (71).

Traditional RCTs examining the effects of CPAP on glycaemic control have been criticised for the low average nightly CPAP usage, with the largest study having an average nightly usage of 4.9 hours/night (46). Whilst this is a common criticism of many RCTs of CPAP as a therapy (72), it may be particularly important when assessing glycaemic control as an outcome. The severity of OSA in rapid eye-movement (REM) sleep is correlated with HbA1c levels and in contrast the severity of non-rapid eye movement sleep (NREM) OSA is not (73). REM sleep tends to predominate in the second half of the night, and the authors argue that low average CPAP usage in previous RCTs would leave patients vulnerable to significant REM OSA in the second half of the night. This assumes that the average 4.9 hours/night in previous RCTs represented CPAP usage mainly in the first half of the night and did not represent intermittent CPAP usage throughout the night or nights where CPAP was used all night mixed with others where CPAP was not used at all. Nevertheless, the low usage of CPAP and mixed results of previous trials means that it is not known whether all night CPAP usage might improve glycaemic control.

Others have used similar short-term CPAP withdrawal protocols to demonstrate changes in glycaemic control both in patients without diabetes, and patients with T2DM not on insulin (74). They conducted randomised cross-over trial of three nights CPAP withdrawal versus continued CPAP. They conducted a full in-lab polysomnography (PSG) on the 3rd night of CPAP withdrawal and compared this to an on CPAP PSG night. They looked at blood glucose levels drawn from a venous catheter at regular intervals throughout the night. They found that CPAP withdrawal increased overnight glucose levels by 5.57 mg/dl (95% confidence interval or CI 0.59, 10.55, p=0.028). In a subgroup analysis they showed that this effect was only in the diabetic patients, with CPAP withdrawal increasing blood glucose levels by 17.2mg/dl in diabetic participants (95% CI 0.13, 34.6, p=0.04). It is worth noting that this was not a pre-planned subgroup analysis and that only 7 of 31 patients were diabetic. Other hospital based studies have explored the effect of CPAP on blood glucose control, with one randomised control trial enrolling patients with OSA and "prediabetes" and admitting them to hospital for two-weeks (75). Patients were randomised to either 8 hours per night of CPAP or oral placebo on a 2:1 basis and had attended PSG every night with CPAP adherence ensured by continual supervision. They then assessed the glucose response curve following an oral glucose tolerance test (OGTT) in the morning. They showed small improvements in the glucose response curve and in insulin sensitivity.

These studies suggest that treating OSA with CPAP can improve aspects of glycaemic control (74, 75) but they have their limitations. First, Chopra *et al.* (74), only studied patients after 3 nights of CPAP withdrawal, which may be an insufficient period of time for OSA to effect of glycaemic control. In addition, it only included seven diabetic patients and made no assessment of whether other patients were prediabetic. Second, Pamidi *et al.* (75), only looked at morning glucose levels following glucose tolerance tests and did not explore the overnight period that is of most interest. A separate uncontrolled trial has shown that 7 days of CPAP therapy supervised for 8 hours/ night showed a 13.5±13.5 mg/dl improvement in 24 hour blood glucose levels (76). All of these studies are removed from normal clinical care in admitting patients to hospital for between 3 and 14 nights. In addition, these studies included a heterogeneous group of patients with T2DM, "prediabetes" or no diabetes. There is a therefore a need to understand the effects of CPAP on glycaemic control outside of the setting of hospital with careful description of diabetes/prediabetes. In this study we aim to use CPAP withdrawal to assess the effects of OSA on 24-hour glycaemic control over a period of one week in patients with known OSA and diabetes/prediabetes.

Patient involvement in shaping this research

This research has been directly informed from recognising the priorities of patients. We surveyed patients with OSA from the membership of the Sleep Apnoea Trust Association, a patient led OSA support group. We received 585 responses to our survey of their membership. 566 (97%) of the respondents agreed that "research to help understand if OSA causes of worsens diabetes is important". 377 (64%) of respondents would be likely to "consider stopping CPAP for 10-14 days for a research study to enable better understanding of the effects of OSA" (See *Figure 2*).

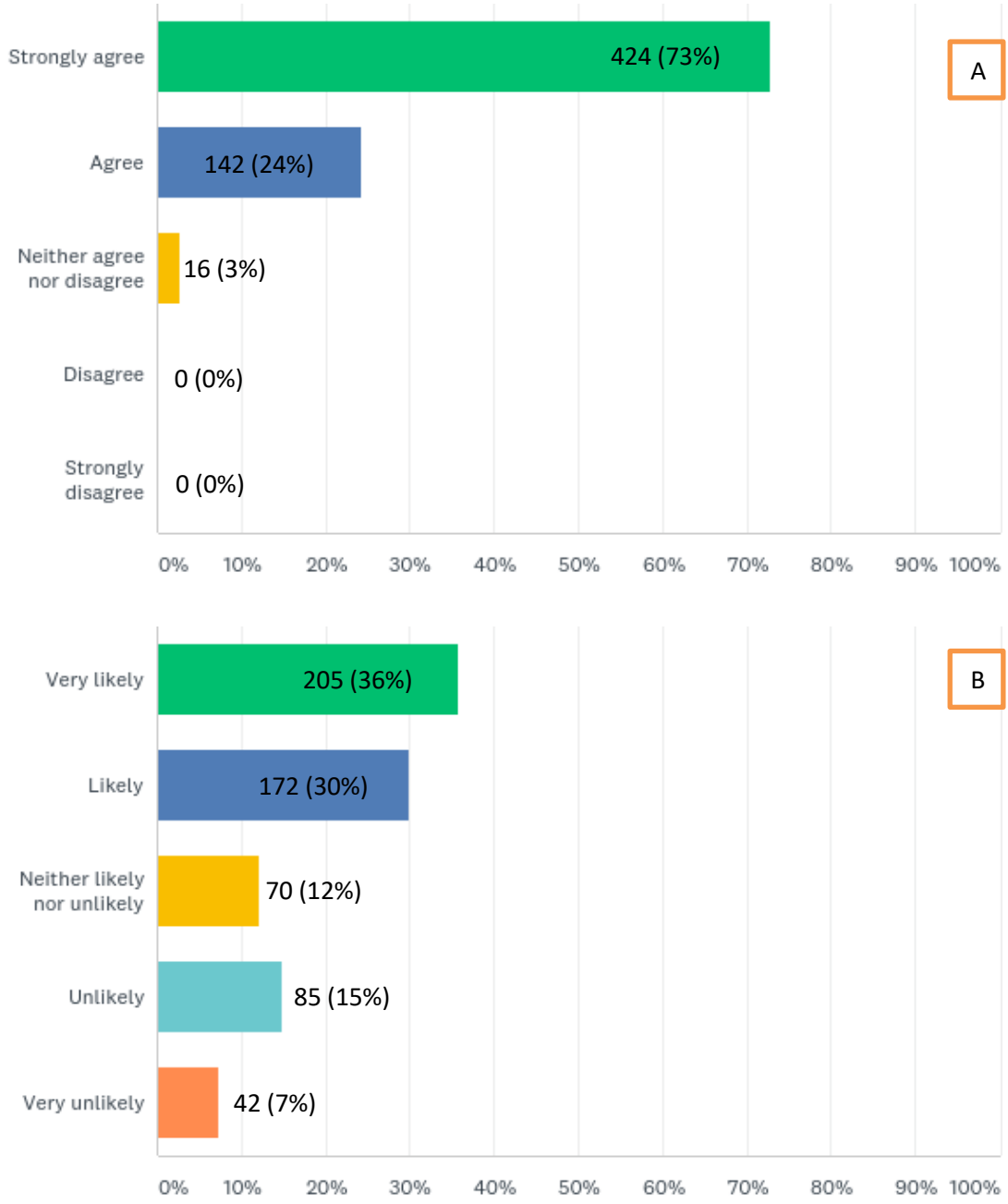


Figure 2: A) Results of response to the statement "research to help understand if OSA causes or worsens diabetes is important. B) Results of response to the question "how likely would it be that you would consider stopping CPAP for 10-14 days for a research study to enable better understanding of the effects of OSA".

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)

Primary Objective The effect of one week of CPAP withdrawal versus continued CPAP on continuous interstitial glucose levels overnight	Continuous interstitial glucose measurements from 12 midnight to 7am overnight for each treatment arm	Nights 5, 6, 7 of each arm.
Secondary Objectives The effect of one week of CPAP withdrawal versus continued CPAP on other derivatives from continuous nocturnal and 24-hour interstitial glucose levels, such as the mean glycaemic excursions	Continuous interstitial glucose measurements during 24 hours for each treatment arm	Days and nights 5, 6, 7 of each arm.
Exploratory objectives		
The effect of CPAP withdrawal on average glucose levels	Blood fructosamine levels	Follow-up visit each arm
The effect of CPAP on withdrawal on cortisol levels	Morning blood cortisol levels	Baseline and follow-up clinic visits
The effect of one week of CPAP withdrawal versus continued CPAP on the overnight oximetry	Overnight pulse oximetry from during sleep for each treatment arm	Nights 5, 6 and 7 of each arm.

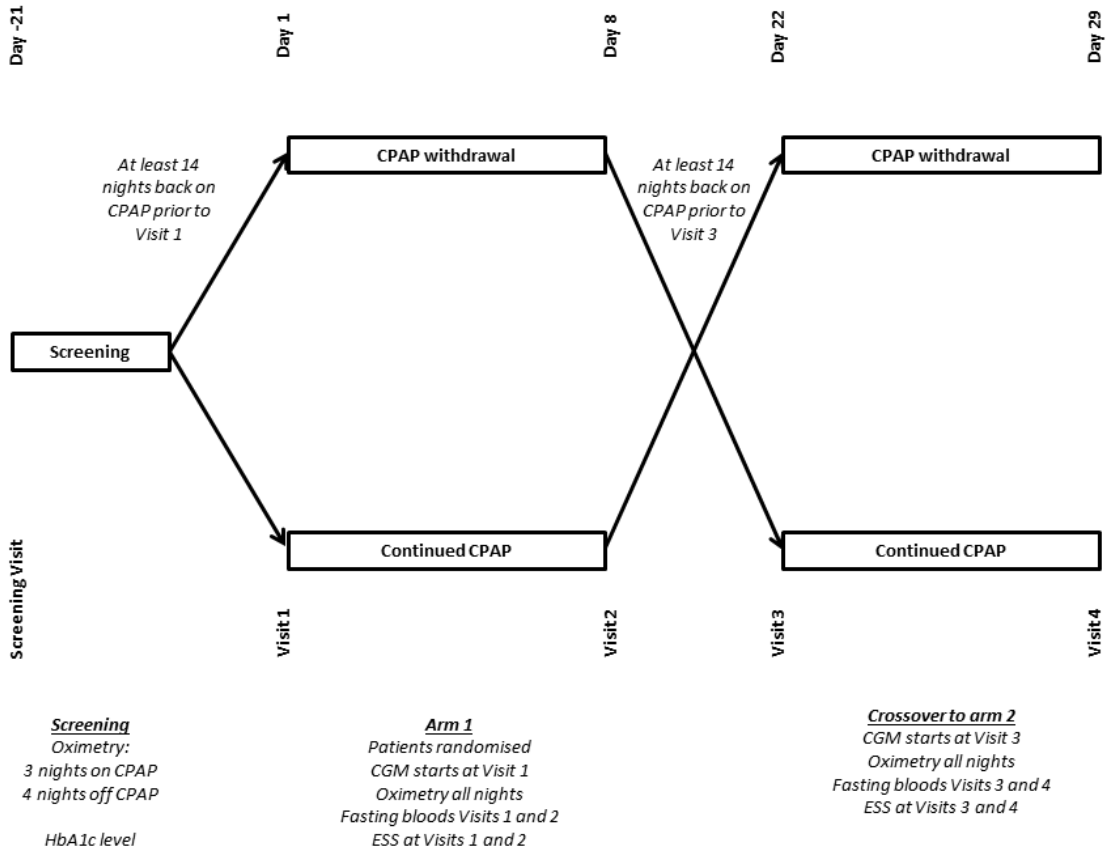
7. STUDY DESIGN

The study is a single tertiary-centre, crossover, randomised controlled trial to evaluate the effects of CPAP withdrawal versus continued CPAP on overnight interstitial glucose levels and other measures of cardiovascular risk, OSA severity, and daytime symptoms in patients with CPAP-treated obstructive sleep apnoea and T2DM (not on insulin therapy) or “prediabetes”, following withdrawal of CPAP for 7 days.

Data will be collected using a continuous glucose monitor which is a semi-invasive way of monitoring interstitial glucose levels at home over the whole of the day and night up to a maximum period of 10 days. This method of monitoring glucose levels has been chosen because it allows monitoring of overnight glucose levels in a “real-world” setting. Alternative means of monitoring overnight glucose levels would

require hospital admission, intravenous cannulation and frequent blood draws during sleep. In addition, overnight oximetry will be measured at home along with other markers of cardiovascular disease. A blood test will be taken at the screening visit to screen for the presence of undiagnosed diabetes. Further blood tests will be taken at visits 1, 2, 3 and 4 to measure fasting glucose and insulin levels to establish if CPAP withdrawal affects these measures. Subjective sleepiness will be recorded by a questionnaire at screening and visits 1, 2, 3, and 4.

The trial consists of a consent visit which will also be the screening visit, a randomisation visit which also forms the first study visit (visit 1) and three subsequent trial visits following randomisation (visits 2, 3, and 4). Screening consists of one week of pulse oximetry while on CPAP for 3 nights and off CPAP for 4 nights. Following screening, there will be at least 14 days, and no more than 12 weeks, back on CPAP prior to the randomisation visit. Following the randomisation visit participants will then use either sham CPAP or continued therapeutic CPAP for 7 days. They will be placed back onto their own CPAP for at least 14 nights before crossing over. There will be four study visits within 18 weeks of the start of screening. Details of the study visits are shown below in the study flow diagram:



Study flow diagram. CGM=Continuous glucose monitoring, CPAP=continuous positive airway pressure, ESS=Epworth sleepiness score,

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Adult participants with OSA of moderate to severe severity and either T2DM not on insulin therapy or "prediabetes" who have been effectively treated with CPAP for over 3 months with good compliance with therapy (mean >6 hours/night).

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Male or Female, aged 18 years or above.
- Objectively confirmed obstructive sleep apnoea (at the time of original diagnosis) with an oxygen desaturation index (ODI ≥4% dips) of >20/h or/and an apnoea/hypopnoea index of >20/hour (this threshold will exclude subjects with borderline OSA, in whom there may be little treatment effect).
- Type 2 diabetes mellitus or HbA1c ≥6.0% (42mmol/l) at screening visit.
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.
- Currently >20/h oxygen desaturations (≥4% dips) returning on any night during a screening period of ambulatory nocturnal pulse oximetry performed during a 4-night period without CPAP.
- Treated with CPAP for more than 3 months, minimum compliance 6h per night, where available an AHI <10 with treatment (according to machine download data), and ODI < 10 confirmed on CPAP during screening oximetry.

8.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Diabetes mellitus requiring treatment with regular insulin therapy.
- Previous ventilatory failure (awake resting arterial oxygen saturation <93% or known arterial PCO_2 > 6kPa) or severe respiratory disorders other than OSA.
- Unstable, untreated coronary or peripheral artery disease, severe arterial hypertension (>180/110mmHg), severe arterial hypotension (<90/60mmHg).
- Poorly controlled diabetes with HbA1c ≥10.0% (86mmol/mol).
- Unstable diabetic retinopathy requiring or currently undergoing specialist treatment.
- Previously diagnosed with Cheyne-Stokes breathing.
- Current professional driver or vigilance critical occupation.
- Any sleep-related accident.
- Mental or physical disability precluding informed consent or compliance with the protocol.
- Non-feasible trial follow-up (for example, distance from follow-up centre, physical inability).

9. PROTOCOL PROCEDURES

Procedures	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Daily during trial
Informed consent	X					
Demographics	X					
Medical history	X					
Fasting blood glucose (8 hours)		X	X	X	X	
HbA1c level	X					
CPAP download	X		X		X	
Eligibility assessment (includes 7 nights of pulse oximetry)	X	X				
Continuous glucose monitoring		X[a]				X
Randomisation		X				
Laboratory tests (blood)		X	X	X	X	
Clinic blood pressure and heart rate		X	X	X	X	
ESS (questionnaire)	X	X	X	X	X	
Overnight Pulse oximetry*	X					X

a) continuous glucose monitor supplied and fitted at visits 1 and 3. This will then continually record throughout the trial until it is collected at visits 2 and 4.

* every night during the trial starting the night after visit 1 (not including washout)

9.1. Recruitment

Participants will be recruited from database records of patients with OSA treated with CPAP at the Oxford Centre for Respiratory Medicine and from patients attending routine clinical appointments with the Oxford Centre for Respiratory Medicine.

Potential participants will be identified for trial enrolment according to the eligibility and ineligibility criteria outlined by members of the clinical team. Participants will be contacted by letter sent by a member of the clinical team on behalf of the research team. A Patient Information Sheet and Consent Form will be enclosed for patients to read at home. Patients will have an option to send off a reply slip or email/phone the study team to confirm they wish to or do not wish to be contacted by the research team. If no response is received within three weeks, the letter will be followed up by a phone call from the clinical team. Patients interested in taking part in the trial will be invited for a screening/enrolment visit.

In addition, patients enrolled in the Oxford Respiratory Research Register who had consented to being approached directly about future research trials will be directly approached by the research team, initially by invitation letter as outlined above.

9.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site.

9.3. Screening and Eligibility Assessment

Potentially eligible participants that are interested will be invited to meet with the research team on a screening visit. Exclusion and inclusion criteria will be reviewed and informed consent will be obtained prior to any trial specific procedures as described above. Participants will then undergo ambulatory nocturnal pulse oximetry for 7 nights. The first three nights are carried out on the participants' normal CPAP therapy to confirm adequate control with an ODI < 10 events/ hour. The participant is then taken off CPAP therapy for 4 nights with oximetry monitoring on all four nights. A return of > 20/h oxygen desaturations (≥4% dips) on any of the 4 nights confirms that sufficiently severe OSA has returned to satisfy the entry criteria. Manual editing for clear awake periods or clear periods of artefact will be allowed at the discretion of the investigator.

The initial phase of the study where CPAP is withdrawn for 4 nights provides additional interesting data, as not all patients do experience a return of OSA in that time period. Those that do not experience a return

of OSA do not enter the main study, however this data will be retained to try and understand why some patients relapse quickly on withdrawal and others do not.

At the screening visit, participants will have a blood test to measure HbA1c levels to confirm eligibility (HbA1c ≥6.0% (42mmol/l) at screening visit). This procedure is described in more detail later. Participants will not need to be fasted prior to this assessment. Participants will be contacted by telephone prior to stopping their CPAP therapy if they are not eligible on the basis of their HbA1c. Data from the first three nights of oximetry recordings on CPAP will provide useful clinical data ensuring they are on the correct CPAP settings. Data from these recordings will be passed on to the clinical team for onwards clinical care.

Following the screening week eligible participants resume their CPAP therapy for at least 14 days and no more than 12 weeks prior to randomisation. Participants eligible for entry into the study will then be contacted by the research team to arrange randomisation and subsequent study visits.

In addition, participants' demographic, past medical history, medications and eligibility criteria will be assessed. Participant's height, weight and neck circumference will be recorded. Data from participants' own CPAP machine will be downloaded to ensure an average use of CPAP of >6 hours/night over all days in the last 30 days prior to the screening visit.

Rescreening will be allowable only for participants in whom there is a technical failure in a screening procedure or participants with an on-CPAP ODI of >10 events/hour on any of three nights. In the case of a technical failure, there are no time constraints for when rescreening can be repeated. In the case of an ODI > 10 events/hour rescreening can be repeated following adjustments to participants' CPAP therapy and at least 14 nights on this adjusted CPAP therapy. Only assessments with technical failure will be repeated (e.g. overnight pulse oximetry or HbA1c measurements) and a maximum of two rescreening attempts will be allowed.

9.4. Randomisation

Randomisation of treatment order will be performed using "Sealed Envelope" (http://www.sealedenvelope.com/). As this is a cross-over study randomisation will be simple and not minimised or stratified.

9.5. Blinding and code-breaking

This is a single blinded trial so the investigator will be aware of the blinding and can unblind the participant if required. The researcher will not be blinded as they will need to set-up and supply either the sham-CPAP or CPAP. Out of hours unblinding will not be required due to the low risk of the intervention of CPAP withdrawal. Patients are sometimes aware that the sub-therapeutic CPAP is not as effective as their usual, so are not truly blind. However, the measurements in this study are all objective rather than subjective. This has been the case in previous CPAP withdrawal studies.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

CPAP therapy/CPAP withdrawal

All subjects will have been using CPAP for more than three months and will be familiar with it. They will continue to use their usual CPAP mask for the duration of the study but will swap to a ResMed S9 or S10 autoCPAP machine which is essentially no different, but is able to record nightly compliance, mask leak and residual apnoeas accurately. Sub-therapeutic CPAP will be delivered as in all our previous studies (41, 67, 69-71). The CPAP is rendered sub-therapeutic by first setting it to the lowest pressure possible (4cms H_2O), and the pressure lowered still further (to 1cm H_2O) using extra blow-off holes in the mask tubing at the patient end (which also ensures full blow off of exhaled CO_2). The machine is restrained from trying to compensate for this extra leak with a 5mm restriction introduced at the machine end of the tubing.

9.6.1. Description of study procedure(s)

Bloods

Participants will have blood samples taken at the screening visits and visits 1, 2, 3 and 4. These will be performed using sterile technique using standard venepuncture technique. Samples will be analysed as detailed below.

Continuous glucose monitoring

At visits 1 and 3 participants will have continuous glucose monitoring supplied and established (G6 sensor and transmitter, Dexcom). They consist of a sensor with of a small needle, usually the width of a small hair attached to a patch that is inserted under the skin on the upper arm or the abdomen. The researcher will fit the participant with the sensor using a one-touch applicator to insert a small sensor just beneath the skin, either sited on the upper arm or the abdomen (participant's preference). This will be performed as per the manufacturers standard operating procedures. The device will then continuously record glucose levels. This device will then be worn for seven days until it is removed at visit 2. The device is water resistant meaning that participants will be able to shower but not swim or bathe during the trial.

9.7. Baseline Assessments

Participants will attend for Visit 1 at least 14 days and no more than 12 weeks from their screening visit. Eligibility criteria will be checked including screening oximetry and HbA1c levels.

Participants will need to have fasted for 8 hours prior to this visit.

First, participants will have their office blood pressure and heart rate recorded in triplicate following at least 5 minutes of rest in a seated position from their left arm. At least one minute will be allowed between each blood pressure measurement.

Second, participants will have blood tests taken, totalling a maximum of 35ml (around two tablespoonsful). These will be sent for glucose levels, insulin levels, full blood count, urea, creatinine and electrolytes, lipid profile and for plasma/serum storage for markers of cardiovascular disease.

Participants will be requested to complete an Epworth sleepiness score, an eight-point questionnaire.

At Visit 1 the researcher will supply the participant with a continuous glucose monitor (Dexcom G6®) sensor and transmitter as described in the procedures section. Participants will have this process repeated at Visit 3 after crossing over.

At Visit 1 participants will be supplied with pulse oximetry (Minolta 300i). Every night, oxygen saturation measurements (and pulse rate rises) will be performed at home using this simple overnight pulse oximeter. Participants will have this process repeated at Visit 3 after crossing over.

Data from participants' CPAP machine will be downloaded for an average use of CPAP over all days in the last 14 days prior to the visit. This will not be assessed as an eligibility criterion as this will have already been assessed at the screening visit (see section 9.3).

Eligibility criteria will be checked prior to randomisation. Participants will then be supplied with a new CPAP machine, either therapeutic or sham. The participant's own CPAP machine will be collected and securely stored until Visit 2.

9.8. Subsequent Visits

The assessments at these visits will be identical to the baseline assessments at Visit 1 described in Section 9.6 aside from the following assessments.

Participants will attend Visit 2 seven days after Visit 1, and Visit 4 seven days after Visit 3. Following Visit 2 participants will return to using their own CPAP machine for at least 14 days prior to returning for Visit 3.

CGM and oximetry data will be downloaded at visits 2 and 4. At Visit 3 participants will be supplied with a continuous glucose monitor (Dexcom G6®) as described in Section 9.6.

Data from participants CPAP machine will be downloaded for an average use of CPAP over all intervention days at Visits 2 and 4. At visit 3 data from participants' CPAP machine will be downloaded for an average use of CPAP over all days in the last 14 days prior to visit. This will not be assessed as an eligibility criterion as this will have already been assessed at the screening visit.

At visits 2 and 4 participants will have their own CPAP machine returned and will be instructed to restart using this from the night following this visit. At Visit 3 participants will then be supplied with a new CPAP machine, either therapeutic or sham. The participant's own CPAP machine will be collected and securely stored until Visit 4.

At the end of study visit 4 the participants will be asked to return all study equipment and participants' involvement in the study will end.

9.8.1. COVID-19 alterations

All visits, including the screening visit and visits 1-4, require face-to-face appointments given the requirement for blood tests at all time points. Face-to-face visits will be conducted in line with the latest government advice and the latest hospital infection control procedures including but not limited to the use of hand hygiene, face masks, and personal protective equipment. Should face-to-face hospital visits not be possible, home face-to-face visits will be considered providing this is in line with the latest government advice.

9.9. Sample Handling

9.9.1. Sample handling for trial purposes

Participants will have blood drawn at their screening visit. This will involve a 5ml (one teaspoonful) blood sample for HbA1c level which will be analysed in the OUH NHS Trust laboratory and destroyed once the sample has been analysed. At visits 1, 2, 3 and 4 participants will have further blood tests taking a maximum of 35ml (around two tablespoonsful) of blood on each occasion. Some of these will be sent to the OUH NHS Trust laboratory for glucose levels, insulin levels, fructosamine levels, full blood count, lipid profile, urea, creatinine and electrolytes. Samples handled by the NHS laboratory will be disposed of after analysis. In addition, plasma and serum will be spun in ORTU's research lab and stored as described below.

9.9.2. Sample handling for long term storage

Plasma and serum samples will be collected at visits 1, 2, 3, and 4. These will be spun, and plasma/serum will be aliquoted for storage in a -80^{o}C freezer. These samples will be stored long-term for use in future ethically approved studies. Consent for this long term sample storage will be sought from participants.

9.10. Early Discontinuation/Withdrawal of Participants

Participants can withdraw at any time without giving a reason and without affecting their quality of future medical care. This may happen for a number of reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with trial procedures
- Participant decision

Consent can be withdrawn at three levels:

No further contact – means that the research team no longer contacts the patient directly, but still has their permission to use information, samples and to obtain further information from health records.

No further access – means that the research team no longer contacts the patient or obtains information from their health records, but still has permission to use the information and samples already collected.

No further use – means that the research team no longer contacts the patient or obtains further information, and aims to destroy all samples already collected (though tracing previously distributed samples may not always be possible). Data already entered on to the database cannot be deleted.

In addition, the Investigator may discontinue a participant from the trial treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

The reason for withdrawal, if known, will be recorded in the CRF. If the participant is withdrawn due to an adverse event, the investigator will arrange for visits or telephone calls to collect follow-up information on the adverse event until the adverse event has resolved or stabilised. Withdrawals/discontinuations will be replaced to ensure that the appropriate number of participants completing the trial as per protocol.

9.11. Definition of End of Study

The end of study is defined as the last visit of the last patient undergoing the study follow-up and when all the samples have been analysed.

10. SAFETY REPORTING

Safety data will be collected as described below for serious adverse events that occur from the participant's Screening Visit until their Visit 4.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Assessment results outside of normal parameters as SAEs

Abnormal blood results will only be reported as SAEs if thought to be clinically significant and to require ongoing management or treatment. Abnormal blood glucose results (fasting glucose levels or HbA1c levels) will not be reported as SAEs even if clinically significant as this data will be captured in the primary and secondary outcome data. Any abnormal blood results will be treated/managed as appropriate by the trial clinician and the participants GP will be informed when appropriate.

10.3. Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Unrelated – Where an event is not considered to be related to the intervention

Possibly Related – although a relationship to the intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably Related – the temporal relationship and absence of a more likely explanation suggest the event could be related to the intervention

Definitely Related – the known effects of the IMP, its therapeutic class or based on challenge testing suggests that the intervention is the most likely cause.

All SAEs labelled possibly, probably or definitely related will be considered as related to the intervention.

10.4. Reporting Procedures for Serious Adverse Events

All SAEs will be reported to ORTU using the ORTU SAE Reporting Form. The Site Study Team will report to ORTU as soon as possible after becoming aware of the event being defined as serious. ORTU will perform an initial check of the report, request any additional information, and ensure a nominated Medical Reviewer provide a review. It will also be reviewed at the next Trial Safety Oversight Group meeting. All SAE information must be recorded on an SAE form and scanned and emailed, to ORTU respiratorytrialsunit@ouh.nhs.uk.

Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and scanned/emailed to ORTU.

The ORTU Safety Oversight Group will review all SAEs for the study reported during the reporting period and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

10.5. Expectedness

As the trial intervention, CPAP withdrawal is not an IMP, there is no separate IMP brochure. The only expected AEs are:

- Daytime sleepiness
- Rise in blood pressure (average expected, 9 mmHg)

Depending on the severity of these events they may become unexpected. For example, it is expected that participants may experience excessive daytime sleepiness or hypertension. It is not expected that daytime sleepiness will lead to road traffic collisions or that the rise in blood pressure will require treatment or hospitalisation. In previous CPAP withdrawal studies, with a similar but longer CPAP-withdrawal periods, there have been no serious adverse events in over 100 participants.

10.6 Reporting Procedures for Related Unexpected Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Medical Reviewer the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The plans for the statistical analysis of the trial are outlined below. A separate SAP document will be produced prior to study analysis.

11.2. Description of Statistical Methods

The primary outcome measure will be analysed using a mixed effect model with the mean of the overnight (12 midnight to 7am) glucose levels from Days 5, 6, and 7 from both treatment arms as the dependent variable. Treatment allocation will be included as a binary factor with adjustments for age, sex, diabetes status (confirmed or prediabetic), BMI and other important factors.

Secondary outcomes will also be assessed using mixed effect models as described above. A separate secondary analysis of 24 hour glucose profiles will be analysed by comparing the area under the curve analysis.

11.3. Sample Size Determination

The sample size calculation is based on the difference in mean overnight glucose levels. This was chosen as the primary outcome as paired pilot data exists for this outcome, unlike other CGM metrics like MAGE or NMAGE which are instead included as secondary outcomes. The sample size calculation is based on pilot data from Chopra *et al.* (74), who looked at the difference in overnight blood glucose levels measured in a hospital setting over three nights of CPAP withdrawal in patients with T2DM and OSA. They found a between group difference of 17.2 ± 19.0 mg/dl. Based on this, in order not to miss a between-group difference in overnight glucose levels of 17.2mg/dl between CPAP withdrawal and continued CPAP with a two-sided alpha of 0.05 and a beta of 0.8 would require 22 participants in a crossover study. An alternative would be to base our power calculation on data from Mokhlesi *et al.* (76), who looked at the difference in 24 hour blood glucose levels measured in hospital over 7 days in patients treated with CPAP with T2DM

and OSA. They found a 13.5 ± 13.5 mg/dl improvement in 24 blood glucose levels with CPAP therapy. Based on this, in order not to miss a between group difference in 24-hour glucose levels of 13.5 mg/dl between CPAP withdrawal and continued CPAP with a two-sided alpha of 0.05 and a beta of 0.8 would require 18 participants in a crossover study.

Taking the more conservative estimate of 22 participants, and allowing for only 87% of CGM monitoring sensors surviving the 10 day follow-up period (53) from application, gives 25 patients. In previous parallel CPAP withdrawal trials drop-out rates following randomisation has been 1% (65). Therefore, allowing for a more conservative drop-out rate of 10% we will aim to randomise 30 patients. However, when 22 patients have completed the trial per protocol with sufficient CGM data recruitment will be stopped.

11.4. Analysis Populations

As this is a physiological mechanistic study, analysis will be on all evaluable participants and not on an intention-to-treat basis. Analysis will be conducted on all evaluable participants defined as participants who have evaluable CGM data from Days 5, 6, and 7 of both treatment arms, and who have completed the trial as per protocol.

11.5. Decision Points

No interim analyses are planned for this trial.

11.6. Stopping Rules

As no interim analyses are planned there are no pre-specified stopping rules for this trial.

11.7. The Level of Statistical Significance

Statistical significance is defined as a two-sided alpha of 0.05 for this trial.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Data will not be imputed in the analyses of the primary outcome will be analysed on a completed cases/ per-protocol basis.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.3. Data Recording and Record Keeping

Data will be entered directly into the database by the research staff at site. All trial data will be entered on to a web-based, trial data management system (REDcap). The study database is bespoke and hosted on the University of Oxford server with services provided through Oxford University Medical Sciences Division IT Services (MSD-IT). The server and database are protected by a number of measures including anti-virus and anti-spyware applications, firewalls, encryption technology and permissions. The database will be backed up on a daily basis. The University of Oxford remains the owner of all data stored on the database in relation to this study.

The database will be accessed using a secure weblink. The database will be secure and password-protected. Any person entering data (site personnel or delegated member of the team) require their own unique log-in to access the database, with a system-generated password that can be changed at first log-in. Each individual user will have specified permissions and authorisations (e.g. Investigator, Data Entry). All activity will be recorded on the database as part of the audit trail. The data stored will be checked for missing or unusual values and for consistency within participants over time. If any problems are identified, the appropriate CRFs will be reviewed by the research team. Should any data require changing, this will be electronically tracked (name of reviewer, changes made and date) for the purposes of any future audit or external review. Further details will be listed in the DMP.

The data will be securely stored in line with ICH-GCP standards and the data protection principles. Participants will be identified by a unique study-specific number within the database. The name and any other identifying detail will not be included in any study data electronic file. The Chief Investigator and authorised staff based at the ORTU will have access to participants' data. The Chief Investigator will facilitate access to study records for the purpose of monitoring, audits, ethics committee reviews and regulatory inspections. Participant's consent to this will be sought at the time of enrolment into the study.

Further details on the clinical database system and the governing of data transfer are available as part of an ORTU SOP.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

The study will be conducted in accordance with the current approved protocol, ICH GCP guidelines, relevant regulations and local standard operating procedures. The study will be monitored as per risk assessment.

13.2. Study Monitoring

Central monitoring will be performed according to the trial specific Risk Assessment, Management and Monitoring Plan (RAMMP). Site monitoring visits will not be performed unless required as per RAMMP.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

The most common “side- effect” of CPAP withdrawal is recurrence of OSA symptoms, mainly excessive daytime sleepiness and unrefreshing sleep. Participants will be advised not to drive if sleepy, standard advice to all OSA patients. Those who are professional drivers or in vigilance critical jobs will not be recruited. CPAP withdrawal for two weeks has been safe in all our previous trials and some patients often stop CPAP for short periods such as when on holiday. On initial contact, if patients are concerned that they cannot stop CPAP without a problematic return of sleepiness or that this return of sleepiness interferes significantly with daily living, they will not be recruited.

This trial may diagnose patients with diabetes mellitus or prediabetes, where such a diagnosis had not previously been made. Patients will be informed of this as part of the process of informed consent.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRFs, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

17. FINANCE AND INSURANCE

17.1. Funding

This study is funded by the NIHR Oxford Biomedical Research Centre (BRC4PP-09 £50,000) and the Oxford Hospitals Charities. CGM equipment is provided by Dexcom (Investigator Initiated Study Grant).

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR Oxford Biomedical Research Centre, Dexcom and the Oxford Hospital Charities. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable

19. ARCHIVING

The study documents (including the Trial Master File (TMF), Informed Consent Forms along with the study database) will be kept for a minimum of five years. They will be stored long term in secure off-site archiving facilities. Copies of the consent forms will be stored long-term for those who consented to long-term storage of samples. The CI is responsible for the secure archiving of study documents. The study database will also be kept electronically on the University of Oxford, for a minimum of five years.

20. REFERENCES

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21. APPENDIX A: STUDY FLOW CHART

Not applicable, appears above.

22. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Not applicable, appears above.

23. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).