The Impact of Sleep Disorders in Patients with Type 2 Diabetes: A Cohort Study and Feasibility RCT

SLEEP T2D TRIAL PROTOCOL

Sponsor reference number: RG_14-149

ISRCTN12361838

REC reference number: 18/WM/0070, West Midlands - Solihull

IRAS reference number: 236540

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

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Compliance statement

This protocol describes the Sleep T2D study only. The protocol should not be used as a guide for the treatment of patients not taking part in the Sleep T2D study.

The study will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018 and the EU General Data Protection Regulation 2018, and the principals of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Study Committees and Administration

Study Management Group

The Study Management Group's (SMG) role is to monitor all aspects of the conduct and progress of the study on a day-to-day basis and to ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself.

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The funder had no role in respect to study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

The views expressed are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health.

Reference numbers

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Protocol amendments

The following amendments and / or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
SA1	30th November 2018	V4.0	Substantial	Changes to eligibility; changes to consent processes

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been approved by:

Trial Name:	
Protocol Version Number:	Version: __ __
Protocol Version Date:	__ __ / __ __ / __ __ __ __
CI Name:	
Trial Role:	Chief Investigator
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor of this trial confirm approval of this protocol.

PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

This protocol has been approved by:

Trial Name:	
Protocol Version Number:	Version: __ __
Protocol Version Date:	__ __ / __ __ / __ __ __ __
PI Name:	
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Signature and date:	_____ __ __ / __ __ / __ __ __ __

The Principal Investigator should sign this page and return a copy to the SLEEP T2D Trial Office

General Queries

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Abbreviations

ACR	Albumin/Creatinine Ratio	**ISRCTN**	International Standard Randomised Control Trial Number
AHI	Apnoea-Hypopnea Index	**ISF**	Investigator Site File
AE	Adverse Event	**IQR**	Interquartile Range
AGE	Advanced Glycation End products	**MEQ**	Morningness-Eveningness Questionnaire
AV	Air View	**MNSI**	Michigan Neuropathy Screening Instrument
BP	Blood Pressure	**NICE**	National Institute for Health and Care Excellence
BCTU	Birmingham Clinical Trial Unit	**NIHR**	National Institute for Health Research
BMI	Body Mass Index	**NHS**	National Health Service
CAN	Cardiac Autonomic Neuropathy	**ONS**	Office of National Statistics
CI	Chief Investigator	**OSA**	Obstructive Sleep Apnoea
CKD	Chronic Kidney Disease	**PARP**	Poly ADP Ribose Polymerase
CPAP	Continuous Positive Airway Pressure	**PI**	Principal Investigator
CRF	Case Report Form	**PIS**	Participant Information Sheet
DM	Diabetes Mellitus	**PKC**	Protein Kinase C
DPN	Diabetic Peripheral Neuropathy	**PSQI**	Pittsburgh Sleep Quality Index
DR	Diabetic Retinopathy	**REC**	Research Ethics Committee
EDS	Excessive Daytime Sleepiness	**RCT**	Randomised Clinical Trial
eGFR	estimated Glomerular Filtration Rate	**QOL**	Quality of Life
ESC	Electrochemical Skin Conductance	**R&D**	Research and Development
ESS	Epworth Sleepiness Scale	**SAE**	Serious Adverse Event
ESRD	End Stage Renal Disease	**SF-MPQ**	Short Form McGill Pain Questionnaire
GCP	Good Clinical Practice	**SF-12**	Short Form Health Survey
GP	General Practitioner	**SMG**	Study Management Group
HbA1c	Glycated haemoglobin	**SOC**	Study Oversight Committee
HES	Hospital Episode Statistics	**STDR**	Sight Threatening Diabetic Retinopathy
HRA	Health Research Authority	**T2D**	Type 2 Diabetes Mellitus
HRV	Heart Rate Variability	**TMF**	Trial Master File
ICF	Informed Consent Form	**UoB**	University of Birmingham

Definitions

Term	Abbreviation	Description
Policies	POL	Policies are developed to describe the approach of the University of Birmingham (UoB) on areas that heavily regulated. Policies may also be developed when there is ambiguity in how regulatory requirements should be implemented in the Quality Management System (QMS) or when procedures to be captured in the QMS address areas controversial within UoB at the time of implementation. Policies explain why UoB has its procedures, especially when they seem to deviate from the regulatory requirements. Policies should be read in conjunction with the relevant Standard Operating Procedure (SOP). Policies that are not part of a Quality Manual are coded up as 'POL'.
Quality Control Documents	QCD	Quality Control Documents can be instructions, forms, templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise needed to develop similar documents. Unless indicated otherwise in the relevant SOP, QCDs are not mandatory and are designed to be an optional aid to UoB staff.
Quality Management System	QMS	A Quality Management System is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Standard Operating Procedures	SOP	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event		An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening • Requires hospitalisation or prolongation of existing hospitalisation* • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator *Hospitalisation for elective procedures (unless brought forward due to worsening symptoms), social reasons, or logistical reasons are not regarded as a SAE. (See Section 10).
Unexpected and Related Event		An event which meets the definition of both an Unexpected Event and a Related Event.
Unexpected Event		The type of event that is not listed in the protocol as an expected occurrence.
Source data		All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.
Birmingham Clinical Trials Unit	BCTU	The co-ordinating centre for the trial.

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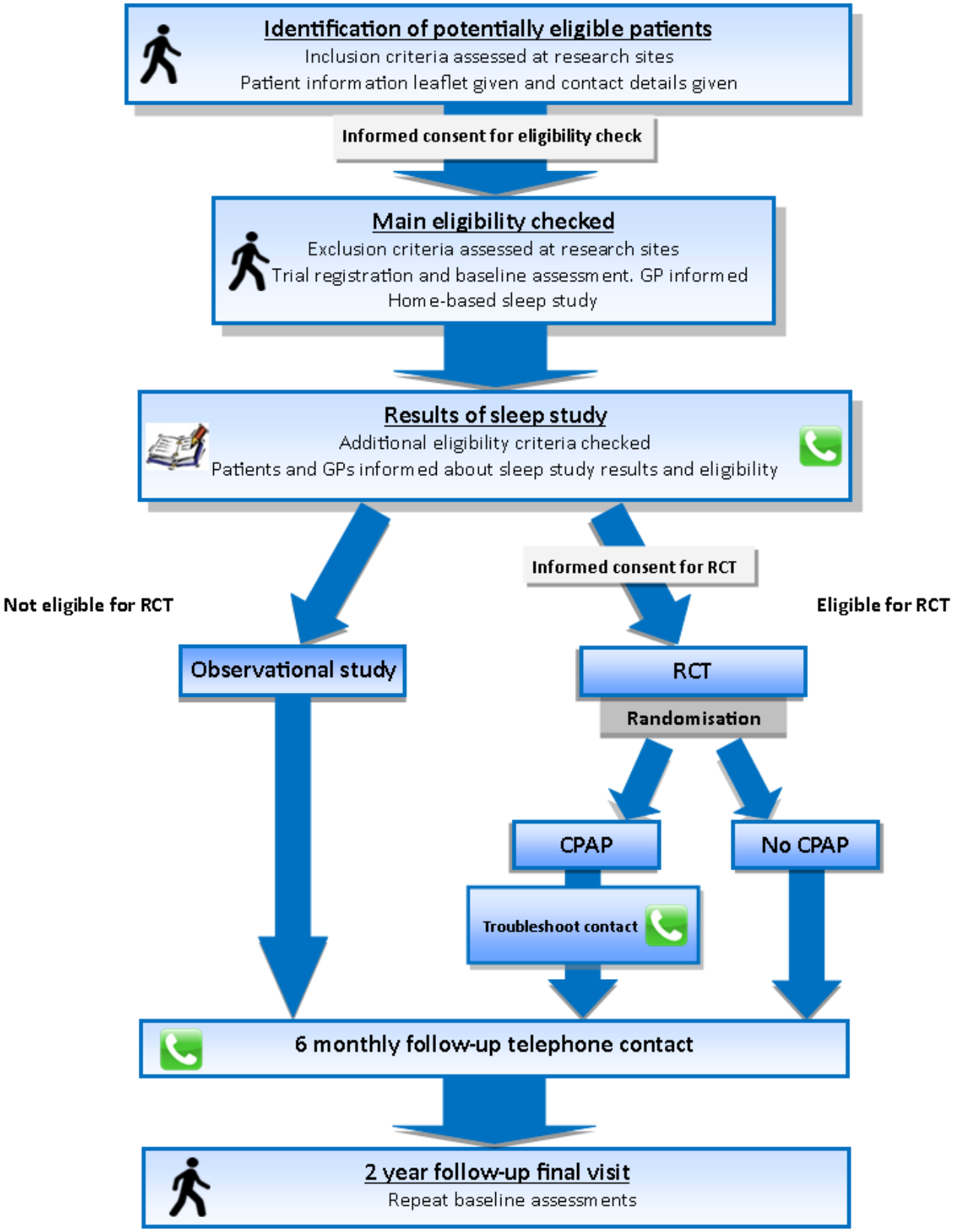
Study summary

Title	The Impact of Obstructive **Sleep** Apnoea Treatment on Microvascular Complications in Patients With **T**ype **2 D**iabetes: A Feasibility Trial
Acronym	**SLEEP T2D**
Study Aim	The primary aim of **SLEEP T2D** is to assess the feasibility of running a substantive RCT in patients with T2D, randomising participants between CPAP and no CPAP. The aim of such a substantive RCT would be to determine the impact of OSA treatment (CPAP vs no CPAP) on the progression of diabetic nephropathy/CKD in patients with T2D. The proposed clinical primary outcome would be eGFR as measured by serum creatinine levels.
Study Design	**SLEEP T2D** is a feasibility and observational cohort study with a subset of participants included in an RCT of a CE marked medical device used within its intended purpose. The RCT is a randomised controlled parallel arm trial where participants will be randomised in a 1:1 ratio to CPAP or no CPAP. 140 participants will be randomised.
Objectives	**Primary objectives** 1. To assess willingness of participants to be randomised 2. To assess willingness of clinicians to recruit participants 3. To assess follow-up rates and adherence/compliance rates 4. To provide data to inform the sample size for a substantive trial 5. To optimise the choice of outcome measures for a substantive trial **Secondary objectives** To assess the impact of OSA treatment (CPAP) in patients with T2D on: 1. Measures of diabetic nephropathy and chronic kidney disease including eGFR, Cystatin-C, and albumin/creatinine ratio 2. Diabetic neuropathy (including peripheral painless and painful peripheral neuropathy, cardiac autonomic neuropathy and peripheral autonomic neuropathy) 3. Diabetic retinopathy and maculopathy 4. Metabolic parameters such as weight, HbA1c, BP, and lipids profile **Tertiary objectives** 1. To explore the utility of different biomarkers in screening for OSA in patients with T2D 2. To explore the mechanisms via which CPAP might have an impact on diabetes-related complications 3. To assess the relationship between other sleep-related disorders, such as sleep duration, sleep quality and sleeping patterns and metabolic parameters and vascular disease in patients with T2D 4. To build up a cohort of well characterised patients for longitudinal follow up to inform us about the natural history of OSA, sleep-related disorders, and diabetes-related complications

Participant Population and Sample Size	Up to 500 patients will be enrolled into the study. One hundred and forty of these, with confirmed OSA who also fulfil additional eligibility criteria, will be randomised into a RCT of CPAP vs. no CPAP. Participants who do not fulfil the RCT eligibility criteria will remain in the study as part of an observational cohort; those participants in the RCT will also be included in the observational cohort.
Main eligibility criteria	**Main Inclusion criteria** Potential participants will be considered eligible for trial if the patient: • Is aged 18 years or above • Has Type 2 Diabetes • Has an eGFR ≥15mL/min/1.73 m^2 in last 12 months **Main Exclusion criteria** Potential participants will **not** be considered eligible for the trial if patient: • Has Type 1 diabetes • Has known OSA, active malignancy or chronic kidney disease from reasons other than diabetes • Is receiving chemotherapy, immunosuppressant or home oxygen treatment • Has a history of recurrent hospital admissions due to infective exacerbation of a respiratory condition • Has received contrast imaging within the last 2 months • Is pregnant • Is intending to undergo bariatric surgery during the study duration • Is unable to comply with the study protocol • Is unable to give consent • Is a professional driver, operator of heavy machinery and/or working at high altitude Has a history of falling asleep whilst driving within last two years
Additional (RCT) eligibility criteria	After baseline tests the following criteria must be satisfied for all patients to be randomised into the RCT: **RCT Inclusion Criteria** Potential participants will be considered eligible for randomisation if patient: • Is willing to be randomised to CPAP or no CPAP • Has ESS <11 • Has an Apnoea–Hypopnea Index (AHI) ≥ 10 **RCT Exclusion Criteria** Potential participants will **not** be considered eligible for randomisation if patient: • Has a resting oxygen saturation <90% or has central apnoeas >15/ hour (as detected during the sleep assessment recording).
Study duration per participant	2 years
Recruitment period	2 years
Estimated total study duration	5 years (6 months for set up, 6 months for analysis)

Figure 1. **Study Schema**



1. Background and Rationale

1.1. Background

1.1.1. Diabetes microvascular complications

Diabetes-related microvascular complications (nephropathy, neuropathy, and retinopathy) are common and are associated with significant morbidity, mortality and economic burden [1-3]. Diabetes mellitus (DM) is the most common cause of end-stage renal disease (ESRD). ESRD requires dialysis and/or renal transplant and is associated with increased cardiovascular disease [4]. Furthermore, diabetic neuropathy is the leading cause of non-traumatic amputations and diabetic foot ulceration [5]. Diabetic retinopathy (DR) is the leading cause of blindness in working-age people in the Western world [2, 3]. The mainstay of the treatment of these complications is intensive control of glucose, blood pressure (BP) and lipids [6-12] and the use of angiotensin converting enzyme inhibitors [13]. Despite that, microvascular complications remain very common and new treatments based on better understanding of the pathogenesis are needed.

1.1.2. The pathophysiology of microvascular complications

Hyperglycaemia induced oxidative and nitrosative stress are essential steps in the pathogenesis of microvascular complications resulting in DNA damage and excessive poly (ADP-ribose) polymerase (PARP) activation and inhibition of glyceraldehyde 3-phosphate dehydrogenase resulting in activation of aldose reductase, protein kinase C (PKC), the hexosamine pathway and advanced glycation end products (AGE); all of which result in endothelial and microvascular dysfunction resulting in microvascular complications [14-16].

Data from non-diabetics has shown that obstructive sleep apnoea (OSA) can result in similar molecular consequences to those of hyperglycaemia including increased oxidative and nitrosative stress, activation of PKC and AGE production, increased inflammation, and endothelial dysfunction [17-38]. Our previous work has expanded those findings to patients with type 2 DM (T2D) as OSA[1] and nocturnal hypoxaemia were associated with nitrosative stress, oxidative stress, PARP activation and impaired microvascular regulation in patients with T2D and OSA compared to those with T2D only [39, 40]. Therefore, it is reasonable to assume that OSA might aggravate microvascular complications.

1.1.3. Obstructive sleep apnoea and dysglycaemia

OSA is characterized by upper airway instability during sleep resulting in recurrent episodes of reduced (hypopnea) or absent (apnoea) airflow [41]. These episodes are usually associated with recurrent oxygen desaturations, cyclical changes in BP, heart rate, and intrathoracic pressure and sleep fragmentation [41]. OSA is associated with T2D [42, 43], hypertension [44-47], road traffic accidents

[1] The severity of OSA is measured by the apnoea-hypopnoea index (AHI), the average number of apnoea and hypopnoea events per hour of sleep.

[47-49], cardiovascular disease [50-54], mortality [55], cognitive impairment and reduced quality of life (QOL) [47]. OSA is very common in patients with T2D (23%-86%) [40, 56-59].

1.1.4. Obstructive sleep apnoea and diabetes

Our previous work demonstrated an OSA prevalence of 65% in patients with T2D [40] which leads to the hypothesis that OSA plays a role in the development and progression of diabetes-related microvascular complications. This was further tested by utilising an NIHR research training fellowship, and the preliminary data is presented below.

OSA is associated with diabetic microvascular complications: Cross-sectional analysis

In a cross-sectional study, it was found that diabetic nephropathy, diabetic neuropathy and sight threatening DR (STDR) were more common in patients with OSA and T2D compared to those with T2D alone [39, 40, 60]. After adjustment for confounders (e.g. age, BP, glycated haemoglobin [HbA1c] and demographics), OSA remained independently associated with diabetic nephropathy (OR 2.6, 95%CI 1.1-6.2, p=0.02), neuropathy (OR 2.7, 95%CI 1.3–5.6, p=0.006) and STDR (OR 3.7, 95% CI 1.6-8.9, p=0.003) [39, 40, 60].

OSA predicts the progression of diabetic microvascular complications: Longitudinal analysis

After a follow-up of 2.5 years, the change in estimated glomerular filtration rate (eGFR) (based on the 4-variable MDRD equation) was larger in patients with T2D and OSA compared to patients with T2D only (median (inter-quartile range (IQR)) (-5.0 (-14 to 1.8) vs. -1.5 (-8.5 to 4.0), p=0.006) [39, 60]. The eGFR change calculated as a percentage of baseline eGFR showed a greater decline in the OSA group (-1.4% (-7.7% to 5.2%) vs. -5.3% (-16.5% to 2.7%) vs. -8.7% (-16.1% to 2.0%), for no OSA vs. mild vs. moderate to severe OSA, p=0.003 for trend) [39]. Baseline OSA (B=-4.2, p=0.03) and AHI (B=-4.6, p=0.02) were independent predictors of study-end eGFR after adjustment for baseline eGFR, age, obesity, diabetes duration, medications and other confounders [39]. OSA was also an independent predictor of eGFR decline (B=-3.8, p=0.04) after similar adjustments [39, 60].

Baseline OSA was an independent predictor of progression to pre-proliferative/proliferative DR (OR 6.6, 95% CI 1.2-35.1, p=0.03) after adjustment over a 5 year follow-up period [60].

Continuous positive airway pressure slows nephropathy and retinopathy progression: Observational data

In the study, patients diagnosed with OSA were referred to local NHS services and were treated in accordance with routine care. Continuous positive airway pressure (CPAP) treatment was offered to all patients with moderate to severe OSA only. Hence, the study population can be divided into 4 groups in regard to CPAP and OSA status: no OSA; mild OSA; moderate to severe OSA CPAP-compliant; and moderate to severe OSA CPAP-noncompliant. CPAP usage data was downloaded directly from the CPAP equipment; compliance was defined as average usage > 4 hours/night on 70% of days [61].

The eGFR decline was greater in non-compliant CPAP patients (eGFR change: -1.4% (-7.7% to 5.2%) vs. -5.3% (-16.5% to 2.7%) vs. -7.7% (-15.9% to -1.8%) vs. -10.0% (-17.2% to 2.3%) for no OSA vs. mild OSA vs. moderate to severe OSA CPAP-compliant vs. moderate to severe OSA CPAP-

noncompliant respectively, p=0.01 for trend); particularly in those with baseline eGFR < 90 ml/min/1.73 m^2 (1±12.6% vs. -10.7±19.8% vs. -4.5±8.5% vs. -12.2±20.4% for patients with no OSA, mild OSA, OSA CPAP-compliant and OSA CPAP non-compliant [39].

Progression to pre-proliferative/proliferative DR over 5 years follow up occurred in 2.9% vs. 17.9% vs.17.9% vs. 0% in patients with no OSA, mild OSA, moderate to severe OSA CPAP-noncompliant and moderate to severe OSA CPAP-compliant (p=0.01 for trend) [60]. There were no significant differences in participants' characteristics between the different OSA categories.

Data from the observational study suggests that OSA (both mild and moderate to severe) is associated with worsening of microvascular complications in patients with T2D and that CPAP treatment might be effective in slowing this progression. This result is supported by mechanistic data from the literature showing that CPAP improves oxidative stress [62], nitrosative stress [63], inflammation [64], and endothelial dysfunction [65-67] in patients without DM. However, there are no interventional data regarding the impact of CPAP on diabetes-related microvascular complications.

Our overall hypothesis is that OSA treatment slows the progression of microvascular complications in patients with T2D, which needs to be tested in a full scale randomised controlled trial (RCT).

1.1.5. Treatment of obstructive sleep apnoea

The current clinical guidelines suggest that patients with mild OSA do not require CPAP unless symptomatic and other treatment such as lifestyle fail [68]. Patients with moderate to severe OSA are recommended to be treated with CPAP if they are symptomatic, particularly if they have excessive daytime sleepiness (EDS) [68].

1.2. Trial Rationale

Our preliminary data suggests that OSA (both mild [AHI<15] and moderate to severe [AHI≥15]) is associated with worsening of microvascular complications in patients with T2D and that treatment of OSA might be effective in slowing this progression. Since only observational studies have been performed to date, there is a need for a randomised controlled trial to determine whether mild and moderate to severe OSA treatment slows the progression of microvascular complications in patients with T2D.

This feasibility study will also provide us with better assessment of the impact of OSA treatment on peripheral neuropathy, cardiac autonomic neuropathy and retinopathy allowing more confident sample size calculations for future RCTs.

In addition, a cohort of well-characterised patients with T2D will be followed up to inform us about the natural history of OSA, sleep-related disorders, and diabetes-related complications.

1.2.1. Justification of participant population

As described previously, our observational data on the impact of CPAP on eGFR decline in patients with moderate to severe OSA data strongly suggest that CPAP treatment significantly slows the decline in eGFR in these patients. Therefore it will be more accurate to estimate the sample size for future RCTs based on interventional rather than observational data in this patient group.

Furthermore, we do not currently have data regarding the impact of OSA treatment on eGFR decline in patients with mild OSA. Hence this feasibility study will allow us to assess the possible impact of OSA treatment on eGFR decline and other outcomes in patients with mild OSA and T2D. Although the impact of mild OSA might be perceived as small this is currently unknown in patients with T2D as the presence of hyperglycaemia and its associated oxidative stress might exacerbate the impact of mild OSA in patients with T2D. Pre-clinical work performed in our laboratory in rats showed that the combination of intermittent hypoxia and hyperglycaemia was more powerful than either alone in regards to generating nitrosative stress and PARP activation (unpublished data).

In this study, patients with OSA and AHI <10 (i.e. 5-10) will not be randomised as these patients are likely to be asymptomatic and their adherence with CPAP is likely to be very poor. In addition there is a greater prevalence of mild OSA than moderate to severe OSA, so including patients with mild OSA and AHI <10 in the study would likely result in a significant reduction in the number of patients with moderate to severe OSA being randomised. By using a cut off of AHI≥10 (which is also widely used in the literature) to include patients in the RCT, we aim to get balanced numbers of patients with mild and moderate to severe OSA randomised. There is a need to investigate patients with AHI <10 but the best treatment for them is likely to be a mandibular advancement device rather than CPAP. These patients are not currently offered treatment in routine NHS care and investigation of their treatment is outside the scope of this protocol.

1.2.2. Justification of trial interventions

Patients with moderate to severe OSA are recommended to be treated with CPAP if they are symptomatic, particularly if they have EDS [68]. Therefore randomising patients with EDS to no treatment would raise ethical concerns. To avoid this, the Epworth Sleepiness Scale (ESS) will be used to assess the presence of EDS. Patients with EDS (ESS ≥11) will be excluded from the RCT and their General Practitioner (GP) and/or diabetologist will be informed as these patients will be at high risk of OSA. Patients with OSA but without EDS will be included in this study and randomised if they meet the RCT inclusion/exclusion criteria.

Adherence to CPAP is widely reported to be poor [61], and certainly this was the case in our observational data, but in RCTs adherence rates of ≥80% have been reported [69, 70]. In the Sleep 2013 conference in Baltimore, USA it was highlighted that the National Institute for Health in the USA will not fund CPAP RCTs without prior demonstration that adequate adherence to CPAP treatment (≥80%) can be achieved.

In this study we will take several steps to improve compliance as detailed by others [71]. These will include: a combination of motivational interviewing (using guiding style to engage the patient, clarify the patient's strengths and aspirations, explore treatment benefits, evoke the patient's motivations to adhere to treatment and promote the patient's autonomy in decision making); education regarding the usage of CPAP and its apparent and less apparent benefits; and remote wireless monitoring with troubleshooting as and when needed. In addition, we are using the latest available technology in CPAP equipment to maximize adherence. This includes the use of the Airsense 10 Autoset™, which features built-in wireless connectivity capability to monitor compliance remotely via a secured website; AutoRamp™ with sleep onset detection; expiratory pressure relief and Easy-Breathe technology; and the use of humidifiers, all of which are aimed at making the use of CPAP easier and to encourage patient compliance.

Hence, the feasibility study will help us to assess the utility of this intensive protocol in maximising the adherence to treatment particularly as we aim to conduct a relatively long RCT (2 years duration) and so it is important to maximise adherence throughout the study.

The control arm is "no treatment". The choice of no treatment over sham CPAP was a pragmatic one. Using sham CPAP is more costly, and more time and resource consuming. Several other reasons contributed to the choice of no treatment. Sham CPAP is created by effectively causing a "hidden" leak in the exhaust port of the mask to disperse the therapeutic pressure. It is difficult to blind patients or the assessors to the treatment allocation as patients on sham CPAP will still have symptoms related to OSA (most commonly snoring). This lack of effect can be associated with treatment non-compliance, which will also affect outcomes measures. Furthermore, although sham CPAP produces much less pressure than active CPAP, this pressure is not 0 and hence might still have some physiological function. Due to the feasibility nature of this study, the limited resources, and the above-mentioned reasons, we elected to use "no treatment" as the control group. This design is consistent with previous studies that avoided randomising patients with EDS to no treatment [69, 70]. The use of no CPAP rather than sham CPAP is common in CPAP trials [69, 70, 72]. Furthermore, we have elected to use no CPAP rather than sham CPAP as the secondary outcomes are objective and not patient reported.

2. Aims, Objectives and Outcome Measures

The primary aim of this study is to assess the feasibility of running a substantive RCT in patients with T2D, randomising participants between CPAP and no CPAP.

The aim of such a substantive RCT would be to determine the impact of OSA treatment (CPAP vs no CPAP) on the progression of diabetic nephropathy/CKD in patients with T2D. The proposed clinical primary outcome would be eGFR as measured by serum creatinine levels.

The cohort study is intended to be hypothesis generating, based on previous cross-sectional studies [73-76] that show associations between sleep quality, sleep duration and circadian rhythm and metabolic parameters in patients with T2D. The direction of these associations is complex and possibly bi-directional. However, there are no longitudinal data regarding these associations in patients with T2D to assess causality. Hence the purpose of some of the tertiary objectives is to explore the longitudinal relationship between sleep duration and quality and circadian cycle and important metabolic and vascular outcomes in patients with T2D. Based on the cross-sectional data available, the hypothesis is that poor sleep quality, short sleep duration and later chronotype will be associated with adverse metabolic and vascular outcomes in patients with T2D.

Primary objectives

1. To assess willingness of participants to be randomised
2. To assess willingness of clinicians to recruit participants
3. To assess follow-up rates and adherence/compliance rates
4. To provide data to inform the sample size for a substantive trial
5. To optimise the choice of outcome measures for a substantive trial.

Secondary objectives

To assess the impact of OSA treatment (CPAP) in patients with T2D on:

1. Measures of diabetic nephropathy and CKD including eGFR, Cystatin-C, and albumin/creatinine ratio (ACR)
2. Diabetic neuropathy (including peripheral painless and painful peripheral neuropathy, cardiac autonomic neuropathy and peripheral autonomic neuropathy)
3. Diabetic retinopathy and maculopathy
4. Metabolic parameters such as weight, HbA1c, BP, and lipids profile.

Tertiary objectives

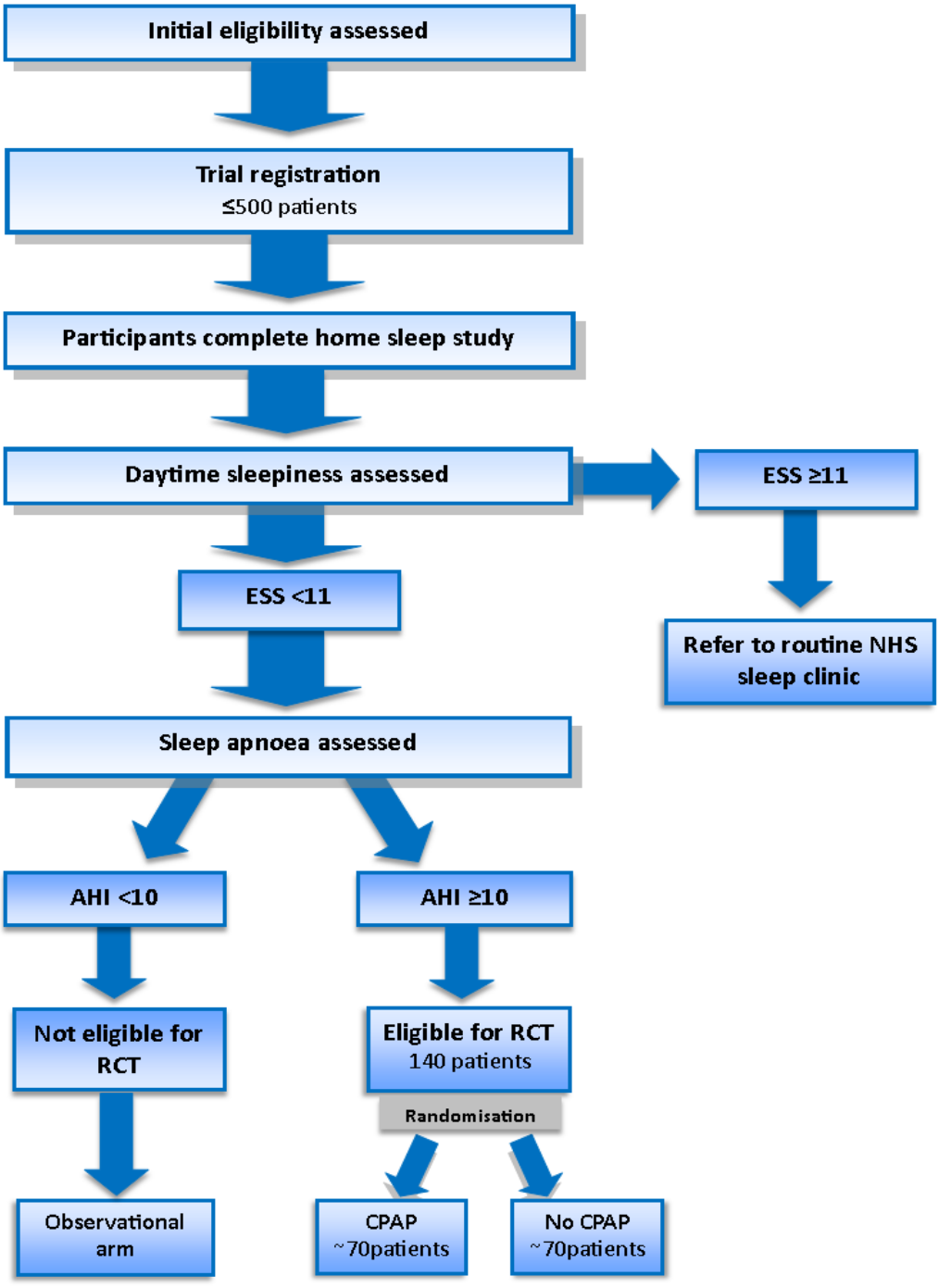
1. To explore the utility of different biomarkers in screening for OSA in patients with T2D
2. To explore the mechanisms via which CPAP might have an impact on diabetes-related complications
3. To assess the relationship between other sleep-related disorders, such as sleep duration, sleep quality and sleeping patterns and metabolic parameters and vascular disease in patients with T2D
4. To build up a cohort of well characterised patients for longitudinal follow up to inform us about the natural history of OSA, sleep-related disorders, and diabetes-related complications.

3. Study Design and Setting

3.1. Study design

SLEEP T2D is a feasibility and observational cohort study with a subset of participants included in an RCT of a CE marked medical device used within its intended purpose. The RCT is a randomised controlled parallel arm trial where participants will be randomised in a 1:1 ratio to CPAP or no CPAP. 140 participants will be randomised. It will be open label as discussed in section 1.2.2 above. The proposed primary outcome for a substantive trial, eGFR, is an objective measure.

Figure 2. **Simplified study schema**



3.2. Treatment arms

All patients registered to enter the study will enter the observational cohort and undergo a sleep assessment to determine if they have OSA.

If they consent to it, patients with an OSA severity of AHI ≥10 will then be randomised to CPAP or no CPAP (see complete list of eligibility criteria below; section 4.2). Randomisation will be stratified by gender, ethnicity and OSA severity.

Patients who are not eligible for the RCT will continue in the observational cohort. Please see Figure 2 on the previous page.

3.3. Study duration

The total duration of the study will be five years, comprising a six month set up period, a two year recruitment period, a two year follow-up period for each participant, and six months for analysis.

One of the main aims of this study is to examine whether we can achieve high compliance with prolonged CPAP treatment in patients with T2D for a future RCT. In addition, sufficient time is required to observe microvascular complications between groups. Outcome measures such as eGFR, retinal images, and diabetic peripheral neuropathy decline slowly in most patients with T2D. Our pilot data showed that two years were adequate to show differences between groups in regards to eGFR [39].

3.4. Study setting

Potential participants will be identified and assessed in at least 8 UK NHS Trust diabetes clinics. Participation in the optional assessments SUDOSCAN and CAN (see section 8.7) will be limited to those Trusts with the required equipment (expected to be 2); participation in the optional samples (see section 8.3) will be limited to those Trusts with the nursing resources able to do so (expected to be the majority, as not overly burdensome).

3.5. Identification of participants

Potential participants will be identified in, and recruited from, secondary care diabetes clinics. This may be expanded to further secondary care departments including community care clinics if needed. Local existing databases of patients, where these patients have explicitly consented to be searched and contacted for research, will be used; this will be done by local research site staff.

3.6. Sample size and recruitment

One hundred and forty patients will be randomised into the RCT of CPAP vs no CPAP. It is expected that up to 500 patients will need to be registered into the study and assessed for OSA to reach 140 participants with confirmed OSA and therefore fulfilling the additional RCT eligibility criteria.

Those who do not fulfil the additional RCT eligibility criteria will remain in the study as part of an observational cohort. Participants in the RCT will also be included in the observational cohort. Once 140

participants are randomised, further registration into the study will stop. Registration of participants will continue beyond 500 if required to reach 140 randomised patients.

OSA is very common in patients with T2D. It is expected that at least 60% of patients attending a secondary care diabetes clinic to be eligible to be recruited, with an OSA prevalence of 66% in patients with T2D (based on previous research studies conducted by Abd Tahrani).

3.7. Payments to participants

Up to £30 per patient per study visit payment is included. This is mainly to cover the cost of travel. Patients willing to receive this payment can chose to, either arrange their own transport and be reimbursed, or sites can organise a taxi for the patients' journeys.

4. Eligibility

Potential participants must have their eligibility confirmed by a medically qualified doctor with access to and a full understanding of the potential participant's medical history. If eligibility has been assessed and documented by a medically qualified doctor, then the process of obtaining informed consent may be delegated as appropriate (as documented on the site Signature and Delegation Log). A Screening Log will be completed for all potential participants approached to join the study, including those who declined participation. A Patient Recruitment and Identification Log will be provided and should be completed for all patients registered into the study.

4.1. Study eligibility criteria

A Registration Form will be provided for investigators to collate the necessary information.

Study inclusion criteria

Potential participants will be considered eligible for registration into the study if they:

- Are ≥18 years old
- Have Type 2 Diabetes
- Have an eGFR ≥15 mL/min/1.73 m^2 in last 12 months*

Study exclusion criteria

Potential participants will **be excluded from the study** if they:

- Have Type 1 diabetes
- Have known OSA, active malignancy or chronic kidney disease from reasons other than diabetes
- Are receiving chemotherapy, immunosuppressant drugs or home oxygen treatment
- Have a history of recurrent hospital admissions due to infective exacerbation of a respiratory condition
- Have received contrast imaging within the last two months
- Are pregnant**

- Are intending to undergo bariatric surgery during the study duration
- Are unable to comply with the study protocol
- Are unable to give informed consent
- Is a professional driver, operator of heavy machinery and/or working at high altitude
- Has history of falling asleep whilst driving within last two years

*eGFR as calculated by the equation used in local routine practice.
** A pregnancy test will only be required if the woman believes that there is the possibility of pregnancy. This is not a safety issue as pregnancy is not a contraindication to CPAP treatment, but it is more appropriate to refer the patient to receive more personalised care from their GP/consultant rather than the mandated trial care in this case. We will not screen for the occurrence of pregnancy but we will ask the participants to inform us if they become pregnant (this will also monitored in 6 monthly phone calls). If a woman in the RCT becomes pregnant her GP will be asked to refer her to NHS care. Regardless of the NHS clinician's decision regarding treatment in these women, they will continue in the study as per protocol unless they decide to withdraw or their clinical care team advises them to do so.

4.2. Additional (RCT) eligibility criteria

When the results of the sleep apnoea assessment that took place at screening are available, all study participants will be assessed against the RCT eligibility criteria. A medically qualified doctor with access to and a full understanding of the potential participant's medical history will undertake this assessment. A Randomisation Form will be provided for investigators to collate the necessary information.

RCT inclusion criteria
Potential participants will be considered eligible for randomisation into the RCT if the patient:

- Is willing to be randomised to CPAP or no CPAP
- Have an ESS <11 (as completed by the participant during the baseline assessment)*
- Has a AHI ≥10**

*The ESS is a measure of daytime sleepiness and correlates with OSA severity. CPAP treatment is indicated according to NICE guidelines in patients with an ESS ≥11 and OSA.
**AHI is a measure of OSA severity. Patients with AHI <10 are not routinely treated in NHS routine care. Even when treatment is considered, there is no evidence that CPAP is the best treatment for this group.

RCT exclusion criteria
Potential participants will **be excluded from the RCT** if they:

- Have a resting oxygen saturation <90% or have central apnoea >15/ hour* (as detected during the sleep assessment recording)

*When patients have central apnoea 5-15/hour their sleep assessment will be reviewed by a sleep physician before confirmation that they can be randomised; this review may result in referral for further investigation being suggested.

5. Consent

The conduct of the study will be in accordance with the principles of GCP. The participant's written informed consent to participate in the study must be obtained before any procedures relating to the study are undertaken and after a full explanation has been given of the study, the treatment options and the manner of treatment allocation and randomisation.

It will be the responsibility of the Principal Investigator (PI) to obtain written informed consent for each participant prior to performing any trial related procedure. Other appropriately trained staff will be allowed to take consent (e.g. Research Nurse) if local practice allows and this responsibility has been delegated by the PI as captured on the site Signature and Delegation Log.

Two Participant Information Sheets (PIS) will be provided to facilitate this process, one for the study as a whole, and one for the RCT. Investigators or delegate(s) will ensure that they adequately explain the aim, study treatment, anticipated benefits and potential hazards of taking part in the study to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the study at any time. The participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions prior to signing and dating the latest version of the consent form. It will also be explained that the participant can withdraw at any time during the trial, without having to give a reason and that their decision will not affect the standard of care they receive.

SLEEP T2D has two stages of consent and therefore two separate Informed Consent Forms (ICF):

- Consent to enter the study as a whole (taken prior to study registration and baseline assessments), and;
- Consent to be randomised into the RCT (for those participants deemed eligible)

In all cases, if the patient is deemed eligible to participate in the study (or RCT, as applicable) they will be asked to sign and date the latest version of the ICF. The participant must give explicit consent for members of the research team and representatives of the sponsor to be given direct access to the participant's medical records.

The Investigator (or delegate(s) as documented on the site Delegation and Signature Log) will then sign and date the ICF. A copy of the ICF will be given to the participant, the original will be filed in the Investigator Site File (ISF), a copy sent to the SLEEP T2D study office at the University of Birmingham and a copy placed in the patient's medical notes. Once the participant is entered into the study the participant's unique trial identification number will be entered onto the ICF.

As part of the consent process, the participant will be asked to give explicit consent to their trial-related information being sent to the study office at the University of Birmingham Clinical Trials Unit (BCTU). The participant will be asked to give explicit consent to their telephone number being sent to the study

office at BCTU, and to being contacted by telephone by the Chief Investigator (CI)/Sleep Technician or delegate (required for the 6 monthly follow-up phone calls and for monitoring/troubleshooting the CPAP device).

Participants to be randomised into the RCT will be asked to give explicit consent to their full name and address being sent to the CPAP manufacturer ResMed in the case of being randomised to CPAP, so that the CPAP equipment may be sent directly to the participant. This will spare the participant the need to attend a further visit at site. Participants to be randomised into the RCT will be asked to give explicit consent to their full name and address being sent to the study office at BCTU in the case of being randomised to CPAP, in order to arrange delivery of the CPAP equipment.

Participants will be asked to consent to blood and urine samples being taken if the related biochemistry results are not already available as described in section 8.2. These samples will not be optional as eGFR is a secondary outcome. Participants will be asked to give explicit consent to additional samples being taken and then transported, stored, and processed outside of their NHS Trust; participants can opt out of these samples and still enter both the overall trial and RCT.

Patients who are not eligible to be randomised into the RCT will continue in the study as part of an observational cohort.

Patients who are deemed eligible to be randomised into the RCT will be provided with a supplement PIS and asked if they are willing to consent to being randomised between CPAP or no CPAP. The study team will provide a separate ICF for this stage of consent. The discussion and patient's response will be entered into patient notes.

Rather than increase the burden on the patient to be randomised into the RCT by making a second hospital visit for consent and randomisation obligatory, sites will have the option to allow the patient to complete the second ICF by post. In this case the second PIS will be posted by the site with a prepaid return envelope and the patient contacted by telephone to ensure the patient has the same opportunity to discuss taking part that they would have during a hospital visit.

This trial will include optional consent to allow linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink, The Health Improvement Network, QResearch), secondary care data (Hospital Episode Statistics) and mortality data from the Office of National Statistics through NHS Digital and other central UK NHS bodies. The participant will consent to the trial team sending their name, address, date of birth and NHS number to the relevant national registry and then for the national registry to link this to their data and send the information back to the trial team. The consent will also allow access to other new central UK NHS databases that will appear in the future. This will allow us to double check the main outcomes against routine data sources, and extend the follow-up of patients in the trial and collect long-term outcome and

health resource usage data without needing further contact with the trial participants. This is important as it will link a trial of treatments that may become a clinical standard of care to long-term outcomes that are routinely collected in clinical data but which may be collected during the follow-up period of the trial.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received.

Where consent is obtained on the same day that the trial related assessments are due to start, a note will be made in the medical notes as to what time the trial information was given, what time the consent was obtained, and what time the procedures started.

At each visit or patient contact (e.g. telephone call), the participant's willingness to continue in the trial will be ascertained and documented in the medical notes and in case report forms (CRF). During the six monthly telephone calls from the centrally based study Sleep Technician, willingness to continue will be only be documented on the CRF as the Sleep Technician will not have access to patient medical notes.

Throughout the study (and RCT) the participant will have the opportunity to ask questions about the research. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the SLEEP T2D study office and will be printed on the headed paper of the local institution. Details of all participants approached about the trial will be recorded on the Screening Log at Site, and with the participant's prior consent their GP will also be informed that they are taking part in the trial.

6. Registration and randomisation

6.1. Pre-Screening

Participating NHS sites will identify potential participants from regular diabetes or other speciality clinics, or existing databases of patients willing to be contacted about participating in research. Potential participants will be approached at site by members of the local research or care teams and provided with an ethically approved PIS, or they may be posted a PIS and invitation letter by the local research or care teams. The PIS will include contact details of the site investigator should the participant wish to ask any questions. The patient will be called or contacted via letter and invited to attend a baseline visit at their local research centre.

An ethically approved poster will also be placed in the patient waiting area and consultation rooms at participating centres containing contact details of the local research team.

6.2. Study Registration

Once eligibility for entry into the study has been confirmed, and patient has consented to participate, the patient can be registered into the SLEEP T2D Study. Registration Forms will be provided and should be completed and used to collate the necessary information. Once completed, patients can be registered via telephone or online (see section 6.4).

Following registration, a unique Study ID will be given to each patient and should be recorded in the Patient Recruitment and Identification Log in the ISF**.** Relevant parties should be notified including the participant's GP (section 6.5). The participant will then receive screening assessments as outlined in Section 8. The complete original Registration Form should be returned to the SLEEP T2D study office for all registered patients and a copy placed in the ISF.

6.3. Randomisation into the RCT

The CI or delegate will contact the applicable participating site with results of the participant's baseline sleep assessment. Using these results, the local PI will determine whether the participant is eligible to be randomised into the RCT.

Once eligibility has been assessed, the PI or delegate will call the participant with the results of their sleep assessment and inform them whether or not they are eligible to be randomised into the RCT.

- Participants who are not eligible to be randomised into the RCT will continue in the study as part of an observational cohort.
- Participants who are eligible to be randomised into the RCT will be invited to attend a study visit at their local research centre where the RCT will be discussed and further informed consent obtained. A Randomisation Form (capturing information on RCT eligibility criteria, minimisation and consent) will be completed.

To randomise eligible patients, recruiting sites should telephone or use the online randomisation service (section 6.4).

When the RCT treatment allocation has been assigned, this will be recorded in the Patient Recruitment and Identification Log maintained at site and the participant's GP and will be notified (see Section 6.5). The complete original Randomisation Form should be returned to the SLEEP T2D Study Office for all randomised patients and a copy placed in the ISF.

6.4. Telephone and Online Registration and Randomisation

Registration and randomisation services will be provided by telephone or a secure online system at the Birmingham Clinical Trials Unit (BCTU). Unique log-in usernames and passwords will be provided to

those who wish to use the online system and who have been delegated the role of registering or randomising participants into the study as detailed on the Site **Signature and Delegation Log**.

The online system

https://bctu-redcap.bham.ac.uk/redcap_v8.3.2/

Available 24 hours a day, seven days a week, apart from short periods of scheduled maintenance.

The telephone toll-free service

0800 953 0274

Available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

The Registration Form and the Randomisation Form will be supplied to research sites to collate all necessary data items required for registration and randomisation respectively. All data items on the Registration Form must be answered before a Study ID can be given. All data items on the Randomisation Form must be answered before a treatment allocation can be given.

Investigators will keep the log which links patients with their allocated Study ID and treatment arm in the Patient Recruitment and Identification Log. The Investigator must maintain this document in the ISF, and should **not** submit it to the SLEEP T2D study office. The Investigator will also keep and maintain the anonymised Screening Log which will also be kept in the ISF, and should be available to be sent to the study office upon request. Following registration or randomisation, a confirmatory email will be sent to the local PI, randomising clinician, CI and Sleep Technician.

6.4.1. Randomisation

Participants who are eligible to be randomised into the RCT will be randomised in a 1:1 ratio to either CPAP or no CPAP. A minimisation algorithm will be used within the computerised randomisation system to ensure balance in the treatment allocation over the following variables:

- ethnicity (white Europeans, others)
- gender (male, female)
- severity OSA (mild [AHI<15], moderate to severe [AHI≥15])

A random element will be included in the minimisation algorithm, so that each patient has a probability (unspecified here) of being randomised to the opposite treatment than they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.5. Informing the Participant's GP

If the participant has consented/agreed, the participant's GP should be notified that they are registered in SLEEP T2D study by the PI or delegate, using the ethically approved SLEEP T2D GP Letter**.**

As part of standard clinical care, the PI or delegate will also notify the patient's GP of the results of sleep studies performed at baseline and 2 year follow-up and of any other matters resulting from information obtained from the patient, with any action required.

7. RCT Interventions

Participants that are allocated to the CPAP arm will be provided with a CPAP machine (Airsense 10 Autoset™). This machine features built-in wireless connectivity capability to monitor compliance remotely via a secured website, AirView (AV); AutoRamp™ with sleep onset detection; expiratory pressure relief and Easy-Breathe technology, all of which aid in the use of CPAP and encourage compliance.

Each patient in the CPAP arm will be given an appropriate mask, connecting hose, a heated humidifier, and all the necessary accessories to operate the CPAP equipment for the duration of the trial.

An important aspect of this trial is the use of the CPAP-integrated remote monitoring technology which will download the CPAP usage data as well as other technical information. The devices feature built-in wireless connectivity so the results can be accessed via a secured website using AV.

AV can create compliance and therapy reports, detailed data reports and allows a suitably qualified person to remotely change settings to improve patient compliance and comfort if required. These online reports will only include the patient study number, a dummy date of birth and initials. Other data included in the report include CPAP usage and technical data/faults related to the CPAP machine.

7.1. International standards

ResMed has over 50 AV accounts which use this method of monitoring in the UK and complies with the NHS IG Toolkit and also the International Data Management Standard ISO 27001.

AV is compliant with the security policies and practices of many national and international standards, including NHS IG Toolkit: Ref: 8J317 *(2015-2016 – Score 90%),* ISO 27001 Certificate (IDS Host), and the Data Protection Act 2018 and the EU General Data Protection Regulation 2018. To fulfil these requirements AV contains security features that ensure only those researchers who need to view patient records are granted access when logging onto AV. These measures include:

- ResMed does not have any access to an AV account.
- Transmissions from the wireless network contains no patient-identifying data.
- Information accessed by the internet is secured using Secure Socket Layer encryption technology.
- Information stored on the centralised servers is located in two secure data centres with tape backups and are protected by firewalls, intrusion detection systems and other securing mechanisms.

- A login session times out after a pre-defined period if AV does not detect any activity.
- The CI will set access permissions so that only the CI and Sleep Technician will have access to the data. Local sites will not have access to the data, but participants will have access to their own data if they choose to do so.

7.2. Data Acquisition and Security

Data Acquisition in AV may be acquired wirelessly or via card data downloads performed by the CI or Sleep Technician if wireless connection is not available. There is a significant difference between these two mechanisms. In wireless monitoring, data enters the system and is allocated to a patient without the intervention of a user, whereas in card data monitoring, data only enters the system as a consequence of a user action.

In the case of card downloads, the user dictates the ultimate destination (i.e. patient record) of the data (provided the user has access to that patient). In the case of wireless acquisition, the received data is routed automatically to the correct patient record. When the patient is set up in AV a device pin number as well as the serial number is added as a safety precaution to prevent a patient being allocated to the wrong device due to an administrative error.

The basic mechanism is to do the routing on the basis of device serial number and device 3 digit pin number. The identifying field is the Device ID. This data is transmitted via the mobile network one hour after use to the AV secure data centres (operated for ResMed and both located in France), then to the AV user.

Inside AV, the nightly treatment data, identified by the Device ID, is kept separate from the patient and organisation data – only by logging on via the web browser that has had the Security Certificate installed and the correct password entered will the two “databases” appear to the user as one database. To ensure security and privacy of information transferred across the public Internet, AV is served with an SSL transport, denoted in URLs with https://. A VeriSign server certificate used to establish the SSL connection ensures that the server is verifiable and users authenticated. It should be noted that the S9 uses a proprietary protocol over TCP/IP and does NOT use HTTP. It operates on Port 31621 and is protected using a message digest. In effect, even if an unauthorised person acquired a data packet, this person would have to know what kind of data it is and in which format it is arranged to understand it. Only by logging into AV via the HTTPS SSL secured webpage will the data be visible/understandable.

7.3. Compliance and Remote Wireless Monitoring

Adequate compliance in this trial will be defined as an average usage of CPAP >4 hours/night on 70% of nights. This does not have to be >4 hours of continuous usage. Compliance will be monitored through the AV remote monitoring: it will not be participant-reported.

The Sleep Technician and CI (only) will have permission to remotely access and change CPAP settings via the secured website using AV. The Sleep Technician and CI will view sleep data of all patients

remotely twice weekly on average and will identify those using CPAP <4h. Patients will be called by the Sleep Technician or CI if CPAP usage is <4h per night for a set number[2] of nights to determine the cause and any action required (which may or may not require meeting the patient in person).

ResMed will supply a starting package used routinely in routine clinical care and which includes an educational DVD and a phone follow-up. If required, the Sleep Technician will supply face-to-face training at a date suitable for patients.

The patient can also register with myAir online, which will give them coaching and reinforcement and educational tools. They can register with myAir at the following web address: - http://www.resmed.com/us/en/consumer/airsolutions/personalized-support/myair.html. This online support is part of the usual routine care given by ResMed and is not part of the trial intervention; therefore, we will not collect metrics on its use.

Crossover from one RCT arm to the other will be at the CI and local PI's discretion based on clinical grounds. There are, ordinarily, no medical circumstances in which CPAP should be stopped. Participants who are not receiving CPAP may require CPAP, but this will be judged on a case-by-case basis by the CI and local PI. If relevant exclusion[3] criteria indicating a possible need for CPAP develop during the RCT, then the local research team should assess the participant for the need for CPAP treatment.

7.4. Training and Information Available at Research Sites

ResMed will provide training to the CI and the Sleep Technician, who will disseminate training to the research sites (during site initiation visits where possible; central study meetings will also be considered). Local sites will then be able to train participants in use of the sleep assessment devices (documentation and a DVD/link to web-based video are also routinely provided to participants). Quality assurance of this training will be carried out automatically, as the Sleep Technician will review all sleep assessments, and will contact sites to address any potential training issues if more than 20% of sleep assessments at a given site result in insufficient data to determine the presence or otherwise of OSA. A recording of at least 4 hours with no OSA can be said to determine the absence of OSA; the presence of OSA may be determined with a shorter recording if there are sufficient events recorded. A log of these reviews will be kept to easily view data quality site by site. Similarly, the Sleep Technician will remotely monitor CPAP usage, and will contact patients in instances of non-compliance as described in 7.3 above.

[2] The number of nights CPAP usage is <4h per night before a call is initiated will initially be 2 consecutive nights. This may change during the course of the trial if it is deemed to be too intensive.

[3] Is a professional driver, operator of heavy machinery and/or working at high altitude; Has a history of falling asleep whilst driving within last two years.

7.5. Troubleshooting

We do not envisage any problems with remote access to patients' CPAP usage. The data is transmitted via the 2G network and it is very rare for a device not to transmit due to no signal. If the signal is poor or the device is not transmitting, when the device is moved into an area where there is signal the device will transmit all the data. If required, the data will be accessed via the data card in the device. The patient will be asked to post the SD card to the Sleep Technician for analysis or a member of the study team will obtain the SD card in person. Pre-paid and addressed envelopes will be supplied in this cases. This will of course mean that CPAP compliance for such patients is not reviewed twice weekly; these cases will be reviewed by the Sleep Technician and CI and suitable action decided upon if CPAP compliance is insufficient.

In case of failure of the CPAP device, this will be detected by remote monitoring (or, less regularly, by review of the SD card date) if not reported by the participant, and ResMed will arrange for replacement equipment.

7.6. Initiation and Supply of Trial Intervention

Once the patient has been randomised to CPAP, an email will be sent to the Sleep Technician and CI, who will contact ResMed to initiate delivery of CPAP equipment and the starting package either directly to the patient's home or to the Sleep Technician/CI who will give the CPAP machine to the patient. Patients in the RCT will give explicit consent for their contact details to be passed on to ResMed. The trial will aim for CPAP initiation to start within 2 weeks of randomisation. This will be closely monitored in the trial. Initiation of CPAP will be performed by the CI or the Sleep Technician face to face or remotely depending on which fits the patient circumstances best. Patients will be contacted by telephone 2-3 times during the first week of use to help with compliance and correct use.

7.7. Return of CPAP Equipment at End of Trial

At end of the trial, the CI or Sleep Technician will contact the relevant PI and make recommendations for future treatment for patients who receive CPAP. All patients who show sufficient compliance with CPAP will be referred to a sleep centre and continued treatment will be recommended. Compliant patients (as defined in section 7.3) who wish to continue using CPAP will be allowed to continue using the SLEEP T2D CPAP equipment until NHS equipment is in place. The CI or delegate will arrange the return of CPAP equipment.

8. Outcome Measures and Study Procedures

See Section 8.10 / Table 2 for the complete schedule of assessments. Table 1 below is a summary of outcome measures and the study objectives they relate to (please see Section 2.1 for a full description of the numbered secondary and tertiary objectives).

Table 1. **Summary of outcome measures and secondary and tertiary objectives**

			Physical exam and BP	Circumferences hip, waist, neck	Routine biochemistry	Peripheral neuropathy – MNSI, SF-MPQ, vibration perception threshold, monofilament test	Retinopathy	ESS & Berlin questionnaire	SF-12, MEQ & PSQU	Cystatin C	Additional bloods for future biomarkers	Saliva kit	SUDOSCAN AND CAN AT SELECTED SITES ONLY DEPENDENT ON EQUIPMENT AVAILABILITY	SUDOSCAN and CAN assessment
Secondary objectives: to assess the impact of CPAP on:	1	Measures of diabetic nephropathy & CKD			x					x				
	2	Diabetic neuropathy				x								x
	3	Diabetic retinopathy & maculopathy					x							
	4	Metabolic parameters	x	x	x									
Tertiary objectives	1	To explore the utility of different biomarkers in screening for OSA in patients with T2D									x	x		
	2	To explore the mechanisms via which CPAP might have an impact on diabetes-related complications									x			
	3	To assess the relationship between other sleep-related disorders & metabolic parameters & vascular disease						x						
	4	To build up a cohort of well characterised patients						x	x					

8.1. Physical Exam and Blood Pressure

Several measures will be taken:

Circumference measurements (routine care)

Waist, hip and neck circumferences will be measured using an inelastic measuring tape as described in previous studies [77-79]. All circumferences will be taken with the subjects standing upright, with the face directed straight, and shoulders relaxed. Two measurements will be entered into the CRF (for average calculation). Waist circumference will be measured at the midpoint between the inferior border of the ribcage and the superior aspect of the iliac crest. Hip circumference will be measured horizontally at the widest circumference of the hips. Neck circumference will be measured in the midway of the neck, between mid-cervical spine and mid-anterior neck. In men with a laryngeal prominence (Adam's apple), it will be measured just below the prominence.

Height and weight measurements (routine care)

Height will be measured to the nearest 0.1 cm with a rigid stadiometer. Body weight will be measured in light indoor clothing to the nearest 0.1 kg

Blood Pressure (routine care)

BP will be measured by an automated device with the patient in sitting position and the arm resting on a table. Two measurements will be taken at least 20 minutes apart with the first measurement to be taken about 20 minutes after the start of the consultation. The two readings will be entered into the CRF (for average calculation).

8.2. Routine Biochemistry

For routine biochemistry (HbA1c, lipids, creatinine, and urinary ACR), recent results (within 3 months from baseline, or 12 months for ACR) can be used from patient notes; otherwise fresh samples will be collected. These will require 1 yellow top tube (for lipids and creatinine, approximate volume 8mL) and/or 1 purple top (for HbA1c; approximate volume 8mL), and/or a morning urine sample (approximate volume 20 mL) for urinary ACR. These tests will be performed by the local NHS laboratory as per routine care.

HbA1c and lipids (routine care, using retrospective data if available)

HbA1C (including percentage, if locally calculated) and total cholesterol, triglycerides, HDL and LDL (where LDL is locally available) will be recorded.

eGFR (routine care, using retrospective data if available)

Serum creatinine levels will be recorded. The eGFR will be calculated by the study database from the creatinine value supplied using the MDRD equation ($175 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ [if female] $\times$ 1.212 [if black], creatinine measured in mg/dL) [80]. Serum creatinine measurements should be avoided during acute illness or following imaging that used contrast. Note that the eGFR value used to check patient eligibility can be taken from patient notes within 12 months of baseline; however, the serum creatinine level recorded at baseline should be taken from within 3 months of the visit.

Urine Albumin (routine care, using retrospective data if available)

Albuminuria will be assessed using a single measurement of urine albumin. Microalbuminuria will be defined as ACR >3.4mg/mmol and macroalbuminuria as ≥30mg/mmol [81, 82]. If the patient has a urinary tract infection then ACR will be measured when free from infection. Please note that an ACR value is not required before registration.

8.3. Biomarkers

Additional samples for biomarker analysis will be taken at sites with the capacity to do so.

Serum Cystatin C (additional care)

A serum sample for the measurement of cystatin C will be taken to analyse for early markers of diabetic CKD. These will be measured by Mologic (National Agri-Food Innovation Campus, Sand Hutton, York, YO41 1LZ).

Saliva kits (additional care)

Saliva samples will be analysed by Mologic for biomarkers that could aid screening for OSA in patients with T2DM. These potential biomarkers include (but are not limited to) markers of oxidative stress, nitrosative stress and inflammatory markers.

Additional biomarker blood samples (additional care)

Additional blood samples will be taken for storage at designated research laboratories within UoB for analysis for OSA biomarkers and potential mechanisms of the impact of OSA on the study outcomes.

8.4. Quality of Life

A general health related QoL measure will be used, the Short Form Health Survey (SF-12) (this is additional care).

8.5. Retinopathy

DR, maculopathy and STDR are assessed using 2 x 45 degrees digital retinal images per eye as per the English National Screening program guidelines [83]. This should be retrospective data take as part of routine care.

The image grades will be obtained from the patient's electronic records, from the national diabetic retinopathy screening program, direct from the appropriate screening centre, or from the letter sent to the patient informing them of their grades. The latest grade prior to each visit will be recorded.

Most clinical centres should have access to the retinopathy grades via one of the methods above and will be able to check this directly. If required, the patients will be asked to bring in a letter of their grade to the centre at each visit. In cases where the patient letter is used, a copy of the letter will be taken and inserted in the patient's medical notes.

8.6. Peripheral Neuropathy

The Michigan Neuropathy Screening Instrument (MNSI) (routine care)

MNSI is a validated questionnaire and foot examination that has been used in several landmark epidemiological studies [84-87]. The questionnaire component (MNSIq) comprises 15 questions [85]. The examination component (MNSIe) comprises a limited foot inspection to identify deformity, skin abnormalities, and ulceration, coupled with an assessment vibratory perception at the great toe (measured using a 128 Hz tuning fork) and ankle tendon reflexes [85].

Short Form McGill Pain Questionnaire (SF-MPQ) (routine care)

The SF-MPQ is used to assess the presence and severity of painful neuropathy [88].

Neuropad (routine care)

The indicator test (Neuropad) is a plaster which is applied to the sole of the feet just below the 1st and 2nd toes of both feet. The Neuropad is a non-invasive method to assess sudomotor function. While the MNSI mainly assess large fibre function, the Neuropad is closely related to small fibre function. The Neuropad is based on the colour change of a cobalt II compound from blue to pink after 10 minutes exposure to dermal foot perspiration at the plantar foot regions [89]. The change in colour will be recorded in the database as none, partial or complete and the time to the start of colour change will also be recorded.

Vibration perception (routine care)

Vibration perception will be tested using a biothesiometer on the great toe of each foot; the average of three measurements will be taken [90].

10-g monofilament test (routine care)

The perception to a 10-g monofilament (applied to 10 positions, the tip of each toe, under 3 metatarsal heads, the plantar surface of the foot and the dorsal space between the first and second toe) will be used as a test for foot insensitivity; an abnormal monofilament test is defined as <8 correct responses [91].

8.7. Additional Peripheral Neuropathy at Selected Sites

SUDOSCAN (additional care)

SUDOSCAN assesses sudomotor function through galvanic skin response. This test is similar to Neuropad in that it measures sweat production in a non-invasive way. It provides an accurate evaluation of sweat gland function. Patients place their hands and feet on stainless-steel sensor plates, and an incremental low direct voltage (lower than 4V) is applied for two to three minutes. Measurement is based on an electrochemical reaction between the sensor plates and chlorides of the sweat after being stimulated by the low-level voltage. Quantitative results are expressed as Electrochemical Skin Conductances (ESC, in microsiemens, µS) for the hands and feet. Training will be provided by the company and the CI. Due to the limitations of equipment availability the SUDOSCAN test will only be performed at selected sites.

Patients with pacemakers, defibrillators or similar implantable devices, who have had a whole hand or foot amputated, or who have an active foot ulcer will be excluded from the SUDOSCAN test

Cardiac Autonomic Neuropathy (additional care)

Cardiac autonomic neuropathy (CAN) will be assessed using heart rate variability (HRV) and will be analysed using the continuous wavelet transform methods to generate numerical and graphical data using the ANX 3.0 software, ANSAR Inc., Philadelphia, USA. Details can be found in our previous work [92]. HRV and BP are recorded with the patient in sitting position during resting, deep breathing, Valsalva manoeuvre and standing position [93]. A diagnosis of CAN will be made when 2 or more of the following tests are abnormal: E/I ratio, Valsalva ratio, 30:15 ratio and postural drop in BP (drop of 20mmHg in systolic or 10mmHg in diastolic BP) [94]. Age-related normal values were defined as previously reported [95].

The test will be performed while the patient is in sitting position and in the fasting state if possible. If not fasting, caffeine intake should be avoided for 2 hours prior to the test. Due to the limitations of equipment availability the CAN test will only be performed at selected sites.

Training on how to perform the CAN will be provided by the CI. The raw data will be analysed on the CAN laptop and a summary sheet of results will be printed off and for purposes of this trial will be classed as source data.

Patients with pacemakers, defibrillators or similar implantable devices will be excluded from doing the CAN test.

8.8. Sleep and Obstructive Sleep Apnoea

One night home-based sleep assessment (additional care)

Presence and severity of OSA will be assessed by performing a one night home-based sleep assessment using a portable multi-channel respiratory device approved for screening sleep apnoea (ApneaLink Air, ResMed). Portable devices are used widely in sleep apnoea research including my previous work [39, 40, 96]. The device records oral/nasal airflow, chest movements, oxygen saturations, and heart rate.

The ApneaLink Air device comes with Airvew diagnostics. This is supplied by ResMed and is similar to AV (see Section 7) but is linked with the sleep assessment and not CPAP. In Airvew diagnostics the study centres will download the sleep assessment from the device once returned by patient. Once downloaded, the sleep assessment will become accessible via a remote website. The sleep studies will be scored and interpreted by the centrally based Sleep Technician remotely; where there are any queries raised by the Sleep Technician (e.g. uncertainty about how to score a particular respiratory event) Dr Asad Ali, a consultant in sleep medicine and/or Prof. Brendan Cooper, both part of the study team, will be consulted and a consensus reached. They will only be provided with anonymised data; they will, where required, review data from all sites.

The Sleep Technician will print off the report, classed as source data, and return to the SLEEP T2D Trials Office. The PI will be informed of the results of the sleep assessment with recommendations by the CI or delegate.

The sleep assessment will give, amongst other data, the AHI, the average number of apnoea and hypopnoea events per hour, which is routinely used to classify the severity of OSA to mild, moderate, and severe (5-14.9, 15-29.9 and ≥30 respectively).

NOTE: Patients receiving CPAP will not require a sleep assessment at their final visit as the CPAP machine records the data required.

The Epworth Sleepiness Scale (ESS) (routine care)

ESS, an 8 item questionnaire, is a measure of day time sleepiness [97]. ESS correlates with sleep latencies [97] and with measures of OSA severity [98].

The Berlin questionnaire (routine care)

The Berlin Questionnaire focuses on a limited set of known risk factors and symptoms for OSA; one introductory question and four follow-up questions concern snoring; three questions address daytime sleepiness, with a sub-question about sleepiness behind the wheel and one question concerns history of high blood pressure and obesity (based on BMI) [99].

Sleeping Habits, Duration and Quality (additional care)

Data regarding sleeping habits, duration and quality will be collected using the Horne Ostberg Morningness-Eveningness questionnaire (MEQ) [100] and the Pittsburgh Sleep Quality Index (PSQI) [101].

8.9. CPAP Usage and Compliance

The Sleep Technician will be responsible for printing off individual patient summary reports at the end of the study. The Sleep Technician or delegate will transcribe relevant information from the report onto the CRF and return it to the SLEEP T2D study office.

8.10. Schedule of Assessments

See Table 2 below for schedule of assessments. All data from the study assessments will be collected for all patients, at the respective research sites unless otherwise specified.

Table 2. **Summary of Assessments**

	TRIAL PERIOD			
	Baseline visit (0)	Allocation (1) **RCT only**	Follow-up (telephone)	Follow-up visit (2)
TIME POINT	0	1m ± 1m	6m, 12m, 18m ± 2m	2 yrs ± 3m
REGISTRATION & TREATMENT ALLOCATION				
Main Eligibility Assessed	x			
Study Consent	x			
Registration onto study	x			
Additional Eligibility for RCT assessed		x		
Consent RCT		x		
Treatment Allocation / Randomisation		x		
GP letter(s)	x	x		x
INTERVENTION (if receiving)				
CPAP Initiation (CPAP use continues until 2 years)		x		
ASSESSMENTS				
QoL Questionnaire SF12	x			x
General Patient Information: Patient details	x			
Review of Medication	x			x
Review of past Medical History	x			
Physical exam and Blood Pressure: Height, Weight , Blood Pressure (standardised)	x			x
Circumferences Hip, Waist, Neck (standardised)	x			x
Routine Biochemistry: lipid profile and HBA1c, eGFR & creatinine, plasma urea, electrolytes & creatinine, ACR	x[a]			x[a]
Additional blood for Serum cystatin C	x			x
Additional blood for future biomarker studies	x			x
Saliva kit (given to patient)	x			x
Peripheral Neuropathy: MNSI; SF-MPQ; Vibration perception threshold; monofilament & Neuropad test	x			x
SUDOSCAN & CAN assessment	x selected sites only			x selected sites only
Retinopathy	x			x
Sleepiness and obstructive sleep apnoea risk: One night home based sleep assessment	x			x
ESS and Berlin Questionnaire	x			x
Sleeping habits, duration and quality: MEQ and PSQI	x			x
6 monthly follow-up form			x	
SAE monitoring (SAE forms)	x	x	x	x

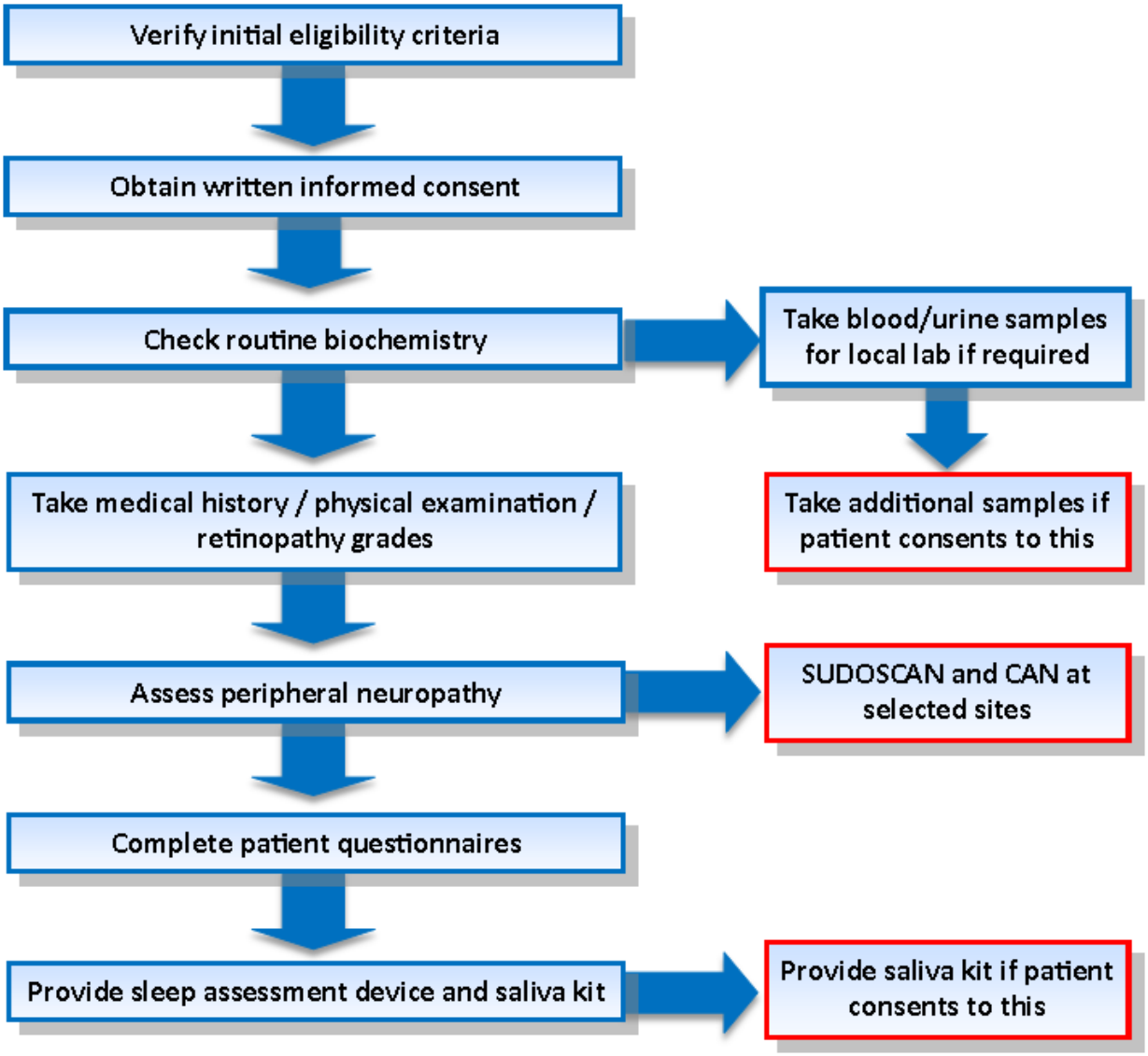
[a] If performed within 3 months of visit (within 12 months for ACR) then previously recorded measurements can be used

8.10.1. Baseline Visit

The baseline visit should take place in the morning if possible for urinary albumin/creatinine ratio (ACR), if an ACR value from the last 12 months is not available from patient notes. If this is not possible the patient should return a morning urine sample at the time that they return the sleep machine.

The baseline visit will involve the procedures described overleaf, and as shown in figure 3 below. If necessary (e.g. to fit local requirements) then the exact order of procedures shown does not have to be followed, although written informed consent must always be received before any trial specific procedures are carried out.

Figure 3. **Baseline assessment day schema**



Baseline assessments:

- Verify initial eligibility criteria
- Obtain written informed consent from the potential participant to undertake the screening procedures
- Register the patient into the study (see Section 6)
- Review recent routine biochemistry results (see Section 8.2) to ensure within 3 months of baseline visit. The exception is ACR, which can be within last 12 months. If not within the time period allowed:
    - collect blood for biochemistry (8-16 ml blood [1 yellow top tube and/or 1 purple top tube])
    - collect morning urine samples for ACR (approximate volume 20 ml)
- Review and record general patient information (See Section 8.13)
- Record results of physical examinations and blood pressure (see section 8.1)
- Collect additional blood for biomarker studies (2 yellow top tubes, 16ml, 2 purple top tubes, 16ml) for spinning and storage at -80^{o}C (see sections 8.3 and 8.12)
- Assess peripheral neuropathy. This involves investigator tests and patient questionnaires (see section 8.6). For the MNSI assessment there are two forms, one to be completed by the assessor and one by the patient
    - MNSI A: patient form
    - MNSI B: health professional form
    - SF-MPQ
- Selected sites: Assess additional peripheral neuropathy. This involves the SUDOSCAN and CAN tests (see section 8.7)
- Administer QOL questionnaire**:** SF12
- Assess sleeping habits, duration and quality (see Section 8.8) using:
    - Epworth Sleepiness Scale
    - Berlin Questionnaire
    - MEQ
    - PSQI
- Provide and arrange return of portable respiratory device for home based sleep assessment (see section 8.8)
- Discuss with patient how results of sleep assessment will be disseminated to participant and GP
- Provide participant with Saliva kit and addressed envelopes for patient to return
- Complete relevant CRFs for Baseline assessments and place copy in Investigator Site File (ISF) and return originals to SLEEP T2D study office

8.10.2. Treatment Allocation for RCT

If the participant is eligible to be randomised into the RCT, they will be invited to attend a visit or contacted by telephone so that the RCT can be discussed. Additional consent will then be gained prior to randomisation as discussed in section 5. If the participant is allocated to CPAP then the aim will be for initiation of treatment to begin within 8 weeks of registration.

8.10.3. Six monthly Follow-Up

All patients will be called at 6 monthly intervals by the CI, Sleep Technician or delegate and asked a number of questions relating to changes in health status. A 6 monthly assessment CRF will be completed and returned to the SLEEP T2D study office. This will include a question asking female participants about pregnancy.

8.10.4. Two Year Follow-Up Visit

The final visit will occur two years after the screening assessments and will follow the same procedures as the baseline visit.

8.10.5. Sleep Studies

The CI/Sleep Technician (or delegate) will inform PIs of the results of the sleep assessment within four weeks of the sleep assessment being returned. Once the results of the sleep assessment are known, the PI will inform the patient's GP of the results if required.

8.11. Training of Research Site Staff

The SLEEP T2D study office will arrange protocol-specific training for staff at participating research sites as required. In addition, training will be provided on:

- Peripheral and autonomic neuropathy assessments
- The use of the ApneaLink Air device and software.

Study-specific training should be recorded in the study Training Log.

The selected PIs will all be qualified diabetologists who use many of the study assessments/tools in their routine clinical practice. The CI (during site initiation visits where possible) and local PI will train local research teams in aspects of the study in which they may not have expertise.

8.12. Processing of Additional Samples

Full details of sample processing are described in the separate study laboratory manual. It is the responsibility of the PI to maintain the Research Sample Log recording samples collected, stored, and couriered. The SLEEP T2D study office may request this log during the study.

8.12.1. Serum Cystatin C

A serum sample for cystatin C will be taken. One yellow top tube will be required. Samples will be pseudo-anonymised using the study number and stored at the participating site in a -80°C freezer after processing. The CI will arrange for the samples to be couriered on dry ice to Mologic in batches.

The cystatin C measurements will be performed by Mologic. Explicit consent will be sought from participants for their samples to be sent to and processed by Mologic. The source data for the tests performed at Mologic will be the results sent from the company to the SLEEP T2D study office.

8.12.2. Additional Bloods

Research blood samples (2 purple and 1 yellow top tubes) will be taken. Blood samples will be pseudo-anonymised using the study number and stored at the participating site in a -80°C freezer after processing. The CI will arrange for the samples to be couriered on dry ice to UoB in batches. These will be stored at the Human Biomaterials Resource Centre at UoB in order to perform further analysis for OSA biomarkers and potential mechanisms regarding the impact of OSA on the study outcomes.

8.12.3. Saliva Kits

Patients will be supplied with saliva sample kits at baseline and 2 years. A pre-paid envelope will be provided and these will be sent to and analysed by Mologic. Saliva samples will be sent anonymised and only labelled with study numbers and no patient identifiable information. The source data for the tests performed at Mologic will be the results sent from the company to the SLEEP T2D study office.

8.13. General Patient Information

The following general information will be collected as part of the participant assessments: Full name, initials, date of birth, gender, diabetes duration, targeted medications history, past medical history, smoking status, and alcohol intake.

8.14. Participant Withdrawal

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the study (or part of) at any time. Participants will be consented to allow their data to still be used and analysed after study withdrawal.

Types of withdrawal as defined are:

- The participant would like to withdraw from study treatment, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the study analysis)
- The participant would like to withdraw from study treatment and does not wish to attend study visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the study analysis, including data collected as part of long-term outcomes)

- The participant would like to withdraw from study treatment and is not willing to be followed up in any way for the purposes of the study and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the study analysis)

or

- The participant wishes to withdraw completely (i.e. from study treatment and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future study analysis

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data. The GP will be informed of the patient withdrawal and will be given further advice regarding the patient's management. On withdrawal the CPAP equipment and accessories will be returned to the research centre.

If exclusion criteria develop during the study then this will not necessitate withdrawal from the study – this will depend on the clinical judgement of the local investigator. As per section 7.3 above, if relevant exclusion[4] criteria indicating a possible need for CPAP develop for RCT participants not receiving CPAP, then the local research team should assess the participant for the need for CPAP treatment.

9. Adverse Event Reporting (RCT only)

9.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of abbreviations and definitions. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant. This should be documented in the source data with reference to the protocol.

9.2. Adverse Events (AE)

There are AEs commonly experienced by patients receiving CPAP. As these events are well characterised, it is highly unlikely that this trial will reveal any new safety information relating to this intervention. AEs other than Serious Adverse Events (SAEs) will therefore not be reported; this will not affect the safety of participants or the aims of the trial.

Any trial-related SAEs will be reported on a trial-specific SAE form and will follow the procedure/timeframes outlined in this section of the protocol.

[4] Is a professional driver, operator of heavy machinery and/or working at high altitude; Has a history of falling asleep whilst driving within last two years.

Other outcomes, which may also be considered safety outcomes, but which are anticipated outcomes for this group of patients (and therefore not considered trial-related), will not be reported as AEs for this trial but will be monitored during the 6 monthly follow up telephone calls.

9.3. Serious Adverse Events (SAE)

All events which meet the definition of serious will be collected and recorded in the participant notes and the CRF. Trial-related SAEs will be reported to the SLEEP T2D study office within 24 hours of site staff being made aware of the event.

Hospitalisation for elective procedures (unless brought forward due to worsening symptoms), social reasons, or logistical reasons are not regarded as a SAE.

Table 3. **SAE Causality**

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication)	Unrelated
Not related	There is no evidence of any causal relationship	

9.4. Reporting Period

SAEs may occur following randomisation into the RCT. The SAE reporting period will end 30 days after the participant's last trial assessment at 2 years.

9.5. Reporting Procedure

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form. When completing the form, the PI will be asked to define the causality and the severity of the AE.

The following categories in Table 3 will be used to define **the relatedness (causality)** of the SAE.
On becoming aware that a participant has experienced an SAE, the Investigator or delegate should report the SAE to their own Trust in accordance with local practice and to the BCTU trials office.

To report an SAE to the BCTU trials office, the Investigator or delegate must complete, date and sign the trial specific **SAE form**. The completed form should be faxed or emailed to the BCTU trials team using the number/email address listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form to 0121 415 9135 or email to SleepT2D@trials.bham.ac.uk.

On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number and return this via fax or email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number, the site should contact the BCTU trials team by telephone within 1 working day. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

Where an SAE Form has been completed by someone other than the Investigator, the original SAE form will be required to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

9.5.1. Provision of Follow-Up Information

Following reporting of an SAE, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new **SAE Form**, using the SAE reference number provided by the BCTU trials team. Once the SAE has been resolved, all follow-up information has been received and the paperwork is complete, the original SAE form that was completed at site must be returned to the BCTU trials office and a copy kept in the Site File.

9.6. Reporting Procedure – BCTU Study Team

On receipt of a SAE form from the site, the BCTU trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. The unique reference number will be sent to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Trial Master File (TMF).

On receipt of an SAE Form, the CI or delegate will independently determine the **seriousness and causality** of the SAE. An SAE judged by the PI, CI or delegate to have a reasonable causal relationship (i.e. possibly, probably or definitely related) with the intervention will be regarded as a related SAE. The causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

The CI or delegate will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

9.7. Expected Adverse Events

Adverse events that are expected in this patient population and using this intervention include:

- Complications related to or deterioration of T2D including:
    - hyperglycaemia, hypoglycaemia; the development of cardiovascular disease (e.g. stroke, heart attack, angina, intermittent claudication, or having a vascular procedure such as coronary stents, coronary artery bypass graft, peripheral vascular stent or bypass); amputation etc.
- Complications related to or deterioration of T2D-related comorbidities including:
    - worsening renal function, end-stage renal disease or dialysis; worsening eye disease (cataract, laser treatment, intra-ocular injection, worsening vision, blindness); foot ulcer, gangrene, amputation, diabetic foot, foot infection, etc.
- CPAP-related adverse events including dry mouth, claustrophobia, discomfort.

9.8. Reporting to the Research Ethics Committee

BCTU will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) and the Sponsor within 15 days.

9.9. Reporting to ResMed

BCTU will not report any expected equipment-related AEs or SAEs to ResMed as the equipment is non-invasive, being used for its licenced use, and has CE mark certification.

9.10. Other Safety Issues Identified During the Course of the Trial

The REC and Sponsor will be notified immediately if a significant safety issue is identified during the course of the trial.

9.11. Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the site file and TMF.

9.12. Study Oversight Committee

The independent Study Oversight Committee (SOC) will review all SAEs.

10. Data Handling and Record Keeping

10.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained. Source data is generally kept as part of the participants' medical notes generated and maintained at site. However, source data will be kept in the TMF at BCTU in the following cases:

- Serum cystatin C. Mologic will supply a report of all Serum cystatin C results at the end of the study
- Saliva kits: Mologic will supply a report of all salivary biomarker results at the end of the study.

NOTE: The PI is still responsible for recording information which is deemed relevant for patient medical care in their medical notes.

Some data variables will be completed by the participant and/or entered directly onto the CRF, and as such will be classed as source data. These are clearly identified and detailed as follows:

- SF-12
- MEQ and PSQI
- ESS and Berlin Questionnaire
- SF-MPQ
- MNSI patient section
- CPAP reports and visits for compliance issues
- Six monthly assessment forms
- Sleep assessment reports (to also be sent from CI/Sleep Technician to PIs)

Where source data is the CRF, the original will be returned and stored in the TMF held at BCTU and a copy/duplicate inserted in ISF at the Site if the assessment performed at the Site.

10.2. Case Report Form (CRF) Completion

Paper CRFs must be completed, signed/ dated and returned to the SLEEP T2D Study Office by the PI or an authorised member of the site research team (as delegated on the SLEEP T2D Trial Signature and Delegation Log) within the timeframe listed in Table 4 overleaf.

Copies of all completed CRFs should be filed in the ISF. Entries on paper CRFs should be made in ballpoint pen, in dark ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each CRF must be consistent with the source data and any discrepancies explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to SLEEP T2D CRF completion guidelines. These include advice on:

- CRF completion and corrections (as above)
- Missing/incomplete data (as above)
- Date format and partial dates (dd/mmm/yyyy)
- Rounding conventions
- Entry requirements for concomitant medications
- Which forms to complete and when
- What to do when a subject changes address
- What to do when a subject withdraws from the trial
- Completing SAE forms and reporting SAEs
- Protocol and GCP non-compliances

Table 4. **CRFs**

Forms	Schedule for submission
Registration Form	Original returned as soon as possible after registration. Copy in ISF
Randomisation Form	Original returned as soon as possible after randomisation. Copy in ISF
Baseline Form	Original returned as soon as possible after baseline visit. Copy in ISF
CAN and Sudoscan Form	Original returned as soon as possible after applicable visit. Copy in ISF
Patient questionnaire booklet	Original returned as soon as possible after applicable visit. Copy in ISF
Home Based Sleep Assessment Form	Original returned as soon as possible by Sleep Technician
Six Monthly Telephone Follow-Up Form	Original returned as soon as possible after telephone call.
Two Year Form	Original returned as soon as possible after visit. Copy in ISF
Exit form	Original returned as soon as possible after the research staff at site become aware of event. Copy in ISF
Serious Adverse Event form	Faxed or emailed within 24 hours of research staff at site becoming aware of event. Copy in ISF

CRF versions may be updated by the SLEEP T2D Trial Office throughout the duration of the trial. Whilst not a protocol amendment, new versions of CRFs must be implemented by sites immediately on receipt.

In all cases it remains the PI's responsibility to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI on the CRF. The

SLEEP T2D Study Signature & Delegation Log will identify all those personnel with responsibilities for data collection.

The completed originals will be submitted to the BCTU trials team and a copy filed in the Investigator Site File. Any questionnaires used for the trial must be specified in the protocol. Only CRFs specified in the protocol must be used.

10.3. Participant Completed Questionnaires

Participant questionnaires will be completed in clinic at the baseline visit and final two year follow up visit. The PI or an authorised member of the site research team should check them for completeness before the participant finishes their visit.

10.4. Data Management

Access to data, including the final study dataset, will be limited to members of the Research Team. The investigator(s)/institution(s) will permit study-related monitoring, audits, and REC review providing direct access to source data/documents as and when required. Study participants are informed of this during the informed consent discussion and will consent to provide access to their medical notes.

CRF data will be input into the SLEEP T2D Study Database at BCTU. The SLEEP T2D study office will raise any queries using a data clarification forms (DCFs). Once the original CRF is received by SLEEP T2D Study Office, no further changes will be made to this CRF.

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific data management plan. Coding and validation will be agreed between the trial coordinator, statistician and programmer and the trial database will be signed off once the implementation of these has been assured.

10.5. Data Security

The security of the System is governed by the policies of UoB. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at UoB have to be registered with the Data Protection Officer and data held in accordance with the Data Protection Act 2018 and the EU General Data Protection Regulation 2018. The University will designate a Data Protection Officer upon registration of the study. The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with UoB policies.

The System incorporates the following security countermeasures:
Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fireproof safe.
Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls used non-identifiable data etc.

Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.

System Management: the System will be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.

System Design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.

Operational Processes: the data will be processed and stored within the Study Centre (UoB).

Data processing: Statisticians will have access to anonymised data.

System Audit: The System will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessments

Data Protection Registration: UoB has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

See section 7.1 for details on the security provisions concerning AV.

10.6. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, ISF, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years.

The TMF will be stored at BCTU under controlled conditions for at least 3 years after the end of the study. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving. Archiving will be authorised by BCTU on behalf of University of Birmingham following submission of the end of trial report.

11. Quality Control and Quality Assurance

11.1. Site Set-Up and Initiation

The CI is required to sign a UoB CI agreement to document the expectations of both parties. The UoB CI agreement document must be completed prior to participation. The CI is required to sign a Clinical Trials Task Delegation Log which documents the agreements between the CI and BCTU. In addition all local PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the CTU and supply a current CV and GCP certificate to BCTU. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed immediately of any change in the site research team.

11.2. Monitoring

Monitoring of this trial will be to ensure compliance with the principals of GCP and will be outlined in the study-specific risk assessment and monitoring plan.

The study office will be in regular contact with the site research teams to check on progress and address any queries that they may have. The study office will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Sites will be requested to send in copies of signed Informed Consent Forms and other documentation for in-house review for all participants providing explicit consent.

Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. This will be detailed in the monitoring plan. If a monitoring visit is required the study office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the SLEEP T2D study staff access to source documents as requested.

11.3. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

11.4. Notification of Serious Breaches

BCTU as delegated by the Sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with the trial or the protocol relating to the trial. Sites are therefore requested to notify the study office of any suspected study-related serious breach of GCP and/or the trial protocol. Where the study office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the study office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Study Management Group (SMG) and the REC. This includes reporting serious

breaches of GCP and/or the trial protocol to the REC. A copy is sent to the UoB Clinical Research Compliance Team at the time of reporting to the REC.

12. End of Trial Definition

The end of trial will be six months after the last data capture, including responses to data queries. The BCTU trial team will notify the main REC and RGT that the trial has ended within 90 days of the end of trial, and will send a summary of the clinical trial report to the main REC and RGT within 12 months of the end of trial.

13. Statistical Considerations

13.1. Sample Size

Since this is a feasibility study, no formal sample size calculations have been undertaken. The feasibility study is not designed or powered to detect a statistically significant difference in efficacy between the two treatment arms.

As the cohort study independent of the RCT's aim is intended to be hypothesis generating, no formal sample size calculation has been undertaken for it.

As described in section 3.5, it is anticipated that up to 500 patients will fulfil the main inclusion criteria and be enrolled into the study and screened for OSA. 140 of these patients will be randomised into the RCT. Registered patients who do not fulfil the additional eligibility criteria for RCT will be eligible for the observational arm; randomised patients will also be included in the observational cohort.

13.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is below.

The primary comparison groups will be composed of those treated with CPAP versus those treated with no CPAP. In the first instance, all analyses will use the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation.

Analyses of feasibility and clinical outcomes will primarily take the form of simple descriptive statistics (e.g. proportions and percentages, means and standard deviations) and where appropriate, point estimates of effect sizes (e.g. mean differences and relative risks) and associated 95% confidence intervals.

For the tertiary objectives, the full cohort will be analysed to look at biomarkers and sleep patterns.

13.2.1. Primary Outcome Measure

The primary outcome of this feasibility study is to determine if a full RCT comparing the effect of CPAP versus no CPAP on the progression of diabetic nephropathy/CKD in patients with OSA is feasible as per section 14.2.2 below.

13.2.2. Criteria for a substantive trial

The decision to undertake a substantive trial will be based on the following feasibility criteria:

1. Recruiting the proposed sample size within the planned time frames
2. Meeting the proposed time frames in regard to interpreting the sleep assessments and initiating patients on treatment
3. Achieving a follow-up rate ≥80% for randomised patients
4. Achieving a CPAP usage ≥4 hours/night on ≥70% of nights in ≥80% patients randomised to CPAP treatment
5. Generating a mean and standard deviation regarding the predicted response to the intervention to allow sample size calculations for a substantive RCT.

13.2.3. Secondary Outcome Measures

Not applicable as this is a feasibility study.

13.2.4. Subgroup Analyses

No subgroup analysis are planned for this feasibility study.

13.2.5. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal and strategies needed to achieve this are part of this feasibility RCT. The main analysis will use available data only, however, the amount of missing data will be assessed, and if necessary, sensitivity analyses will be undertaken. Full details will be included in the Statistical Analysis Plan.

13.3. Planned Interim Analysis

No interim analyses are planned for this study.

13.4. Planned Final Analyses

The primary analysis for the study will occur once all participants have completed the 2 year assessment and corresponding outcome data has been entered onto the study database and validated as being ready for analysis. This analysis will include data items up to and including the 2 year assessment.

14. Study Organisational Structure

14.1. Study Management Group (SMG)

The SMG will comprise the CI, other investigators (clinical and non-clinical) and members of BCTU. The SMG will be responsible for the day-to-day running and management of SLEEP 2TD. It will convene at regular intervals.

14.2. Study Oversight Committee

A joint study oversight committee (SOC) that comprises both Study Steering Committee and Data Monitoring Committee functions will be engaged for this trial.

The role of the SOC is to provide the overall supervision of the trial. The SOC will monitor trial progress and conduct and advice on scientific credibility. Further details of the remit and role of the SOC are available in the SOC Charter.

Additional meetings may be called if recruitment is much faster than anticipated and the SOC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. The SOC will report directly to the SMG who will convey the findings of the SOC to the funder and sponsor. The SOC may consider recommending the discontinuation of the study (and RCT) if the recruitment rate or data quality are unacceptable.

14.3. Finance

The **SLEEP T2D** Study is funded by a Clinician Scientist Fellowship awarded to the CI by the NIHR.

15. Ethical Considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996.

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments (which include the Data Protection Act 2018 and Human Tissue Act 2008), the EU General Data Protection Regulation 2018, and the principles of GCP. The protocol will be submitted to and approved by the REC prior to circulation.

Before any participants are enrolled into the trial, the PI at each site will obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the SLEEP T2D study office.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

16. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 and the EU General Data Protection Regulation 2018.

Participants will always be identified using their unique study identification number, date of birth, and initials on CRFs and correspondence to BCTU. Participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete study records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. ResMed, regulatory authorities, sponsor). Representatives of the SLEEP T2D study team and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

17. Insurance and Indemnity

UoB has Clinical Trials indemnity coverage for this trial that provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion, provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

UoB is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry guidelines for participant compensation.

18. Publication Policy

Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the SLEEP T2D study team and authors will include the CI, recruiting PIs, collaborators and co-investigators, the study Sleep Technician, and BCTU staff (as long as all listed had reasonable contributions). All of the primary outcomes related to feasibility will be published in one publication, with secondary outcomes included in this publication as appropriate. All outcomes will be reported on. Sleep disorders will be published separately. Both RCT cohort and the observational cohort it forms part of will be published together.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the SMG. Manuscripts must be submitted to the SMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of UoB and BCTU. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

Results will be disseminated to participants by using a participant newsletter, through patient charities, and on the trial website.

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