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A randomised, controlled multi-centre trial of 26 weeks subcutaneous liraglutide (a GLP-1 receptor agonist), with or without continuous positive airway pressure (CPAP), in patients with Type 2 Diabetes Mellitus (T2D) and Obstructive Sleep Apnoea (OSA) (ROMANCE): the effects of weight loss on the apnea-hypnoea index (AHI).

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A randomised, controlled multi-centre trial of 26 weeks subcutaneous liraglutide (a GLP-1 receptor agonist), with or without continuous positive airway pressure (CPAP), in patients with Type 2 Diabetes Mellitus (T2D) and Obstructive Sleep Apnoea (OSA) (ROMANCE): the effects of weight loss on the apnea-hypnoea index (AHI).

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Abstract

Introduction: Obstructive sleep apnoea (OSA) and type 2 diabetes mellitus (T2D) often occur concurrently; untreated OSA may potentially amplify the high risk of cardiovascular disease in T2DM. Compliance with continuous positive airway pressure (CPAP), the conventional treatment for OSA, can be poor and considering weight loss is the most effective treatment for OSA, this trial examines whether the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide, a glucose–lowering therapy associated with significant weight loss used in T2DM, can improve the severity and symptoms of OSA.

Methods & Analysis: This is an outpatient, single centre, open label, prospective, phase IV randomised-controlled trial, in a two-by-two factorial design. One hundred and thirty two patients with newly diagnosed OSA (apnoea-hypopnoea index (≥15 events/hour), and existing obesity and T2D (glycated haemoglobin (HbA_{1c}) ≥47mmol/mol), will be recruited from diabetes and sleep medicine outpatient clinics in primary and secondary care settings across Liverpool. Patients will be allocated equally, using computer generated random, permuted blocks of unequal sizes, to each of the four treatment arms for twenty-six weeks: i) liraglutide (1.8 mg o.d.) alone, ii) liraglutide 1.8mg o.d with CPAP, iii) CPAP alone (conventional care) or iv) no treatment (control). The primary outcome measure is change in OSA severity, determined by apnoea-hypopnoea index (AHI). Secondary outcome measures include effects on glycaemic control (HbA1c), body weight, and quality of life measures. Exploratory measures include measures of physical activity, MRI-derived measures of regional body composition including fat mass (abdominal subcutaneous, visceral, neck and liver fat) and skeletal muscle mass (cross-sectional analysis of thigh), indices of cardiac function (using transthoracic echocardiography) and endothelial function.

Ethical approval: The study has been approved by the North West Liverpool Central Research Ethics Committee (14/NW/1019) and is being conducted in accordance with *The Declaration of Helskini* and *Good Clinical Practice*.

Trial Registration numbers: ISRCTN16250774. EUDRACT number 2014-000988-41. UTN U1111-1139-0677.

Strengths and limitations of the study

- This is the first study to address the treatment of T2D and OSA concomitantly using an GLP1 receptor agonist (liraglutide) in combination with CPAP to target long term weight loss and immediate symptomatic relief.
- The study is designed to examine the reduction in AHI; the further assessment of glycaemic control and body composition provide mechanical and physiological correlates.
- The sample size is relatively small though provides sufficient statistical power to address the primary research question.
- Higher doses of liraglutide 3.0 mg o.d. and newer GLP-1 receptor agonists (semaglutide) would produce a greater magnitude of weight loss (and thus potentially a greater reduction in AHI); although recently licenced these were not available at study initiation nor are widely clinically available currently.

Background & rationale

Obstructive sleep apnoea (OSA) is characterised by repeated closure of the upper airway during sleep and has been associated with significant cardiovascular morbidity including hypertension, myocardial infarction, atrial fibrillation, congestive heart failure and stroke. The obstruction causes breathing to be interrupted for up to 60 seconds (with hypopnoea or complete apnoea) resulting in recurrent oxyhaemoglobin desaturations and arousals [1].

There is a particularly high prevalence of OSA in patients with obesity and type 2 diabetes (T2D) (23-86%) [2-4]. Recently it has been shown that this relationship is bidirectional with insulin-treated diabetes associated with a higher risk of OSA, particularly in women [5]. If effective treatment is not administered, OSA is associated with significant long-term health risks including impaired quality of life[6], irritability and depression, decreased performance in work and potentially road traffic accidents[7], hypertension, increased risk of microvascular complications[8] and increased risk of stroke and cardiovascular disease[9]. The standard care option for OSA patients is continuous positive airway pressure (CPAP)[10], which facilitates normal breathing patterns during sleep by splinting open the upper airway. Other treatment options include diet-induced weight loss [11], intensive lifestyle intervention [12] and metabolic (bariatric) surgery [13]. Therefore, the beneficial effects of treatment may be derived from mechanical (CPAP) and/or metabolic interventions (diet and exercise); however, compliance with these current treatment pathways is poor. Weight loss is particularly difficult to achieve and the use of CPAP is usually associated with slight weight gain [14], which may further exacerbate the associated metabolic complications [15]. Thus, the optimal treatment strategy for a T2D patient with OSA would involve

concomitantly targeting both weight loss and glycaemic control (metabolic interventions) in addition to offering CPAP (mechanical intervention) [16].

This research study assesses the impact of pharmacological treatment with liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, a subcutaneously injected agent licensed for glucose lowering in T2DM at doses up to 1.8mg [17]. This therapy has also been licensed at higher dose (3mg) for treatment of obesity [18 19]; however, is important to note that this study commenced prior to approval of 3mg dose of Liraglutide. There have been limited studies examining the impact of liraglutide in patients with OSA [20 21].

We aim to determine whether liraglutide, at the 1.8mg dose approved for type 2 diabetes treatment, can provide a useful therapeutic adjunctive effect in patients with obesity, T2D and OSA, either as a stand-alone treatment or as an adjunct to CPAP. The co-existence of obesity and insulin resistance in T2D and OSA provides a strong rationale for the therapeutic administration of liraglutide to T2D patients with OSA. We assess the effects of liraglutide on OSA symptoms and severity on glycaemic control in obese OSA patients with T2D, either as a monotherapy (without CPAP), or in combination with CPAP. The data collected will help determine optimal treatment strategies for this challenging, and increasingly common clinical disorder.

Methods and Analysis

One hundred and thirty two obese individuals (BMI ≥30 kg/m^2) with a clinical diagnosis of T2D and OSA will be recruited (with the aim of 128 subjects completing the study, *n*=32 per study arm) from across the Liverpool area from both primary and secondary care (diabetes and sleep medicine outpatient clinics and community care).

Primary objective: To determine whether 26 weeks of liraglutide treatment (up to 1.8mg o.d.) can provide a useful treatment for patients with obesity, T2D and OSA, either as a stand-alone treatment or as an adjunct to continuous positive airway pressure (CPAP). The primary outcome measure of interest is change in apnoea-hypopnea index (AHI) (the principal measure of OSA severity) from baseline.

Secondary objectives: The key secondary outcome measures are change in HbA1c (the principal measure of glycaemic control) from baseline and change in total body weight (kg). Additionally, the

trial will provide useful measures of changes in daytime sleepiness (Epworth score), quality of life, and assess treatment compliance as well as the rate of adverse events.

Further exploratory outcome measures include changes in i) physical activity (measured by a multi-sensor array), ii) fat volume and distribution (abdominal visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (SAT), neck fat, submental fat, tongue fat and liver fat) and skeletal muscle mass using MRI-based techniques, iii) cardiac function using transthoracic echocardiography and iv) arterial structure (carotid intima media thickness) and function (flow-mediated dilatation) using duplex ultrasonography.

Trial Design

This is an outpatient, single centre, open label, prospective, phase IV randomised-controlled trial, in a two-by-two factorial design. The trial is designed to provide evidence of benefit of liraglutide on the severity of OSA, on body composition and cardio-metabolic complications of OSA, when used alone or in combination with CPAP over a period of 26 weeks. Patient pubic involvement was not incorporated into the design of this trial.

Methods: Participants, interventions and outcomes

Study Setting

Patients will be recruited from T2D and OSA clinics at University Hospital Aintree, Liverpool, UK commencing September 2015. Further patients will be sourced from approved patient identification centres (PICs) consisting of community clinics across the Liverpool and Knowsley areas. Study sites are controlled and monitored by the Liverpool Cancer Trials Unit (LCTU), University of Liverpool. At study outset we anticpated 5 particpants would be recruited per month based on clinic numbers.

Eligibility Criteria

Population: Type 2 diabetes patients with OSA will be initially identified based on BMI >30 kg/m^2, by screening with the STOP-BANG questionnaire, or based on clinical suspicion from the medical history in patients with T2D. Patients managed by diet alone or any combination of metformin and sulphonylureas can be included. Patients receiving DPP-IV inhibitors may be included if treatment ceases prior to baseline tests. Patients with current CPAP usage or whose diabetes is treated at recruitment with pioglitazone, SGLT2 inhibitors, GLP-1 receptor agonists or insulin or any history of pancreatitis identified in medical history will be excluded. Patients with excessive sleepiness (ESS>14)

will be discussed with a sleep consultant (SC) and excluded if they were a heavy goods vehicle driver or have an occupational risk if not treated.

Potentially eligible patients must perform a screening visit 2-21 days prior to randomisation to assess eligibility to participate as determined by the detailed inclusion/exclusion criteria. This will include medical history and concomitant medications, physical examination, height, weight, waist and neck measurements, blood tests and an overnight home sleep study. Patients can only be randomised if the overnight sleep study confirms moderate-severe OSA as assessed by polysomnographic criteria and HbA1c ≥47 mmol/mol. Detailed inclusion/exclusion criteria are summarised below.

Detailed Inclusion Criteria

1. Males or females, age 18-75 years.
2. A clinical diagnosis of type 2 diabetes.
3. Glycosylated haemoglobin (HbA1c) ≥47mmol/mol.
4. BMI≥30kg/ m^2
5. Currently treated with either diet or any combination of metformin and sulphonylureas (excluding patients treated with DPP-IV inhibitors*, pioglitazone, SGLT2 inhibitors, GLP-1 receptor agonists or insulin).
6. No current use of liraglutide treatment.
7. Patients with moderate-severe OSA as assessed by polysomnographic criteria, either by:

- Apnoea-hypopnea index (AHI) ≥15 events/hour) with overnight domiciliary multichannel sleep study device (Nox T3).
- Overnight desaturation index (pulse oximetry): ODI≥10 (4% dip in oxygen saturation more than 10 events/hour)
- Currently symptomatic for OSA, with daytime sleepiness.

**Patients who are currently treated with DPP-IV inhibitors can be included providing the treatment is discontinued before baseline tests.*

Detailed Exclusion Criteria

Medical History and Concurrent Diseases

1. Females of childbearing age (WOCBP) who are not using adequate contraceptive methods or who are planning a pregnancy in the next 6 months.
2. Treatment with SGLT2 inhibitors, pioglitazone, subcutaneous insulin injections or with any anti-obesity medication, (e.g. orlistat). We wished to avoid other glucose-lowering drugs that would

either promote weight loss (SGLT2 inhibitors) or weight gain (pioglitazone or insulin). DPP-IV inhibitors were contraindicated as they cannot be used in patients who take GLP1-RA.

3. Patients in whom there may be occupational implications to a diagnosis of OSA e.g. professional drivers. or operating machinery

4. Type 1 diabetes mellitus.

5. Congestive heart failure class III-IV.

6. Renal impairment: eGFR less than 30 ml/minute/1.73m^2.

7. Previous history of acute pancreatitis.

8. Hyperthyroidism.

9. Hypothyroidism (subjects with a normal TSH and free T4, and on a stable dose of thyroxine for at least 3 months may be included).

10. Uncontrolled hypertension (blood pressure ≥170/120 mmHg).

11. Recent (< 6 months) myocardial infarction.

12. Previous stroke (with residual neurological deficit).

13. Significant cardiac dysrhythmias (including pacemaker or ICD).

14. Presence of any other medical condition that would, in the opinion of the investigator or their clinician, preclude safe participation in the study. This decision should be informed by Liraglutide precautions for use statements which will be provided to all clinicians and the research team.

15. Alcohol consumption in excess of daily recommended limits (21 units/week females, 28 units/week males). Alcohol consumption was determined using simple recall.

16. History of seizures or unexplained syncope.

17. Severe sleepiness*.

** If a patient scores >14 on the Epworth Sleepiness Scale, the sleep apnoea specialist will be consulted to assess and confirm inclusion/exclusion criteria is met especially regarding driving but will not be an automatic exclusion.*

Allergies and Adverse Drug Reactions

Subjects with a history of any serious hypersensitivity reaction to GLP1-RA.

Sex and Reproductive Status

1. Women of childbearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy for the study duration plus 8 weeks.

2. Women who are pregnant or breastfeeding.

Prohibited Treatments and/or Therapies

1. Diabetes treated with pioglitazone, GLP-1 analogues or insulin.

2. Use of other weight loss medication or any drug that might affect body weight or appetite (including anti-depressants, anti-psychotics, corticosteroids).

Other Exclusion Criteria

1. Prisoners or subjects who are involuntarily incarcerated.

2. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness.

Additional Exclusion Criteria for MRI Scanning

1. Any history of internal metal, pacemakers, ferromagnetic metallic implants, intraocular foreign bodies or cerebral aneurysm clips.

2. Weight > 250kg (due to limitations of MRI scanner).

Outcome measures

Over the course of three visits (Figure 1) the following outcomes will be assessed in all patients at baseline and following the 26-week intervention period. For those patients treated with CPAP, we will perform an additional overnight sleep study at the end of the study period, whilst receiving CPAP and after 4-7 days of CPAP withdrawal.

Primary outcomes

The primary outcome variable is AHI [22] derived via an overnight multi-channel sleep study (NOX T3 PSG recorder, Nox Medical Inc., Reykjavik, Iceland). Although a number of studies using CPAP have used the Epworth Sleepiness Score (ESS) as the primary outcome measure, for the present study analysis of the ESS may lead to misleading conclusions as excessive daytime sleepiness is very common in obese and T2D subjects and is not restricted to those with OSA, particularly in patients with poor glycaemic control (17).

Secondary outcomes

Anthropometric measurements: Weight, height, and waist and hip circumference will be measured by a single research technician. Participants will then be rested for 5 minutes before blood pressure will be determined from an average of three measures.

Questionnaires: A series of self-assessed health and sleep questionnaires will be administered including; (i) STOPBANG questionnaire (sleep apnoea questionnaire), (ii) BERLIN questionnaire (risk of sleep disordered breathing), (iii) Epworth Sleepiness Scale (index of excessive daytime somnolence), (iv) SF-36, (self-administered questionnaire to determine quality of life), and (v) SAQLI (sleep apnoea quality of life index), a sleep apnoea specific quality of life questionnaire.

Oxford sleep resistance test (OSLER): The OSLER test, a modified measure of the 'maintenance of wakefulness' test that gives a validated objective measure of sleepiness will be performed [23]. The test uses a small LED that lights up every 3 seconds, which the patient is required to cancel by tapping a sensor while sitting on a standard chair in a quiet dark room. The test will be terminated if the patient misses a number of lights in succession, at which point the patient is considered to be asleep. Time to sleep onset and/or the number of misses over a 40 minute period will be recorded. The test will be carried out once during the day and will be repeated post-intervention.

Biochemical analysis: All patients will have a routine 15 ml blood sample taken for glucose, insulin, lipid profile and liver function tests (LFTs). Insulin sensitivity will be measured by HOMA-IR [24].

CPAP and liraglutide compliance: We shall examine CPAP usage within the first 3 months of the study; CPAP usage> 4 hours per night will be taken as adherent with total hours and average usage also reported. Similarly, for liraglutide we shall look at patient records and prescriptions returned from pharmacy where this information is available/recorded.

Exploratory analyses and sub-studies

Physical activity monitoring: Physical activity will be tracked throughout using a SenseWear mini armband (BodyMedia Inc., Pittsburgh, PA, USA) for a 4-day period. Patients will be instructed to wear at all possible times. Data collected from the armband includes: daily average step count, total energy expenditure, active energy expenditure and time spent in domains of physical activity including: sleep, lying, sedentary (<1.5 metabolic equivalents, METS), light (1.5-3 METS), moderate (3-6 METS), vigorous (6-9 METS) and very vigorous (>9 METS) and is analysed using SenseWear Professional software (version 8.0).

Food diaries: Patients will be asked to complete a food diary detailing exactly what they eat and drink over the same 4-day period. Total energy consumption, carbohydrate, protein and fat content will be determined from dietary records using Nutritics (Nutrition Analysis Software for Professionals).

Cardio-respiratory fitness: A $\dot{V}O_{2peak}$ cardio-pulmonary exercise test (CPET) will be performed on a treadmill (Model 77OCE, RAM Medisoft Group, Manchester, UK) in a temperature-controlled room. The CPET provided breath-by-breath monitoring and analysis of expiratory gases and ventilation as well as continuous electrocardiographic monitoring (Love Medical Cardiopulmonary Diagnostics, Manchester, UK). The modified Bruce protocol will be employed, after an initial 2 min warm up at 2.2 km/h on a flat gradient, step-wise increments in speed and gradient were employed each minute. $\dot{V}O_{2peak}$ was determined by any of: respiratory exchange ratio > 1.15, heart rate > 90% predicted maximum, plateau in $\dot{V}O_2$, or exhaustion.

Body composition, neck anatomy and liver fat: Magnetic resonance imaging will be carried out at the Liverpool Magnetic Resonance Imaging Centre (LiMRIC), University of Liverpool using a Siemens Symphony 1.5T MR scanner. For body composition, transverse whole-body MRI data will be acquired using a T1 weighted TSE sequence with 1cm slice thickness and gap.

From these scans subcutaneous and visceral fat content will be determined using serial sections of the trunk and skeletal muscle mass from serial sections of the thigh. Liver proton magnetic resonance spectroscopy (^{1}H MRS) will be performed at 3 standardised sites using the integral body coil with TR 1500ms TE 135ms, free-breathing. ^{1}H MRS data will be analysed to determine intrahepatic triglyceride (IHCL) concentration as marker of non-alcoholic fatty liver disease (NAFLD). To assess the neck anatomy,T1 weighted turbo spin echo (TSE) axial contiguous 4mm slices will be acquired from the hard palate to the vocal chords, using a cervical spine coil with subjects lying supine and breathing quietly through their nose [25]. Within the region of interest, volumetric measurements of submental fat, neck fat, tongue, soft palate, lateral pharyngeal walls, and airway will be obtained (Figure 2).

Endothelial function: A 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (Siemens Medical Solutions, Malvern, PA) will be used to image the brachial artery in the distal third of the upper right arm. Once an optimal image is acquired, the probe is held stable and the ultrasound parameters set to optimise longitudinal, B-mode images of the lumen–arterial wall interface. Continuous Doppler velocity assessment will be used also. Nitric oxide–mediated endothelial function will be assessed by measuring flow mediated dilatation (FMD) in response to a 5 minute (min) ischemic stimulus, induced by forearm cuff inflation [26]. Baseline images will be recorded using specialised recording software (Camtasia; TechSmith, Okemos, MI). A rapid inflation and deflation pneumatic device (D.E. Hokanson, Bellevue, WA) will be used with an inflation cuff placed immediately distal to the olecranon process of the imaged arm to provide a stimulus for forearm

ischemia. A baseline recording lasting 1 min will be acquired before the forearm cuff is inflated (È220 mm Hg) for 5 min. Artery diameter and blood flow velocity recordings resumed 30 seconds before cuff deflation and continued for 3 min thereafter (36). Peak brachial artery diameter and blood flow velocity, and the time taken to reach these peaks after cuff release, will be recorded.

Vascular Structure: An image of the carotid artery will be recorded using the same technology and measurement of intima-medial thickness (cIMT), or artery wall thickness, will be calculated using custom designed software [27]. In brief, the anterolateral, posterolateral, and mediolateral planes are to be acquired. Patients will be instructed to lay supine with a slight hyperextension of the neck and a 45° lateral flexion away from the side being scanned (right). An R-wave triggered optimal recording of the far wall, 1 cm proximal to the carotid bulb, will be stored as a digital DICOM file on the PC for analysis of cIMT and common carotid arterial diameter.

Cardiac structure and function: Indices of cardiac function and subclinical indices of myocardial systolic and diastolic function (strain and strain rate) will be determined using tissue Doppler echocardiography [28]. All echocardiograms will be performed using a GE Vivid 7 or E9 machine with a 2.5 MHz phased array transducer and the patient in the left lateral position on a reclining couch. A combination of 2D, M-mode, pulsed wave and continuous wave Doppler and tissue Doppler are to be used. Conventional echocardiographic views will be obtained (parasternal long axis, parasternal short axis, apical 4 chamber, apical long axis, apical 2 chamber and subcostal).

Left ventricular (LV) diameter and wall thicknesses will be measured in the parasternal long axis view using 2D or M-mode measurements. LV mass calculated using Devereux‟s formula and indexed to body surface area. Modified Simpson's biplane method will be used to determine LV ejection fraction. Mitral inflow velocities and deceleration times are to be measured using pulsed wave Doppler in the apical 4 chamber view. Isovolumetric relaxation time will also be calculated using continuous wave Doppler, with the cursor midway between left ventricular outflow and mitral inflow. For tissue Doppler imaging, colour tissue Doppler loops will be recorded using a frame rate >100 frames/sec. Myocardial longitudinal function will be assessed from three consecutive cycles of tissue Doppler imaging in the apical 4 chamber, apical 2 chamber and apical long axis views.

Echocardiographic data is to be analysed using Echopac V9.01, GE, Horten, Norway. Peak systolic and early and late diastolic myocardial tissue velocities obtained from the basal segment of all 6 LV walls. Myocardial deformation curves obtained from the basal segment of all 6 LV walls. Wall motion will be

manually tracked throughout the cardiac cycle to maintain continuity of the sampling area. Data will be excluded if a smooth curve was unobtainable, or if the angle between the ventricular wall and the scan line was >200. From these curves, peak systolic strain, systolic and early and late diastolic strain rates will be obtained. Using data from each of the 3 cardiac cycles, the values from each wall can be averaged to give a mean value.

Follow-up Investigation Repeat procedures identical to the baseline visits will be performed at the end of the 26-week intervention period. Importantly, the time of day of these assessments will remain consistent to control for circadian variation.

Interventions

Patients will be randomised in equal allocation to one of four arms:

- **Arm A:** Control arm, comprising conventional care for existing patients with T2D with no intervention for OSA.
- **Arm B:** Conventional care, plus liraglutide (up to 1.8mg o.d.).
- **Arm C:** Conventional care, plus CPAP.
- **Arm D:** Conventional care, plus liraglutide (up to 1.8mg o.d.) and CPAP.

Randomisation

Sequence generation: Patients will be allocated equally to each of the four treatment arms using computer generated random, permuted blocks of unequal sizes. This will be created by the trial statistician in accordance with the LCTU'S standard operating procedure. The allocation sequence will be held centrally at the LCTU with access confined to the Trial Statistician, the LCTU Trial Coordinator and the Data managers assigned to the study.

Control (no intervention)

This group will not use placebo medication. Patients will be asked to continue with their usual anti-diabetic medications and if titration of any glucose-lowering therapy is necessary, due to worsening glycaemic control, this will be recorded. This diabetes therapy titration may include initiation of subcutaneous insulin therapy if glycaemic control significantly deteriorates. Patients will not be given CPAP for this period for their OSA.

Liraglutide

Liraglutide is administered as a once-daily subcutaneous injection in the abdomen, thigh or upper arm. It will be commenced at a starting dose of 0.6 mg once daily, increasing after one week to 1.2mg once daily and after a further week to 1.8 mg once daily. Those patients who cannot tolerate the increased dose after the first week will be asked to remain at 0.6 mg daily and will be re-challenged with 1.2 mg dose accordingly. Should drug intolerance persist, patients will be asked to remain on the lowest, tolerated dose. This will be managed by the research team on an individual basis. The trial specific prescription will allow the prescriber to specify individual doses and quantities for those patients who do not tolerate the intended dose. Due to the dose-escalation nature of the trial design, dose modifications are not appropriate.

Continuous positive airway pressure (CPAP)

The CPAP device that will be used will be the ResMed AirSense 10 Elite in a fixed pressure delivery mode, with the therapeutic pressure defined in accordance with standard clinical protocols [29].

Preparation, dosage and administration of study treatment: Existing clinical staff within the relevant diabetes and sleep clinics at University Hospital Aintree will initiate the appropriate treatment pathway in patients enrolled onto the study according to their randomisation. It is important to note that individuals who enrol onto the study will be fast-tracked through the referral pathways and will commence their allocated treatment immediately following baseline assessment.

Additional visits

Additional visit for patients randomised to ARMs B, C & D to collect the CPAP device, Liraglutide prescription and instructions for use. This is optional for Arm A patients who should be given the choice of a visit or telephone consultation.

Female patients randomised to Liraglutide will require an additional pregnancy test (within 0 to 72 hours before the first dose of study drug).

Assessment of compliance with study treatment

All patients randomised to arms B or D will be instructed to return used (empty or part full) liraglutide pens at each prescribing visit. These are assessed by pharmacy staff and volumes recorded and compliance can be calculated accordingly as percentage used per protocol and per individual prescription (if maximum dose is not tolerated).

The CPAP device will be interrogated to determine the duration of usage (minutes per night) with the usage recorded on the CRF. The initial 3 months of CPAP data will be used for study analysis as per remote monitoring with Airview (Resmed) or by downloading the CPAP machine directly. Compliance calculations will be described in greater detail in the statistical analysis plan but patients returning their machine will still remain in their allocated study arm. Patients will also be issued with treatment diaries to facilitate discussion at each study visit and the data also recorded. Patients will be routinely counselled on the importance of using their study intervention as prescribed.

Monitoring/dispensing visits

Follow-up visits or telephone calls for patients randomised to ARMs B, C & D will take place at weeks 2, 4 and 6 of treatment intervention to review drug-related side effects and assessment of any CPAP related issues and compliance with regimen. Patients in Arm A will be reviewed by telephone conversation.

After 6 weeks specialist T2DM and OSA nurses will provide fortnightly telephone support to all patients and where necessary face to face reviews to monitor patient compliance to treatment pathways and manage their drug escalation and deal with any problems identified with the CPAP device (Liraglutide and Liraglutide + CPAP Arms).

Follow-up Investigations (Visits 9, 10 & 11)

For patients randomised to ARMs A and B these are repeat procedures identical to visits 2, 3 and 4
For patients randomised to ARMs C and D who have been issued with a CPAP device, an additional sleep study will be performed at visit 10 following a period of 4-7 days without CPAP.

Study withdrawal

If a patient wishes to withdraw from trial treatment, the importance of remaining on trial follow-up should be explained, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up
Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial. Data up to this time can be included in the trial if anonymised. They may need to reaffirm that they consent to follow-up through usual NHS mechanisms. If the patient explicitly states their wish not to contribute further data to the study, an End of Study CRF should be completed documenting the reason for withdrawal. It must be noted that any safety data collected up to the point of withdrawal cannot be removed from the trial analysis.

Pharmacovigilance

All adverse events will be reported and assignment of the severity/grading (mild, moderate, severe, lifethreatening, death) made by the investigator responsible for the care of the participant. The assignment of causality will be made by the chief investigator. All non-serious adverse events (SAEs), whether expected or not, will be recorded and updated at each study visit. All new SAEs will be reported from the point of consent until 70 days after discontinuation of the investigational medical product (IMP); this includes those thought to be associated with protocol-specified procedures. Investigators will report SAEs, serious adverse reactions (SARs) and sudden unexpected adverse reactions (SUSARs) to LCTU within 24 hours of the local site becoming aware of the event. LCTU will notify the Medicines and Healthcare products Regulatory Agency (MHRA) and main REC of all SUSARs occurring during the study: fatal and life-threatening SUSARs within 7 days of notification and non-life-threatening SUSARs within 15 days. All adverse events will be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

Statistical analysis plan

Sample size calculation

We assume a minimum clinically relevant difference in AHI between control and intervention groups of ~10 units, approximating the difference between the mid-points of mild and moderate AHI scores. This assumption is reasonable based on a weight loss of ~5 kg being associated with a reduction in AHI of 14 units in patients with similar baseline characteristics to those proposed in the current study [30].

Treating the two-by-two factorial design as two unrelated comparisons and using the method for the unpaired *t*-test and based on a standard deviation of 15 units[31], 90% power and a 1% significance level we require a total sample size of 128 patients (64 in the marginal total for each group or 32 in each arm). Considering a small dropout rate, this will entail screening approximately 132 patients.

This sample size does not consider the possibility of an interaction effect, but without prior knowledge of any such interaction we believe this assumption is reasonable. Furthermore, we recognise that the power to detect an effect on HbA_{1c} is low.

Statistical methods

Categorical variables will be summarised as frequencies and percentages. Continuous variables will be summarised as mean (95% standard deviation). The analysis of the factorial design will use a general linear model with main effect terms for treatment together with baseline value of the response variable (for each of the response variables). Full details of the planned analyses will be given in a separate statistical analysis plan, to be completed and signed off prior to data lock. Data access is granted to assigned trial statisticians.

Subgroup analyses: A test for interaction will be performed. No others specified at the time of writing.
Significance levels: For analysis of the primary outcome statistical significance will be declared if a two-sided *P*-value of <0.05 is obtained in favour of Liraglutide or CPAP. For the primary endpoint the mean difference from baseline (adjusted for baseline) will be presented with a corresponding 95% two-sided confidence interval. Secondary endpoints will also be presented with 95% confidence intervals and 5% two-sided significance levels.

Analysis Populations: The main analysis for primary and secondary endpoints will use the full analysis set, consisting of all randomised patients, with participants analysed according to the group to which they were originally allocated, and with outcomes included irrespective of protocol adherence, in order to follow the *intention to treat* (ITT) principle.

The *per-protocol* population will consist of those patients in the full analysis set without any major deviations in treatment or assessment that could affect the outcome. This population will be used in a sensitivity analysis for the primary endpoint. The safety population, consisting of all patients who actually receive a trial intervention, according to the treatment received, will be used for analysis of toxicity and adverse events.

Missing data: Missing data will be handled by multiple imputation, performing separate multiple imputations by treatment arm, using the method of chained equations as implemented in Stata v12 or higher.

Safety analysis: Information relating to adverse events (eg. hypoglycaemia) will be tabulated and summarised descriptively.

Trial oversight

Management structure: The trial will be overseen by a trial steering committee (TSC) and operated on a day-to day basis by a trial management group (TMG). The trial coordinator (TC) will produce monthly recruitment reports, to allow the TSC and TMG to regularly review the trial across sites. The TSC will comprise of experienced medical experts and trialists. Meetings will be held at regular intervals dependent on need, but no less than once a year. The responsibilities will include

a. Report to the TSC.
b. Maintain the Trial Master File.
c. Confirm all approvals are in place before release of the trial treatment and the start of the trial at a site.
d. Provide training about the trial.
e. Provide study materials.
f. Data management centre.
g. Give collaborators regular information about the progress of the study.
h. Respond to any questions (eg, from collaborators) about the trial.
i. Ensure data security and quality and observe data protection laws.
j. Safety reporting.
k. Ensure trial is conducted in accordance with the ICH GCP.
l. Statistical analysis.
m. Publication of trial results.

The role of the TSC is to provide overall supervision of the trial. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consideration of new information. The TSC must be in agreement with the final protocol and, throughout the trial, will take responsibility for:

a. Major decisions such as need to change the protocol for any reason.
b. Monitoring and supervising the progress of the trial.
c. Reviewing relevant information from other sources.
d. Considering recommendations from the DMC.
e. Informing and advising the TMG on all aspects of the trial.

Dissemination

This study is being conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in compliance with the European Union Directive 2001/20/EC transposed into UK law as statutory instrument 2004 No 1031: Medicines for

Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The trial protocol has received the favourable opinion of the NRES North West—Liverpool Central Research Ethics Committee (14/NW/1019; protocol number UoL000977). An appropriate patient information sheet and consent forms describing in detail the trial interventions/products, trial procedures and risks were approved by the ethical committee. The investigator will then explain the study to the patient and answer any questions posed. A contact point where further information about the trial may be obtained will be provided. After being given adequate time to consider the information, the patient will be asked to sign the informed consent document by a member of the study team. A copy of the informed consent document will be given to the patient for their records and a copy placed in the medical records, with the original retained in the investigator site file. The patient may withdraw from the trial at any time by revoking their informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline participation.

Regulatory approval

This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA).

Publication

The results will be analysed together and published as soon as possible. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. The ISRCTN allocated to this trial would be attached to any publications resulting from this trial.

Acknowledgements

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Author Contributions

DJC, SEC, JPHW and VSS wrote the study protocol. DJC is the principal investigator for this study. VSS is the postdoctoral research fellow responsible for the running of the clinical trial and is a coinvestigator. VSS drafted the protocol in the journal format. GJK, AW, VA, KM & RJS developed the imaging methodology for the protocol. SE, MT, AM & SEC developed the respiratory assessment and analysis included in the trial. MB developed the cardiac outcome measures. AJN developed the statistical plan. All authors are coinvestigators for the study. All authors have contributed to the revision of the manuscript.

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Competing interests

DJC has competing interests with AstraZeneca, Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly & Novo Nordisk. JW has acted as a consultant, received institutional grants and given lectures on behalf of pharmaceutical companies developing or marketing medicines used for the treatment of diabetes, specifically AstraZeneca, Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly, Novo Nordisk and Sanofi &Takeda. Other authors have no competing interests.

Word Count

5506

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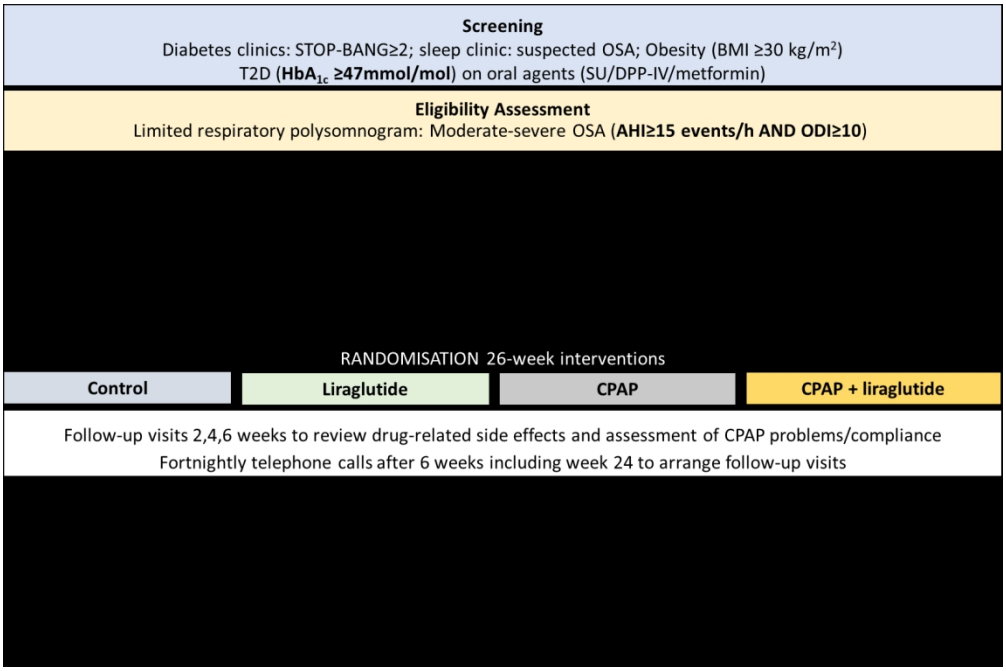

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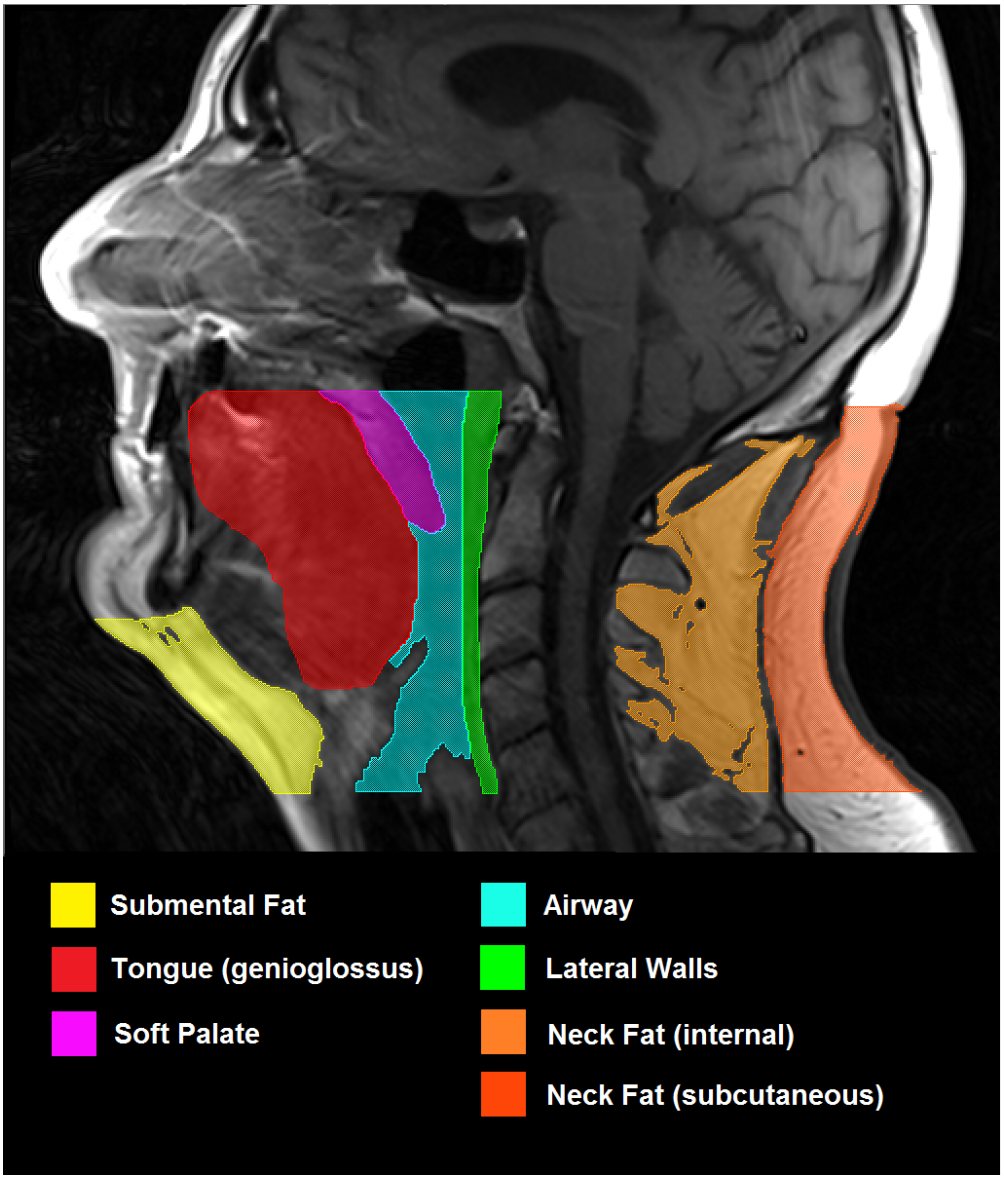

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	PageNo	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry
	N/A	All items from the World Health Organization Trial Registration Data Set
Protocol version	1	Date and version identifier
Funding	17	Sources and types of financial, material, and other support
Roles and responsibilities	1, 17	Names, affiliations, and roles of protocol contributors
	1	Name and contact information for the trial sponsor
	1	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	16	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	3	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	4	Explanation for choice of comparators
Objectives	4	Specific objectives or hypotheses
Trial design	5	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes		
Study setting	5	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	5	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11-13	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11-13	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11-13	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	5, 14	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	8-11	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	8	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	5	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	12	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	12	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	12	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	NA	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	NA	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	8-11	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	13	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	15	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	15	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	16	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	15-16	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	16-17	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	NA	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	14	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	17	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	2	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	17	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	17	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	NA	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	17	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	18	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	15	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	14	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	17	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	18	Authorship eligibility guidelines and any intended use of professional writers
	18	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	NA	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	NA	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A randomised, controlled multi-centre trial of 26 weeks subcutaneous liraglutide (a Glucagon-like Peptide-1 receptor agonist), with or without continuous positive airway pressure (CPAP), in patients with Type 2 Diabetes Mellitus (T2D) and Obstructive Sleep Apnoea (OSA) (ROMANCE): Study protocol assessing the effects of weight loss on the apnea-hypnoea index (AHI)

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Manuscript ID	bmjopen-2020-038856.R1
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Primary Subject Heading:	Diabetes and endocrinology

Secondary Subject Heading:	Respiratory medicine
Keywords:	SLEEP MEDICINE, DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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A randomised, controlled multi-centre trial of 26 weeks subcutaneous liraglutide (a Glucagon-like Peptide-1 receptor agonist), with or without continuous positive airway pressure (CPAP), in patients with Type 2 Diabetes Mellitus (T2D) and Obstructive Sleep Apnoea (OSA) (ROMANCE):

Study protocol assessing the effects of weight loss on the apnea-hypnoea index (AHI).

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Abstract

Introduction: Obstructive sleep apnoea (OSA) and type 2 diabetes mellitus (T2D) often occur concurrently; untreated OSA may potentially amplify the high risk of cardiovascular disease in T2DM. Compliance with continuous positive airway pressure (CPAP), the conventional treatment for OSA, can be poor and considering weight loss is the most effective treatment for OSA, this trial examines whether the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide, a glucose–lowering therapy associated with significant weight loss used in T2DM, can improve the severity and symptoms of OSA.

Methods & Analysis: This is an outpatient, single centre, open label, prospective, phase IV randomised-controlled trial, in a two-by-two factorial design. One hundred and thirty two patients with newly diagnosed OSA (apnoea-hypopnoea index (≥15 events/hour), and existing obesity and T2D (glycated haemoglobin (HbA_{1c}) ≥47mmol/mol), will be recruited from diabetes and sleep medicine outpatient clinics in primary and secondary care settings across Liverpool. Patients will be allocated equally, using computer generated random, permuted blocks of unequal sizes, to each of the four treatment arms for twenty-six weeks: i) liraglutide (1.8 mg o.d.) alone, ii) liraglutide 1.8mg o.d with CPAP, iii) CPAP alone (conventional care) or iv) no treatment (control). The primary outcome measure is change in OSA severity, determined by apnoea-hypopnoea index (AHI). Secondary outcome measures include effects on glycaemic control (HbA1c), body weight, and quality of life measures. Exploratory measures include measures of physical activity, MRI-derived measures of regional body composition including fat mass (abdominal subcutaneous, visceral, neck and liver fat) and skeletal muscle mass (cross-sectional analysis of thigh), indices of cardiac function (using transthoracic echocardiography) and endothelial function.

Ethical approval: The study has been approved by the North West Liverpool Central Research Ethics Committee (14/NW/1019) and is being conducted in accordance with *The Declaration of Helskini* and *Good Clinical Practice*.

Trial Registration numbers: ISRCTN16250774. EUDRACT number 2014-000988-41. UTN U1111-1139-0677.

Strengths and limitations of the study

- This is the first study to address the treatment of T2D and OSA concomitantly using an GLP1 receptor agonist (liraglutide) in combination with CPAP to target long-term weight loss and immediate symptomatic relief.
- The study is designed to examine the impact of weight-loss-induced reductions in AHI.
- The further assessment of changes in glycaemic control and body composition provide metabolic, mechanical and physiological correlates.
- The sample size is relatively small, though provides sufficient statistical power to address the primary research question.
- Higher doses of liraglutide 3.0 mg o.d. and newer GLP-1RAs (semaglutide) would produce a greater magnitude of weight loss (and thus potentially a greater reduction in AHI); although recently licenced these were not available at study initiation, nor are widely available currently.

Introduction

Obstructive sleep apnoea (OSA) is characterised by repeated closure of the upper airway during sleep and has been associated with significant cardiovascular morbidity including hypertension, myocardial infarction, atrial fibrillation, congestive heart failure and stroke. The obstruction causes breathing to be interrupted for up to 60 seconds (with hypopnoea or complete apnoea) resulting in recurrent oxyhaemoglobin desaturations and arousals [1].

There is a particularly high prevalence of OSA in patients with obesity and type 2 diabetes (T2D) (23-86%) [2-4]. Recently it has been shown that this relationship is bidirectional with insulin-treated diabetes associated with a higher risk of OSA, particularly in women [5]. If effective treatment is not administered, OSA is associated with significant long-term health risks including impaired quality of life[6], irritability and depression, decreased performance in work and potentially road traffic accidents[7], hypertension, increased risk of microvascular complications[8] and increased risk of stroke and cardiovascular disease[9]. The standard care option for OSA patients is continuous positive airway pressure (CPAP)[10], which facilitates normal breathing patterns during sleep by splinting open the upper airway. Other treatment options include diet-induced weight loss [11], intensive lifestyle intervention [12] and metabolic (bariatric) surgery [13]. Therefore, the beneficial effects of treatment may be derived from mechanical

(CPAP) and/or metabolic interventions (diet and exercise); however, compliance with these current treatment pathways is poor. Weight loss is particularly difficult to achieve and the use of CPAP is usually associated with slight weight gain [14], which may further exacerbate the associated metabolic complications [15]. Thus, the optimal treatment strategy for a T2D patient with OSA would involve concomitantly targeting both weight loss and glycaemic control (metabolic interventions) in addition to offering CPAP (mechanical intervention) [16].

This research study assesses the impact of pharmacological treatment with liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), a subcutaneously injected agent licensed for glucose lowering in T2DM at doses up to 1.8mg [17]. This therapy has also been licensed at higher dose (3mg) for treatment of obesity [18 19]; however, is important to note that this study commenced prior to approval of 3mg dose of Liraglutide. There have been limited studies examining the impact of liraglutide in patients with OSA [20 21]. There is however, very recent unpublished data, released by NovoNordisk, from the first completed phase 3a trial in the STEP programme, the STEP4 study (Semaglutide Treatment Effect in People with obesity), demonstrating the magnitude of weight loss observed with semaglutide, a once-weekly GLP-1RA. Over a 68-week period, weight loss of up to ~18% of total body weight was observed. These results demonstrate greater weight loss than previously observed with pharmacotherapy in individuals with obesity. It will be interesting to examine the impact of semaglutide, and the greater associated weight loss, in people with obesity complicated by OSA.

We aim to determine whether liraglutide, at the 1.8mg dose approved for type 2 diabetes treatment, can provide a useful therapeutic adjunctive effect in patients with obesity, T2D and OSA, either as a stand-alone treatment or as an adjunct to CPAP. The co-existence of obesity and insulin resistance in T2D and OSA provides a strong rationale for the therapeutic administration of liraglutide to obese individuals with T2D and OSA. We assess the effects of liraglutide on OSA symptoms and severity on glycaemic control in obese individuals with T2D and OSA, either as a monotherapy (without CPAP), or in combination with CPAP. The data collected will help determine optimal treatment strategies for this challenging, and increasingly common clinical disorder.

Methods and Analysis

One hundred and thirty two obese individuals (BMI ≥30 kg/m^2) with a clinical diagnosis of T2D and OSA will be recruited (with the aim of 128 subjects completing the study, *n*=32 per study arm) from across the Liverpool area from both primary and secondary care (diabetes and sleep medicine outpatient clinics and community care).

Primary objective: To determine whether 26 weeks of liraglutide treatment (up to 1.8mg o.d.) can provide a useful treatment for patients with obesity, T2D and OSA, either as a stand-alone treatment or as an adjunct to continuous positive airway pressure (CPAP). The primary outcome measure of interest is change in apnoea-hypopnea index (AHI) (the principal measure of OSA severity) from baseline.

Secondary objectives: The key secondary outcome measures are change in HbA1c (the principal measure of glycaemic control) from baseline and change in total body weight (kg). Additionally, the trial will provide useful measures of changes in daytime sleepiness (Epworth score), quality of life, and assess treatment compliance as well as the rate of adverse events.

Further exploratory outcome measures include changes in i) physical activity (measured by a multi-sensor array), ii) fat volume and distribution (abdominal visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (SAT), neck fat, submental fat, tongue fat and liver fat) and skeletal muscle mass using MRI-based techniques, iii) cardiac function using transthoracic echocardiography and iv) arterial structure (carotid intima media thickness) and function (flow-mediated dilatation) using duplex ultrasonography.

Trial Design

This is an outpatient, single-centre, open-label, prospective, phase IV randomised controlled trial, in a two-by-two factorial design. The trial is designed to provide evidence of benefit of liraglutide on the severity of OSA, on body composition and cardio-metabolic complications of OSA, when used alone or in combination with CPAP over a period of 26 weeks. Patient-public involvement was not incorporated into the design of this trial.

Methods: Participants, interventions and outcomes

This protocol document reflects version 7. Various aspects of the protocol were updated based on early trial monitoring and evaluation by the research team and trial steering committee (TSC).

Study Setting

Patients will be recruited from T2D and OSA clinics at University Hospital Aintree, Liverpool, UK commencing September 2015. Further patients will be sourced from approved patient identification centres (PICs) consisting of community clinics across the Liverpool and Knowsley areas. Study sites are

controlled and monitored by the Liverpool Cancer Trials Unit (LCTU), University of Liverpool. At study outset we anticipated 5 participants would be recruited per month based on clinic numbers. Initially, we projected study completion it be 1 Oct 2017; however early study monitoring revealed a slower recruitment rate, which was evaluated by the TSC, and recruitment was extended accordingly until March 2018. Study amendments were also submitted to maximise patient recruitment opportunities.

Eligibility Criteria

Population: Type 2 diabetes patients with OSA will be initially identified based on BMI >30 kg/m^2, by screening with the STOP-BANG questionnaire, or based on clinical suspicion from the medical history in patients with T2D. Patients managed by diet alone or any combination of metformin and sulphonylureas can be included. Patients receiving DPP-IV inhibitors may be included if treatment ceases prior to baseline tests. Patients with current CPAP usage or whose diabetes is treated at recruitment with pioglitazone, SGLT2 inhibitors, GLP-1RAs or insulin or any history of pancreatitis identified in medical history will be excluded. Patients with excessive sleepiness (ESS >14) will be discussed with a sleep consultant (SC) and excluded if they drive a heavy goods vehicle or have any other occupational risk if not treated.

Potentially eligible patients must perform a screening visit 2-21 days prior to randomisation to assess eligibility to participate as determined by the detailed inclusion/exclusion criteria. This will include medical history and concomitant medications, physical examination, height, weight, waist and neck measurements, blood tests and an overnight home sleep study. Patients can only be randomised if the overnight sleep study confirms moderate-severe OSA as assessed by polysomnographic criteria and HbA1c ≥47 mmol/mol. Detailed inclusion/exclusion criteria are summarised below.

Detailed Inclusion Criteria

1. Males or females, age 18-75 years.
2. A clinical diagnosis of type 2 diabetes.
3. Glycosylated haemoglobin (HbA1c) ≥47mmol/mol.
4. BM I≥30kg/m^2
5. Currently treated with either diet or any combination of metformin and sulphonylureas (excluding patients treated with DPP-IV inhibitors*, pioglitazone, SGLT2 inhibitors, GLP-1RAs or insulin).
6. No current use of liraglutide treatment.
7. Patients with moderate-severe OSA as assessed by polysomnographic criteria, either by:

- Apnoea-hypopnea index (AHI) ≥15 events/hour) with overnight domiciliary multichannel sleep study device (Nox T3).
- Overnight desaturation index (pulse oximetry): ODI ≥10 (4% dip in oxygen saturation more than 10 events/hour)
- Currently symptomatic for OSA, with daytime sleepiness.

**Patients who are currently treated with DPP-IV inhibitors can be included providing the treatment is discontinued before baseline tests.*

Detailed Exclusion Criteria

Medical History and Concurrent Diseases

1. Females of childbearing age (WOCBP) who are not using adequate contraceptive methods or who are planning a pregnancy in the next 6 months.
2. Treatment with SGLT2 inhibitors, pioglitazone, subcutaneous insulin injections or with any anti-obesity medication, (e.g. orlistat). We wished to avoid other glucose-lowering drugs that would either promote weight loss (SGLT2 inhibitors) or weight gain (pioglitazone or insulin). DPP-IV inhibitors were contraindicated as they cannot be used in patients who take GLP1-RA.
3. Patients in whom there may be occupational implications to a diagnosis of OSA e.g. professional drivers or machinery operators
4. Type 1 diabetes mellitus.
5. Congestive heart failure class III-IV.
6. Renal impairment: eGFR less than 30 ml/minute/1.73m^2.
7. Previous history of acute pancreatitis.
8. Hyperthyroidism.
9. Hypothyroidism (subjects with a normal circulating TSH and free T4 concentrations, and on a stable dose of thyroxine for at least 3 months may be included).
10. Uncontrolled hypertension (blood pressure ≥170/120 mmHg).
11. Recent (< 6 months) myocardial infarction.
12. Previous stroke (with residual neurological deficit).
13. Significant cardiac dysrhythmias (including pacemaker or ICD).
14. Presence of any other medical condition that would, in the opinion of the investigator or their clinician, preclude safe participation in the study. This decision should be informed by Liraglutide precautions for use statements which will be provided to all clinicians and the research team.
15. Alcohol consumption in excess of daily recommended limits (21 units/week females, 28 units/week males). Alcohol consumption was determined using simple recall.

16. History of seizures or unexplained syncope.

17. Severe sleepiness*.

** If a patient scores >14 on the Epworth Sleepiness Scale, the sleep apnoea specialist will be consulted to assess and that confirm inclusion/exclusion criteria are met, especially regarding driving, but will not be an automatic exclusion.*

Allergies and Adverse Drug Reactions

Subjects with a history of any serious hypersensitivity reaction to GLP-1RA.

Sex and Reproductive Status

1. Women of childbearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy for the study duration plus 8 weeks.

2. Women who are pregnant or breastfeeding.

Prohibited Treatments and/or Therapies

1. Diabetes treated with pioglitazone, GLP-1RA analogues or insulin.

2. Use of other weight loss medication or any drug that might affect body weight or appetite (including anti-depressants, anti-psychotics, corticosteroids).

Other Exclusion Criteria

1. Prisoners or subjects who are involuntarily incarcerated.

2. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious) illness.

Additional Exclusion Criteria for MRI Scanning

1. Any history of internal metal, pacemakers, ferromagnetic metallic implants, intraocular foreign bodies or cerebral aneurysm clips.

2. Weight > 250kg (due to limitations of MRI scanner).

Outcome measures

Over the course of three visits (Figure 1) the following outcomes will be assessed in all patients at baseline and following the 26-week intervention period. For those patients treated with CPAP, we will perform an additional overnight sleep study at the end of the study period, whilst receiving CPAP and after 4-7 days of CPAP withdrawal.

Primary outcomes

The primary outcome variable is AHI [22] derived via an overnight multi-channel sleep study (NOX T3 PSG recorder, Nox Medical Inc., Reykjavik, Iceland). Although a number of studies using CPAP have used the Epworth Sleepiness Score (ESS) as the primary outcome measure, for the present study analysis of the ESS may lead to misleading conclusions as excessive daytime sleepiness is very common in obese and T2D subjects and is not restricted to those with OSA, particularly in patients with poor glycaemic control (17).

Secondary outcomes

Anthropometric measurements: Weight, height, and waist and hip circumference will be measured by a single research technician. Participants will then be rested for 5 minutes before blood pressure will be determined from an average of three measures.

Questionnaires: A series of self-assessed health and sleep questionnaires will be administered including; (i) STOPBANG questionnaire (sleep apnoea questionnaire), (ii) BERLIN questionnaire (risk of sleep disordered breathing), (iii) Epworth Sleepiness Scale (index of excessive daytime somnolence), (iv) SF-36, (self-administered questionnaire to determine quality of life), and (v) SAQLI (sleep apnoea quality of life index), a sleep apnoea specific quality of life questionnaire.

Oxford sleep resistance test (OSLER): The OSLER test, a modified measure of the 'maintenance of wakefulness' test that gives a validated objective measure of sleepiness will be performed [23]. The test uses a small LED that lights up every 3 seconds, which the patient is required to cancel by tapping a sensor while sitting on a standard chair in a quiet dark room. The test will be terminated if the patient misses a number of lights in succession, at which point the patient is considered to have fallen asleep. Time to sleep onset and/or the number of misses over a 40-minute period will be recorded. The test will be carried out once during the day and will be repeated post-intervention.

Biochemical analysis: All patients will have a routine 15 ml blood sample taken for glucose, insulin, lipid profile and liver function tests (LFTs). Insulin sensitivity will be measured by HOMA-IR [24].

CPAP and liraglutide compliance: We shall examine CPAP usage within the first 3 months of the study; CPAP usage> 4 hours per night will be taken as adherent with total hours and average usage also reported. Similarly, for liraglutide we shall look at patient records and prescriptions returned from pharmacy where this information is available/recorded.

Exploratory analyses and sub-studies

Physical activity monitoring: Physical activity will be tracked throughout using a SenseWear mini armband (BodyMedia Inc., Pittsburgh, PA, USA) for a 4-day period. Patients will be instructed to wear at all possible times. Data collected from the armband includes: daily average step count, total energy expenditure, active energy expenditure and time spent in domains of physical activity including: sleep, lying, sedentary (<1.5 metabolic equivalents, METS), light (1.5-3 METS), moderate (3-6 METS), vigorous (6-9 METS) and very vigorous (>9 METS) and is analysed using SenseWear Professional software (version 8.0).

Food diaries: Patients will be asked to complete a food diary detailing exactly what they eat and drink over the same 4-day period. Total energy consumption, carbohydrate, protein and fat content will be determined from dietary records using Nutritics (Nutrition Analysis Software for Professionals).

Cardio-respiratory fitness: A $\dot{V}O_{2peak}$ cardio-pulmonary exercise test (CPET) will be performed on a treadmill (Model 77OCE, RAM Medisoft Group, Manchester, UK) in a temperature-controlled room. The CPET provided breath-by-breath monitoring and analysis of expiratory gases and ventilation as well as continuous electrocardiographic monitoring (Love Medical Cardiopulmonary Diagnostics, Manchester, UK). The modified Bruce protocol will be employed, after an initial 2 min warm up at 2.2 km/h on a flat gradient, step-wise increments in speed and gradient were employed each minute. $\dot{V}O_{2peak}$ was determined by any of: respiratory exchange ratio > 1.15, heart rate > 90% predicted maximum, plateau in $\dot{V}O_2$, or exhaustion.

Body composition, neck anatomy and liver fat: Magnetic resonance imaging will be carried out at the Liverpool Magnetic Resonance Imaging Centre (LiMRIC), University of Liverpool using a Siemens Symphony 1.5T MR scanner. For body composition, transverse whole-body MRI data will be acquired using a T1 weighted TSE sequence with 1cm slice thickness and gap.

From these scans subcutaneous and visceral fat content will be determined using serial sections of the trunk and skeletal muscle mass from serial sections of the thigh. Liver proton magnetic resonance spectroscopy (^{1}H MRS) will be performed at 3 standardised sites using the integral body coil with TR 1500ms TE 135ms, free breathing. ^{1}H MRS data will be analysed to determine intrahepatic triglyceride (IHCL) concentration as marker of non-alcoholic fatty liver disease (NAFLD). To assess the neck anatomy,T1 weighted turbo spin echo (TSE) axial contiguous 4mm slices will be acquired from the

hard palate to the vocal chords, using a cervical spine coil with subjects lying supine and breathing quietly through their nose [25]. Within the region of interest, volumetric measurements of submental fat, neck fat, tongue, soft palate, lateral pharyngeal walls, and airway will be obtained (Figure 2).

Endothelial function: A 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (Siemens Medical Solutions, Malvern, PA) will be used to image the brachial artery in the distal third of the upper right arm. Once an optimal image is acquired, the probe is held stable and the ultrasound parameters set to optimise longitudinal, B-mode images of the lumen–arterial wall interface. Continuous Doppler velocity assessment will be used also. Nitric oxide–mediated endothelial function will be assessed by measuring flow mediated dilatation (FMD) in response to a 5 minute (min) ischemic stimulus, induced by forearm cuff inflation [26]. Baseline images will be recorded using specialised recording software (Camtasia; TechSmith, Okemos, MI). A rapid inflation and deflation pneumatic device (D.E. Hokanson, Bellevue, WA) will be used with an inflation cuff placed immediately distal to the olecranon process of the imaged arm to provide a stimulus for forearm ischemia. A baseline recording lasting 1 min will be acquired before the forearm cuff is inflated (È220 mm Hg) for 5 min. Artery diameter and blood flow velocity recordings resumed 30 seconds before cuff deflation and continued for 3 min thereafter (36). Peak brachial artery diameter and blood flow velocity, and the time taken to reach these peaks after cuff release, will be recorded.

Vascular Structure: An image of the carotid artery will be recorded using the same technology and measurement of intima-medial thickness (cIMT), or artery wall thickness, will be calculated using custom designed software [27]. In brief, the anterolateral, posterolateral, and mediolateral planes are to be acquired. Patients will be instructed to lay supine with a slight hyperextension of the neck and a 45° lateral flexion away from the side being scanned (right). An R-wave triggered optimal recording of the far wall, 1 cm proximal to the carotid bulb, will be stored as a digital DICOM file on the PC for analysis of cIMT and common carotid arterial diameter.

Cardiac structure and function: Indices of cardiac function and subclinical indices of myocardial systolic and diastolic function (strain and strain rate) will be determined using tissue Doppler echocardiography [28]. All echocardiograms will be performed using a GE Vivid 7 or E9 machine with a 2.5 MHz phased array transducer and the patient in the left lateral position on a reclining couch. A combination of 2D, M-mode, pulsed wave and continuous wave Doppler and tissue Doppler are to be used. Conventional echocardiographic views will be obtained (parasternal long axis, parasternal short axis, apical 4 chamber, apical long axis, apical 2 chamber and subcostal).

Left ventricular (LV) diameter and wall thicknesses will be measured in the parasternal long axis view using 2D or M-mode measurements. LV mass calculated using the Devereux formula and indexed to body surface area. Modified Simpson's biplane method will be used to determine LV ejection fraction. Mitral inflow velocities and deceleration times are to be measured using pulsed wave Doppler in the apical 4 chamber view. Isovolumetric relaxation time will also be calculated using continuous wave Doppler, with the cursor midway between left ventricular outflow and mitral inflow. For tissue Doppler imaging, colour tissue Doppler loops will be recorded using a frame rate >100 frames/sec. Myocardial longitudinal function will be assessed from three consecutive cycles of tissue Doppler imaging in the apical 4 chamber, apical 2 chamber and apical long axis views.

Echocardiographic data is to be analysed using Echopac V9.01, GE, Horten, Norway. Peak systolic and early and late diastolic myocardial tissue velocities obtained from the basal segment of all 6 LV walls. Myocardial deformation curves obtained from the basal segment of all 6 LV walls. Wall motion will be manually tracked throughout the cardiac cycle to maintain continuity of the sampling area. Data will be excluded if a smooth curve was unobtainable, or if the angle between the ventricular wall and the scan line was >200. From these curves, peak systolic strain, systolic and early and late diastolic strain rates will be obtained. Using data from each of the 3 cardiac cycles, the values from each wall can be averaged to give a mean value.

Follow-up Investigation Repeat procedures identical to the baseline visits will be performed at the end of the 26-week intervention period. Importantly, the time of day of these assessments will remain consistent to control for circadian variation.

Interventions

Patients will be randomised in equal allocation to one of four arms:

- **Arm A:** Control arm, comprising conventional care for existing patients with T2D with no intervention for OSA.
- **Arm B:** Conventional care, plus liraglutide (up to 1.8mg o.d.).
- **Arm C:** Conventional care, plus CPAP.
- **Arm D:** Conventional care, plus liraglutide (up to 1.8mg o.d.) and CPAP.

Randomisation

Sequence generation: Patients will be allocated equally to each of the four treatment arms using computer generated random, permuted blocks of unequal sizes. This will be created by the trial statistician in accordance with the LCTU'S standard operating procedure. The allocation sequence will be held centrally at the LCTU with access confined to the Trial Statistician, the LCTU Trial Coordinator and the Data managers assigned to the study.

Control (no intervention)

This group will not use placebo medication. Patients will be asked to continue with their usual anti-diabetic medications and if titration of any glucose-lowering therapy is necessary, due to worsening glycaemic control, this will be recorded. This diabetes therapy titration may include initiation of subcutaneous insulin therapy if glycaemic control significantly deteriorates. Patients will not be given CPAP for this period for their OSA.

Liraglutide

Liraglutide is administered as a once-daily subcutaneous injection in the abdomen, thigh or upper arm. It will be commenced at a starting dose of 0.6 mg once daily, increasing after one week to 1.2mg once daily and after a further week to 1.8 mg once daily. Those patients who cannot tolerate the increased dose after the first week will be asked to remain at 0.6 mg daily and will be re-challenged with 1.2 mg dose accordingly. Should drug intolerance persist, patients will be asked to remain on the lowest, tolerated dose. This will be managed by the research team on an individual basis. The trial specific prescription will allow the prescriber to specify individual doses and quantities for those patients who do not tolerate the intended dose. Due to the dose-escalation nature of the trial design, dose modifications are not appropriate.

Continuous positive airway pressure (CPAP)

The CPAP device that will be used will be the ResMed AirSense 10 Elite in a fixed pressure delivery mode, with the therapeutic pressure defined in accordance with standard clinical protocols [29].

Preparation, dosage and administration of study treatment: Existing clinical staff within the relevant diabetes and sleep clinics at University Hospital Aintree will initiate the appropriate treatment pathway in patients enrolled onto the study according to their randomisation. It is important to note that individuals who enrol onto the study will be fast-tracked through the referral pathways and will commence their allocated treatment immediately following baseline assessment.

Additional visits

Additional visit for patients randomised to ARMs B, C & D to collect the CPAP device, Liraglutide prescription and instructions for use. This is optional for Arm A patients who should be given the choice of a visit or telephone consultation.

Female patients randomised to Liraglutide will require an additional pregnancy test (within 0 to 72 hours before the first dose of study drug).

Assessment of compliance with study treatment

All patients randomised to arms B or D will be instructed to return used (empty or part full) liraglutide pens at each prescribing visit. These are assessed by pharmacy staff and volumes recorded and compliance can be calculated accordingly as percentage used per protocol and per individual prescription (if maximum dose is not tolerated).

The CPAP device will be interrogated to determine the duration of usage (minutes per night) with the usage recorded on the CRF. The initial 3 months of CPAP data will be used for study analysis as per remote monitoring with Airview (Resmed) or by downloading the CPAP machine directly. Compliance calculations will be described in greater detail in the statistical analysis plan but patients returning their machine will still remain in their allocated study arm. Patients will also be issued with treatment diaries to facilitate discussion at each study visit and the data also recorded. Patients will be routinely counselled on the importance of using their study intervention as prescribed.

Monitoring/dispensing visits

Follow-up visits or telephone calls for patients randomised to ARMs B, C & D will take place at weeks 2, 4 and 6 of treatment intervention to review drug-related side effects and assessment of any CPAP related issues and compliance with regimen. Patients in Arm A will be reviewed by telephone conversation.

After 6 weeks specialist T2DM and OSA nurses will provide fortnightly telephone support to all patients and where necessary face to face reviews to monitor patient compliance to treatment pathways and manage their drug escalation and deal with any problems identified with the CPAP device (Liraglutide and Liraglutide + CPAP Arms).

Follow-up Investigations (Visits 9, 10 & 11)

For patients randomised to ARMs A and B these are repeat procedures identical to visits 2, 3 and 4

For patients randomised to ARMs C and D who have been issued with a CPAP device, an additional sleep study will be performed at visit 10 following a period of 4-7 days without CPAP.

Study withdrawal

If a patient wishes to withdraw from trial treatment, the importance of remaining on trial follow-up will be explained, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial. Data up to this time can be included in the trial if anonymised. They may need to reaffirm that they consent to follow-up through usual NHS mechanisms. If the patient explicitly states their wish not to contribute further data to the study, an End of Study CRF should be completed documenting the reason for withdrawal. It must be noted that any safety data collected up to the point of withdrawal cannot be removed from the trial analysis.

Pharmacovigilance

All adverse events will be reported and assignment of the severity/grading (mild, moderate, severe, life-threatening, death) made by the investigator responsible for the care of the participant. The assignment of causality will be made by the chief investigator. All non-serious adverse events (SAEs), whether expected or not, will be recorded and updated at each study visit. All new SAEs will be reported from the point of consent until 70 days after discontinuation of the investigational medical product (IMP); this includes those thought to be associated with protocol-specified procedures. Investigators will report SAEs, serious adverse reactions (SARs) and sudden unexpected adverse reactions (SUSARs) to LCTU within 24 hours of the local site becoming aware of the event. LCTU will notify the Medicines and Healthcare products Regulatory Agency (MHRA) and main REC of all SUSARs occurring during the study: fatal and life-threatening SUSARs within 7 days of notification and non-life-threatening SUSARs within 15 days. All adverse events will be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

Statistical analysis plan

Sample size calculation

We assume a minimum clinically relevant difference in AHI between control and intervention groups of ~10 units, approximating the difference between the mid-points of mild and moderate AHI scores.

This assumption is reasonable based on a weight loss of ~5 kg being associated with a reduction in AHI of 14 units in patients with similar baseline characteristics to those proposed in the current study [30].

Treating the two-by-two factorial design as two unrelated comparisons and using the method for the unpaired *t*-test and based on a standard deviation of 15 units[31], 90% power and a 1% significance level we require a total sample size of 128 patients (64 in the marginal total for each group or 32 in each arm). Considering a small dropout rate, this will entail screening approximately 132 patients. Given the non-invasive nature of the interventions and the short follow-up planned, patient retention is not envisaged to be an issue. Further, early study withdrawals formed part of the evaluation by the joint DMC/TSC oversight committee so that this assumption could be evaluated during the course of the study.

This sample size does not consider the possibility of an interaction effect, but without prior knowledge of any such interaction we believe this assumption is reasonable. Furthermore, we recognise that the power to detect an effect on HbA_{1c} is low.

Statistical methods

Categorical variables will be summarised as frequencies and percentages. Continuous variables will be summarised as mean (95% standard deviation). The analysis of the factorial design will use a general linear model with main effect terms for treatment together with baseline value of the response variable (for each of the response variables). Full details of the planned analyses will be given in a separate statistical analysis plan, to be completed and signed off prior to data lock. Data access is granted to assigned trial statisticians.

Subgroup analyses: A test for interaction will be performed. No others are specified at the time of writing.

Significance levels: For analysis of the primary outcome statistical significance will be declared if a two-sided *P*-value of <0.05 is obtained in favour of Liraglutide or CPAP. For the primary endpoint the mean difference from baseline (adjusted for baseline) will be presented with a corresponding 95% two-sided confidence interval. Secondary endpoints will also be presented with 95% confidence intervals and 5% two-sided significance levels.

Analysis Populations: The main analysis for primary and secondary endpoints will use the full analysis set, consisting of all randomised patients, with participants analysed according to the group to which

they were originally allocated, and with outcomes included irrespective of protocol adherence, in order to follow the *intention to treat* (ITT) principle.

The *per-protocol* population will consist of those patients in the full analysis set without any major deviations in treatment or assessment that could affect the outcome. This population will be used in a sensitivity analysis for the primary endpoint. The safety population, consisting of all patients who actually receive a trial intervention, according to the treatment received, will be used for analysis of toxicity and adverse events.

Missing data: Missing data will be handled by multiple imputation, performing separate multiple imputations by treatment arm, using the method of chained equations as implemented in Stata v12 or higher. Imputation is planned only for cases of missing follow-up outcome data, which is anticipated to be small and therefore the scope for any bias due to the MI routine is limited. Multiple imputation using chained equations will be applied to each treatment arm individually. Imputation methods will include baseline outcome data as well as other key prognostic information (e.g. sex, age).

Safety analysis: Information relating to adverse events (e.g. hypoglycaemia) will be tabulated and summarised descriptively.

Trial oversight

Management structure: The trial will be overseen by a trial steering committee (TSC) and operated on a day-to day basis by a trial management group (TMG). The trial coordinator (TC) will produce monthly recruitment reports, to allow the TSC and TMG to regularly review the trial across sites. The TSC will comprise of experienced medical experts and trialists. Meetings will be held at regular intervals dependent on need, but no less than once a year. The responsibilities will include

a. Report to the TSC.
b. Maintain the Trial Master File.
c. Confirm all approvals are in place before release of the trial treatment and the start of the trial at a site.
d. Provide training about the trial.
e. Provide study materials.
f. Data management centre.
g. Give collaborators regular information about the progress of the study.
h. Respond to any questions (eg, from collaborators) about the trial.

i. Ensure data security and quality and observe data protection laws.
j. Safety reporting.
k. Ensure trial is conducted in accordance with the ICH GCP.
l. Statistical analysis.
m. Publication of trial results.

The role of the TSC is to provide overall supervision of the trial. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consideration of new information. The TSC must be in agreement with the final protocol and, throughout the trial, will take responsibility for:

a. Major decisions such as need to change the protocol for any reason.
b. Monitoring and supervising the progress of the trial.
c. Reviewing relevant information from other sources.
d. Considering recommendations from the DMC.
e. Informing and advising the TMG on all aspects of the trial.

Patient and public involvement

No patient or public involvement.

Ethics and Dissemination

This study is being conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in compliance with the European Union Directive 2001/20/EC transposed into UK law as statutory instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The trial protocol has received the favourable opinion of the NRES North West—Liverpool Central Research Ethics Committee (14/NW/1019; protocol number UoL000977). An appropriate patient information sheet and consent forms (supplementary files) describing in detail the trial interventions/products, trial procedures and risks were approved by the ethical committee. The investigator will then explain the study to the patient and answer any questions posed. A contact point where further information about the trial may be obtained will be provided. After being given adequate time to consider the information, the patient will be asked to sign the informed consent document by a member of the study team. A copy of the informed consent document will be given to the patient for their records and a copy placed in the medical records, with the original retained in the investigator site file. The patient may withdraw from the trial at any time by revoking their informed consent. The rights and welfare of the patients will be

protected by emphasising to them that the quality of medical care will not be adversely affected if they decline participation.

The results will be analysed together and published as soon as possible. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. The ISRCTN allocated to this trial would be attached to any publications resulting from this trial.

Dissemination plan (publications, data deposition and curation): It is our intention to present our research findings to all our research participants, in a written lay summary and hold an open feedback session where the results will be presented in a lay-friendly manner. We plan to present the scientific findings as oral communications and abstracts at regional, national and international scientific meetings relating to obesity, type 2 diabetes, respiratory and sleep medicine. We also intend to publish our findings in peer-reviewed journals in the sub-specialties described above.

Regulatory approval

This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA).

Figure 1. Schematic of protocol.

Figure 2. Magnetic resonance imaging (T1 weighted, spin-echo, 4mm slice thickness) showing the mid-sagittal slice of head and neck. Region of interest includes all tissue inferior to hard palate and superior to vocal cords. The following structures to be included in analysis have been highlighted: Submental fat, defined as all fat anterior to hyoid and inferior to mandible; tongue (genioglossus); soft palate; airway; lateral parapharyngeal walls; internal neck fat; subcutaneous neck fat.

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Author Contributions

DJC, VSS, SEC and JPHW wrote the study protocol. DJC is the principal investigator for this study. VSS is the postdoctoral research fellow responsible for the running of the clinical trial and is a co-investigator. VSS and DC drafted the protocol in the journal format. GJK, AW, VA, KM & RJS developed the imaging methodology for the protocol. SE, MT, AM & SEC developed the respiratory assessment and analysis included in the trial. MB developed the cardiac outcome measures. AJN developed the statistical plan. All authors are co-investigators for the study and all authors have contributed to the revision of the manuscript.

Funding Statement

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Competing interests statement

DJC has competing interests with AstraZeneca, Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly & Novo Nordisk. JW has acted as a consultant, received institutional grants and given lectures on behalf of pharmaceutical companies developing or marketing medicines used for the treatment of diabetes, specifically AstraZeneca, Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly, Novo Nordisk and Sanofi &Takeda. Other authors have no competing interests.

Acknowledgements

We would like to acknowledge the Liverpool Clinical Trials Unit, particularly Emma Clark, Kate Culshaw, Julie Perry along with trial statisticians, particularly James Dodd, for their contributions to the study.

Word Count

5872

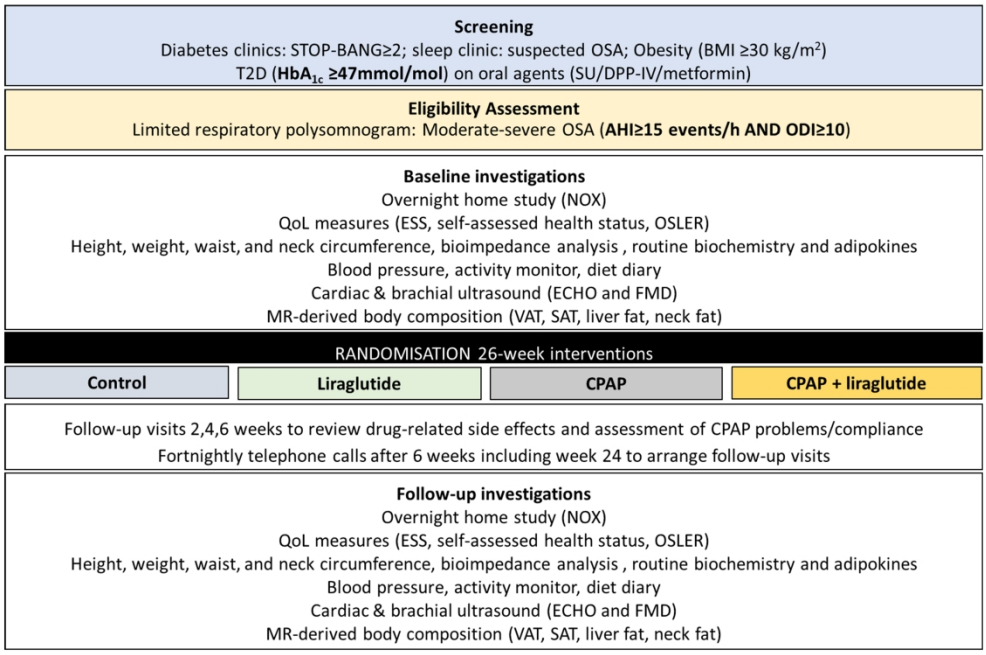

Figure 1. Schematic of protocol.

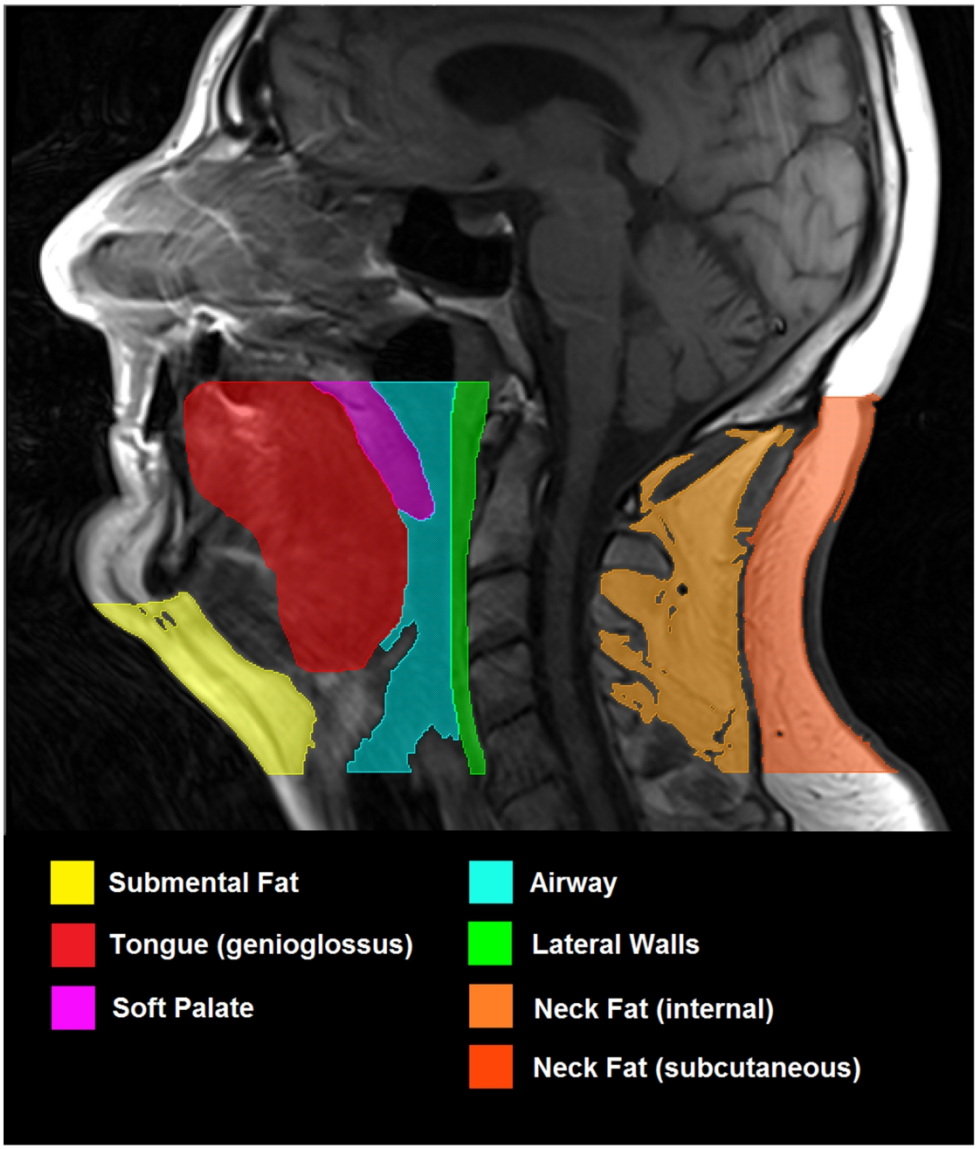

Figure 2. Magnetic resonance imaging (T1 weighted, spin-echo, 4mm slice thickness) showing the mid-sagittal slice of head and neck. Region of interest includes all tissue inferior to hard palate and superior to vocal cords. The following structures to be included in analysis have been highlighted: Submental fat, defined as all fat anterior to hyoid and inferior to mandible; tongue (genioglossus); soft palate; airway; lateral parapharyngeal walls; internal neck fat; subcutaneous neck fat.

EudraCT Number: 2014-000988-41

ROMANCE

UNIVERSITY OF LIVERPOOL

PATIENT CONSENT FORM (please read carefully)

ROMANCE

A randomised, controlled multi-centre trial of 26 weeks of subcutaneous Liraglutide (a GLP1 receptor agonist), with or without continuous positive airway pressure (CPAP), in patients with Type 2 Diabetes Mellitus (T2DM) and Obstructive Sleep Apnoea (OSA)

Name of Researcher:_____
(Principal Investigator)

Please initial each box

1. I confirm that I have read and understand the patient information sheet date: …… (Version: ……) describing the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of my medical notes and data collected during the study may be looked at by responsible individuals involved in this research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to allow my General Practitioner and any other relevant medical practitioner to be informed of my involvement in the study. ☐

5. I agree for a copy of this completed consent form to be sent to the Liverpool Cancer Trial Unit (where it will be kept securely) to allow confirmation that my consent for the trial has been given. ☐

6. I understand that information held by the NHS and records maintained by the NHS Information Centre may be used to keep in touch with me and follow-up my health status. ☐

EudraCT Number: 2014-000988-41 ROMANCE

UNIVERSITY OF LIVERPOOL

7. I understand that, under the Data Protection Act, I can at any time ask for access to the information I provide and I can also request the destruction of that information if I wish. ☐

8. I understand that my data may be transferred outside the European Economic Area to countries which may have a lower level of data protection. ☐

9. I understand that the information that I provide will be processed and analysed as is required by this clinical study. ☐

10. I agree to the annonymised data collected from me being used in future ethically approved research. ☐

11. I agree to take part in the above study. ☐

POINTS 12, 13 AND 14 BELOW ARE OPTIONAL

12. I agree to take part in the optional ECHO tests which will require two additional visits to be scheduled on a Saturday/Sunday. ☐

13. I agree to donate the required samples of my blood as specified in the Participant Information Sheet. No genetic analysis will be performed on these samples. I understand that these projects may be conducted both within and outside the European Union and that some countries outside Europe may not have laws which protect my privacy to the same extent as the Data Protection Act in the UK or European Law. ☐

14. I give permission for additional adipose tissue samples to be provided for later biochemical analysis. No genetic analysis will be performed on these samples. I understand that these projects may be conducted both within and outside the European Union and that some countries outside Europe may not have laws which protect my privacy to the same extent as the Data Protection Act in the UK or European Law. ☐

Name of patient	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature
Researcher (Principal Investigator)	Date	Signature

EudraCT Number: 2014-000988-41

ROMANCE

EudraCT Number: 2014-000988-41

ROMANCE

UNIVERSITY OF LIVERPOOL

PATIENT CONSENT FORM – MRI SCANNING (please read carefully)

ROMANCE

A randomised, controlled multi-centre trial of 26 weeks of subcutaneous Liraglutide (a GLP1 receptor agonist), with or without continuous positive airway pressure (CPAP), in patients with Type 2 Diabetes Mellitus (T2DM) and Obstructive Sleep Apnoea (OSA)

Name of Researcher:_____
(Principal Investigator)

Please initial each box

1. I confirm that I have read and understand the patient information sheet (Date: …… Version: ……) describing the optional MRI scanning as part of the study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation in this optional subset of the study is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of my medical notes and data collected during the study may be looked at by responsible individuals involved in this research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to allow my General Practitioner and any other relevant medical practitioner to be informed of my involvement in the study. ☐

5. I agree for a copy of this completed consent form to be sent to the Liverpool Cancer Trial Unit (where it will be kept securely) to allow confirmation that my consent for the trial has been given. ☐

6. I understand that information held by the NHS and records maintained by the NHS Information Centre may be used to keep in touch with me and follow-up my health status**.** ☐

EudraCT Number: 2014-000988-41 ROMANCE

UNIVERSITY OF LIVERPOOL

7. I understand that, under the Data Protection Act, I can at any time ask for access to the information I provide and I can also request the destruction of that information if I wish. ☐
8. I understand that my data may be transferred outside the European Economic Area to countries which may have a lower level of data protection. ☐
9. I understand that the information that I provide will be processed and analysed as is required by this clinical study. ☐
10. I agree to the annonymised data collected from me being used in future ethically approved research. ☐
11. I agree to take part in the above study. ☐

Name of patient	Date	Signature	☐
Name of person taking consent (if different from researcher)	Date	Signature	
Researcher (Principal Investigator)	Date	Signature	

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	PageNo	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry
	N/A	All items from the World Health Organization Trial Registration Data Set
Protocol version	1	Date and version identifier
Funding	17	Sources and types of financial, material, and other support
Roles and responsibilities	1, 17	Names, affiliations, and roles of protocol contributors
	1	Name and contact information for the trial sponsor
	1	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	16	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	3	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	4	Explanation for choice of comparators
Objectives	4	Specific objectives or hypotheses
Trial design	5	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes		
Study setting	5	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	5	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11-13	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11-13	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11-13	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	5, 14	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	8-11	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	8	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	5	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	12	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	12	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	12	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	NA	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	NA	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	8-11	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	13	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	15	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	15	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	16	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	15-16	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	16-17	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	NA	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	14	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	17	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	2	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	17	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	17	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	NA	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	17	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	18	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	15	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	14	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	17	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	18	Authorship eligibility guidelines and any intended use of professional writers
	18	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	NA	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	NA	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.