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STATISTICAL ANALYSIS PLAN

Effectiveness and cost of integrating a protocol with use of Liraglutide 3.0mg into an obesity service (STRIVE Study)

SAP Version: *1.1*
Date: *03/08/2022*

Based on protocol: Effectiveness and cost of integrating a protocol with use of Liraglutide 3.0mg into an obesity service, Version 7.0; 29/01/2021

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Revision History

Version	Date	Author(s) and Role	Summary of Changes/Comments
0.1	02/11/2017	Shaun Barber	Started drafting SAP
0.2	13/02/2022	Danielle Bodicoat	Completion of draft SAP ready for finalisation
0.3	08/03/2022	Danielle Bodicoat	Update of draft SAP based on initial review
0.4	01/04/2022	Danielle Bodicoat	Update of draft SAP based on review
0.5	05/07/2022	Shaun Barber	Update of draft SAP based on review
1.0	12/07/2022	Shaun Barber	Updated and finalised draft as v1.0 based on review
1.1	01/08/2022	Shaun Barber	Updated the definition of Glycaemic Status at baseline and follow-up add more detail in terms of medication and previous history of diabetes or pre-diabetes. Addition of summarising Glycaemic Status at follow-up by baseline status. Addition of summarising the proportion that met diabetes HbA1c targets (<6.5% and <7.0%)

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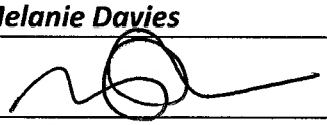
SAP approval for finalised version:

Trial Statistician ***Shaun Barber***

Signature **03/08/2022** **Date**

Chief Investigator ***Melanie Davies***



Signature 12/10/2022. **Date**

Senior Statistician ***Cassey Brookes***

Signature **03/08/2022** **Date**

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AE	Adverse Event
BMI	Body Mass Index
CSR	Clinical Study Report
EQ-5D	European Quality of Life -5 Dimensions
GP	General Practitioner
HSRUQ	Health Services and Resources Use Questionnaire
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFG	Impaired fasting glycaemia
IGT	Impaired glucose tolerance
IPAQ-Long	International Physical Activity Questionnaire-Long
ITT	Intention-to-treat
IWQOL-Lite	Impact of Weight on Quality of Life-Lite
LIRA	Liraglutide
OSA	Obstructive Sleep Apnoea
PHQ-9	Patient Health Questionnaire-9
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TSQM	Treatment Satisfaction Questionnaire for Medication
TZD	Thiazolidinediones

Contents

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the following study: *Effectiveness and cost of integrating a protocol with use of Liraglutide 3.0mg into an obesity service (STRIVE Study).* The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society for statistical practice.

The reader of this SAP is encouraged also to read the clinical trial protocol.

The purpose of this SAP is to outline the planned analyses that are to be performed on the data to support the completion of the Clinical Study Report (CSR), i.e., this SAP only covers the final analyses. The SAP will be amended if there are substantial changes to the planned analyses, and in any case will be finalized and signed off before the database lock for this study.

Exploratory post-hoc or unplanned analyses not necessarily identified in this SAP may be performed on these data as required. These analyses will be clearly identified in the CSR and in any subsequent publications of the data that include post-hoc or unplanned analyses.

It is planned that health economics analyses will be performed. These will be handled separately and are not described in this SAP.

Interim analyses have not been performed for this study. Safety analyses were conducted for the Data Monitoring Committee reports, but no efficacy analyses took place.

Throughout the document, any verbatim text from the protocol is provided inside a box, i.e.:

Text from the protocol

1.1 Study Objectives

1.1.1 Primary Objectives

The primary objective will be to compare the proportion of participants with severe and complicated obesity (defined as BMI ≥35 kg/m^2 with at least one major obesity-related comorbidity) achieving weight loss ≥15% at 1 year (52 weeks) with a targeted prescribing pathway (i.e. use of LIRA 3mg according to a pre-specified protocol in combination with standard care provided in Tier 3 services) versus standard care provided in Tier 3 services alone.

1.1.2 Primary Aim

The aim of the study is to compare the effectiveness, budget impact, and cost-effectiveness between two treatment pathways (standard care vs a targeted prescribing pathway plus standard care) in a real-world setting among otherwise largely unselected patients.

The secondary objectives are to compare the targeted prescribing pathway and standard care in terms of:

1. *improving obesity-related co-morbidities (obstructive sleep apnoea, prediabetes, diabetes, hypertension, dyslipidaemia, depression)*
2. *referral rates to other obesity interventions*
3. *long-term maintenance (defined as the proportion of participants maintaining weight loss of ≥15% at 104 weeks among those who achieved ≥15% weight loss at 52 weeks)*
4. *budget impact on a Tier 3 weight management service*
5. *long-term cost-effectiveness*
6. *direct healthcare costs in terms of admissions, frequency, and cost of appointments*
7. *safety-related outcomes*
8. *adherence*
9. *patient satisfaction.*

1.1.3 Secondary Objectives

Secondary objectives number 4-6 will be dealt with as part of the health economics analysis and are not included in this SAP.

1.1.4 Subgroup Objectives

None

1.2 Study Design

1.2.1 Overview

A 26 month, parallel, two group, open-label, real-world, randomized controlled trial design for patients with severe and complex obesity who are referred to a Tier 3 obesity service (including patients who are referred to a Tier 3 service as part of the bariatric surgery pathway). The total duration of participation will be 104 weeks (+/-2 weeks). Figure 1 shows an overview of the study design.

The first 52 weeks of the study (after randomisation) will determine whether using the

targeted prescribing pathway in a Tier 3 setting will result in more participants attaining ≥15% weight loss compared with standard care. The purpose of the long-term (52-104 weeks) follow-up is to examine whether LIRA 3mg will help the "early and good" responders to maintain weight loss ≥15% in comparison with the control group over a longer period of time compared with standard care. Further, budget impact, cost-effectiveness, improvement in obesity-related co-morbidities, complementary aspects of safety, effectiveness, adherence, and treatment satisfaction of both treatment groups will be assessed and compared.

Participants will be randomised in a 2:1 fashion (2 intervention: 1 control) to either 1) the intervention of targeted prescribing pathway (obesity-specialist care plus targeted use of Liraglutide 3.0mg [LIRA 3mg] with pre-specified stopping rules for the medication) plus standard care, or 2) control (standard care). All participants will be analysed in the group to which they are randomised; in particular, participants in the intervention group who stop receiving LIRA 3mg will remain in the intervention group and will continue to receive standard care for the remainder of the study as per the targeted prescribing pathway (albeit, the part of the pathway where LIRA 3mg is not prescribed; see Figure 1).

The study is intentionally designed to reflect a pragmatic "real-world" scenario and each Tier 3 provider may require a different number of visits for their programme. However, study appointments for data collection, titration reviews, application of the stopping rules of LIRA 3mg, and dispensing were standardised for all of the five sites. Where participants were lost to follow up or missed a study visit, the study team attempted to access data for weight measurements from existing hospital, GP or health records, where appropriate consent was in place, to ensure that the primary outcome was as complete as possible.

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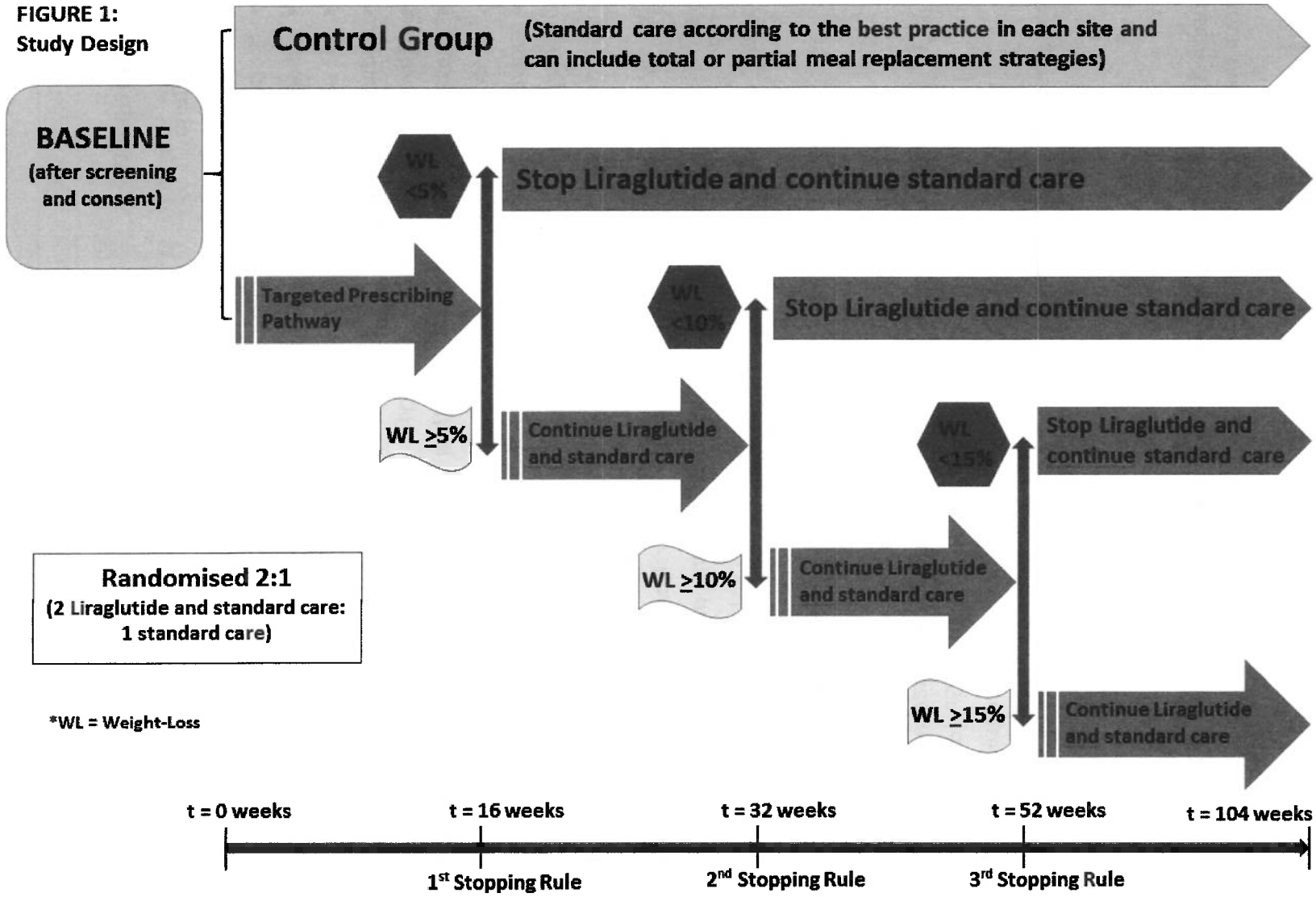
FIGURE 1:
Study Design



1.2.2 Participants

Inclusion Criteria

To be considered eligible to participate in this study, a patient must:

- *be aged between 18-75 years old (inclusive)*
- *understand written and spoken English*
- *be able to give informed consent*
- *have a BMI ≥35 kg/m^2*
- *have been referred to the Tier 3 service in one of the participating sites*
- *have a stable body weight (less than 5kg self-reported change during the previous 12 weeks)*
- *have at least one of prediabetes, diabetes, hypertension, and/or obstructive sleep apnoea*, as defined below:
  - *prediabetes (defined as established diagnosis of impaired fasting glycaemia (IFG) from GP and/or established diagnosis of impaired glucose tolerance (IGT) from GP and/or HbA1C 42-47 mmol/mol (6-6.4%) without glucose lowering medications, at a blood test during the last 6 months)*
  - *diabetes (defined as established diagnosis of Type 2 diabetes from GP and/or HbA1C ≥48 mmol/mol (≥6.5%) at a blood test during the last 6 months] and/or being treated with any combination of lifestyle, metformin, sulphonylureas, Thiazolidinediones (TZDs) or SGLT-2)*
  - *hypertension treated (defined as being on antihypertensive treatment with or without a diagnosis of hypertension from GP) or untreated (defined as Systolic Blood Pressure ≥140 mmHg at two consecutive visits at the Tier 3 clinic),*
  - *obstructive sleep apnoea (on CPAP or established diagnosis of Apnoea Hypopnoea Index ≥15 at sleep studies during the last 12 months).*

Exclusion criteria are stated in the protocol, and cover contradictions to LIRA 3mg and criterion that would be likely to prevent full participation in the study protocol.

1.2.3 Treatment groups

1.2.3.1 Intervention group (Targeted Prescribing Pathway)

The NHS Weight Management pathway is divided into four distinct tiers:

Tier 1: *health promotion*

Tier 2: *lifestyle interventions*

Tier 3: *specialist multidisciplinary weight management services*

Tier 4: *bariatric surgery*

Across the UK, each region has a specialist Tier 3 obesity and/or weight management service or equivalent, usually referred to as Tier 3. This includes a clinician led multidisciplinary team approach, potentially including a specialist physician, nurse, dietician, psychologist, physiotherapist, etc. From this point forwards, Tier 3 specialist weight management and/or equivalent services will be referred to as 'Tier 3' throughout the remainder of this protocol.

Participants in the intervention group will receive the same standard care as those in the control group, i.e. the best medical practice delivered by the Tier 3 service at each site. Additionally, at baseline, LIRA 3mg will be prescribed to all of the participants in the intervention group at a starting dose of 0.6mg daily. Dose escalation of Liraglutide will occur according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg daily. Liraglutide dose will be initiated at 0.6mg and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5. Participants in the intervention group will be aware that the LIRA 3mg treatment may be stopped at various time points throughout the duration of the study and that continued use of LIRA 3mg is based upon their response to the treatment in terms of them achieving pre-defined weight loss targets at 16, 32 and 52 weeks. Specifically, participants in the intervention group will continue to be prescribed LIRA 3mg for the 104 week duration of the study, unless one of the following stopping rules applies:

1st stopping rule

After 16 weeks (± 14 days) on the medication, only those participants who have lost ≥5% of their baseline weight will be offered further treatment with LIRA 3mg for another 16 weeks. Participants who have not met this weight loss target will have their LIRA 3mg treatment stopped but will still continue in the targeted prescribing pathway but will receive standard care only during the remainder of the study.

2nd stopping rule

After 32 weeks (± 14 days) on the medication, only those participants who have lost ≥10% of their baseline weight and are still on treatment with LIRA 3mg will be offered another 20 weeks on LIRA 3mg. Participants who have not met this weight loss target will have their LIRA 3mg treatment stopped but will still continue in the targeted prescribing pathway but will receive standard care only during the remainder of the study.

3rd stopping rule

After the first year of treatment (week 52; ± 14 days), only those participants who have lost ≥15% of their baseline weight and are still on treatment with LIRA 3mg will be offered another 52 weeks on LIRA 3mg. Participants who have not met this weight loss target will

have their LIRA 3mg treatment stopped and will still continue in the targeted prescribing pathway but will receive standard care only during the remainder of the study.

Participants who fail to reach the pre-defined weight-loss targets to continue LIRA 3mg treatment, or who choose to stop receiving LIRA 3mg, will continue to be offered the standard care provided by the Tier 3 service. These participants will still attend the Clinical Review Visits but not the additional visits for participants who are still on LIRA 3mg (e.g. Weeks 65 & 91) because these visits will not be relevant to them; visits at Weeks 65 and 91 are intended to provide a new prescription of LIRA 3mg and to discuss adherence and any side effects).

Participants will remain routinely in the Tier 3 service in-line with NICE guidance throughout the duration of the research study. Participants may be offered treatment options within the duration of the study, including bariatric surgery, as per NICE guidance and according to the decision of the local Tier 3 Multidisciplinary Team.

1.2.3.2 Control group (standard care)

Participants in the control group will follow the best medical care provided by the Tier 3 service at the relevant site. This typically involves dietary advice to reduce energy intake (and may include a period of partial or total meal replacement), accompanied – if available – by a physical activity programme, both supported by behavioural change techniques with regular professional contacts. The nature of the standard care will vary between the different Tier 3 services at each site, as this is a pragmatic 'real-world' study. Clinician input will include the medical assessment of participants for severe and complicated obesity and the prescription of anti-obesity drugs (such as Orlistat) as per local Tier 3 service policy. As with the LIRA 3mg group those patients taking antihypertensive or antidepressant medication will be assessed and it will be at the clinician's discretion as to whether these medications are changed. Participants will remain routinely in the Tier 3 service in line with NICE guidance throughout the duration of the research study. Participants may be offered treatment options within the duration of the study, including bariatric surgery, as per NICE guidance and according to the decision of the local Tier 3 Multidisciplinary Team.

1.2.4 Sample size

Based on previous studies, it is expected that at one year approximately 5% of the participants in the standard care group will have achieved ≥15% weight loss (likely range: 3%-5%). An achievable target for ≥15% weight loss at one year in the intervention group is 16% (likely range: 14%-20%). Based on these proportions, 25% drop out, 5% alpha and a 2:1 randomisation ratio with the higher proportion of participants being randomised to the

intervention group, we would need to recruit 392 participants (261 intervention group; 131 standard care) to have 80% power to detect a significant difference between the groups at one year. With 261 participants randomised to the intervention group, and based on 16% achieving ≥15% weight loss at 12 months, an estimated 40 participants in the intervention group will be eligible for the responder analyses. All 131 participants in the standard care group will be eligible for the responder analyses.

1.2.5 Randomisation and blinding

This is an open-label study and so there is no blinding.

Randomisation will be conducted through a validated online system (sealedenvelope.com) provided through the LCTU. Eligible participants will be randomly assigned at their Baseline Visit (Day 0) in a 2:1 ratio to participate in a Tier 3 service with:

1) *Targeted prescribing pathway - The use of once daily subcutaneous injections of Liraglutide (if they meet the pre-specified criteria), starting at a dose of 0.6 mg with gradual and pre-specified increments to 3.0mg*

or

2) *Control Group - No additional treatment.*

A 2:1 ratio will be used so that a sufficient number of responders will be available for responder analyses. Randomisation will be stratified by centre and BMI (≥45kg/m^2; <45kg/m^2).

Participants will be informed of their randomisation assignment during the Baseline Visit. A letter will be sent to the participant's GP notifying them of their patient's participation in the study. Both the participant and their GP will have the randomisation assignment confirmed by letter.

1.3 Visit schedule

The original visit schedule was as follows:

- Screening and Consent Visit (Day -42 to -1)
- Data Collection Visits – All participants
  - Baseline Visit (Day 0) - including randomization and treatment initiation for participants randomized to the intervention arm
  - Week 52
  - Week 104

- Clinical Review (safety and retention) Visits – All participants
  - Weeks 2, 4, 8, 12, 16, 20, 32, 40, and 78
- Additional Clinical Review (safety and retention) Visits for LIRA 3mg group
  - Weeks 65 and 91

In response to the COVID-19 global pandemic, an interim time point for the quality-of-life questionnaires was added. The following questionnaires were sent out to all participants during the COVID-19 pandemic:

- Health Services and Resources Use Questionnaire (HSRUQ)
- Treatment Satisfaction Questionnaire for Medication (TSQM)
- European Quality of Life -5 Dimensions (EQ-5D)
- Impact of Weight on Quality of Life-Lite (IWQOL-Lite)
- International Physical Activity Questionnaire-Long (IPAQ-Long)
- Patient Health Questionnaire-9 (PHQ-9).

Where possible, the week 52 visit continued to be scheduled within the ± 14 days study visit window, however to aid retention and to help maximise data collection for the study primary end point, the week 52 visit window could be extended to ± 3 months. Where it was not possible to conduct a week 52 visit (e.g., because of COVID-19 restrictions in place at the time), weight data were obtained from the participant's hospital, GP or health record instead where a measurement was available within a window of +/- 12 weeks from the scheduled week 52 visit to ensure that the primary outcome was as complete as possible.

2 Outcomes and other variables

2.1 Primary Endpoint

2.1.1 Definition and Derivation of Primary Endpoint

Binary outcome indicating whether weight loss of ≥15% was achieved at 52 weeks.

Percentage weight loss at 52 weeks will be derived for each participant using the following formula:

$$\frac{(weight_{baseline\ visit} - weight_{52\ week\ visit})}{weight_{baseline\ visit}} x\ 100$$

The primary endpoint will then be coded as 1 if the percentage weight loss at 52 weeks is ≥15%, and as 0 otherwise.

As stated in section 1.3 where weight is not available from week 52 visit, weight from routinely collected data will be used instead if possible.

2.1.2 Hypothesis to be investigated

The primary hypothesis is that a targeted prescribing pathway using LIRA 3mg according to a pre-specified protocol in combination with standard care provided in Tier 3 services will be associated with more participants achieving weight loss of ≥15% at 1 year than receiving standard care provided in Tier 3 services alone.

2.2 *Secondary Endpoints*

2.2.1 Definition and Derivation of Secondary Endpoints

Endpoint	Time point (weeks)	Endpoint derivation
Anthropometric endpoint		
Absolute change in weight (kg) from baseline	16, 32, 52, 104	Follow-up weight – baseline weight
Relative change in weight (%) from baseline	16, 32, 52, 104	(Baseline weight – follow-up weight)/baseline weight * 100
Weight loss of ≥5%, ≥10% and ≥15%	16, 32, 52, 104	Binary indicator of 1 if relative change in weight from baseline is ≥5% loss (or ≥10% or ≥15%, respectively), 0 otherwise
Maintenance of weight loss of ≥15% among those who lost ≥15% at 52 weeks	104	Binary indicator of 1 if relative change in weight from baseline is ≥15% loss, 0 otherwise, only calculated for those who lost ≥15% of baseline weight at 52 weeks.
Absolute change in BMI (kg/m^2) from baseline	52, 104	Follow-up BMI – baseline BMI
Absolute change in waist circumference (cm) from baseline	52, 104	Follow-up waist circumference – baseline waist circumference
Obesity-related co-morbidities and their treatments (General)		
Score on King's College Obesity Staging System assessment	52, 104	Scored as per Staging System (Appendix 1) as Stage 0 (normal health), 1 (at risk of disease), 2 (established disease), 3 (advanced disease) with baseline values also presented
Quality of life (EQ5D) – Descriptive System	52, 104	Scored as per https://www.unmc.edu/centric/_documents/EQ-5D-5L.pdf with change from baseline value analysed separately for each dimension
Quality of life (EQ5D) – Visual Analogue Scale	52, 104	Scored as per https://www.unmc.edu/centric/_documents/EQ-5D-5L.pdf with change from baseline value analysed
Impact of Weight on Quality of Life-Lite (IWQOL-Lite)	52, 104	Transformed total score on scale of 0-100 scored as per https://www.qualityoflifeconsulting.com/iwqol-lite.html with change from baseline

		value analysed
Patient Health Questionnaire-9 (PHQ-9)	52, 104	Scored as per Appendix 2 as minimal depression, mild depression, moderate depression, moderately severe depression, severe depression with baseline values also presented
Patient Health Questionnaire-9 (PHQ-9)	52, 104	Total score generated as per Appendix 2 with change from baseline analysed
Obesity-related co-morbidities and their treatments (Obstructive Sleep Apnoea; OSA)		
Epworth Sleepiness Scale	52, 104	Scored as per Appendix 3 as binary outcome for possible OSA or not with baseline values also presented
Epworth Sleepiness Scale	52, 104	Total score generated as per Appendix 3 with change from baseline analysed
Stop Bang questionnaire	52, 104	Scored as per Appendix 4 as no OSA (0-2), possible OSA (3-4), likely OSA (5-8) with baseline values also presented
Stop Bang questionnaire	52, 104	Total score generated as per Appendix 4 with change from baseline analysed
On CPAP	52, 104	Binary indicator of 1 if participant is on CPAP, 0 otherwise with baseline values also presented
Apnoea Hypopnea Index for participants with sleep apnoea who cannot tolerate CPAP or for participants on fixed pressures CPAP	52, 104	Recorded as an integer in MACRO (AHI = sum of the number of apneas (pauses in breathing) plus the number of hypopneas (periods of shallow breathing) occurring, on average, each hour.)
Oxygen desaturation index for participants with sleep apnoea who cannot tolerate CPAP or for participants on fixed pressures CPAP	52, 104	Recorded as integer in MACRO (The average number of desaturation episodes per hour can be measured using PSG and is called the oxygen desaturation index (ODI).)
Obesity-related co-morbidities and their treatments (Prediabetes/Diabetes)		
Change in HbA1C from baseline (mmol/mol)	52, 104	Follow-up HbA1c – baseline HbA1c. Will be calculated for each Glycaemic Status separately as well as for all individuals, see Appendix 8 for Glycaemic Status definitions.

Change in HbA1C from baseline (%)	52, 104	Follow-up HbA1c – baseline HbA1c Will be calculated for each baseline Glycaemic Status separately as well as for all individuals, see Appendix 8 for Glycaemic Status definitions)
Glycaemic Status	52, 104	Individuals are classified as having Diabetes remission, Diabetes, Pre-diabetes or Normoglycaemia. The Glycaemic Statuses will be summarised overall as well as for each baseline Glycaemic Status separately. Appendix 8 has the definitions of Glycaemic Status at baseline and follow-up.
Number of agents for diabetes	52, 104	Change from baseline in the total number of medications taken for diabetes defined as medications in any of the following classes: metformin, sulphonylurea, thiazolidinedione, SGLT-2, GLP-1, and insulin.
Proportion of those with diabetes at baseline with HbA1C<7.0%	52, 104	From HbA1c measurement, a binary indicator will be derived, being 1 if participant achieves the target and 0 if they do not.
Proportion of those with diabetes at baseline with HbA1C<6.5%	52, 104	From HbA1c measurement, a binary indicator will be derived, being 1 if participant achieves the target and 0 if they do not.
Change in Albumin-Creatinine Ratio (ACR; mg/mmol) from baseline for participants with diabetes, prediabetes, or hypertension	52, 104	Follow-up ACR – baseline ACR, only for participants defined as having diabetes, prediabetes, or hypertension
Obesity-related co-morbidities and their treatments (Hypertension)		

Systolic blood pressure (mmHg)[b]	52, 104	Follow-up systolic blood pressure – baseline systolic blood pressure
Diastolic blood pressure (mmHg)[b]	52, 104	Follow-up diastolic blood pressure – baseline diastolic blood pressure
Hypertension	52, 104	Binary indicator of 1 if participant is on antihypertensive medications or systolic blood pressure>140mmHg[c], 0 otherwise with baseline values also presented
Number of agents for hypertension	52, 104	Change from baseline in total number of medications taken for hypertension defined as medications in any of the following classes: ACE-inhibitors, calcium channel blockers, thiazide diuretics, alpha-blockers, and beta-blockers.
Obesity-related co-morbidities and their treatments (Dyslipidaemia)		
LDL cholesterol (mmol/L)	52, 104	Follow-up LDL cholesterol – baseline LDL cholesterol
HDL cholesterol (mmol/L)	52, 104	Follow-up HDL cholesterol – baseline HDL cholesterol
Total cholesterol (mmol/L)	52, 104	Follow-up total cholesterol – baseline total cholesterol
Triglycerides (mmol/L)	52, 104	Follow-up triglycerides – baseline triglycerides
Number of agents for dyslipidaemia	52, 104	Change from baseline in total number of medications taken for dyslipidaemia defined as medications in any of the following classes: statins, fibrates, and ezetimibe.
Number of participants referred for other obesity intervention		
Referred to Tier 4 for bariatric surgery	104	Binary indicator of 1 if participant was referred to Tier 4 for bariatric surgery over 104 week period, 0 otherwise
Treatment satisfaction		
Treatment Satisfaction Questionnaire for Medication (TSQM)	52, 104	Change from baseline in TSQM scale score. Scored as per version II (detailed in Appendix B on vhe_066.fm (iqvia.com).
Safety/adverse events		
Gastrointestinal symptoms	52, 104	Binary indicator of 1 if participant experienced any nausea or vomiting in study up until the time point of interest (captured in the expected AEs), 0 otherwise
Overall hypoglycaemia rate – ADA definition	52, 104	Hypoglycaemia events will be defined as per Appendix 5 for people without

		diabetes and as per the ADA definition in Appendix 5 for people with diabetes. Hypoglycaemia rate will be calculated per participant as total number of hypoglycaemia events divided by the total follow-up time.
Overall hypoglycaemia rate – Novo Nordisk definition	52, 104	Hypoglycaemia events will be defined as per Appendix 5 for people without diabetes and as per the Novo Nordisk definition in Appendix 5 for people with diabetes. Hypoglycaemia rate will be calculated per participant as total number of hypoglycaemia events divided by the total follow-up time.
AEs	Continual	Defined as in protocol with MEDRA coding used to classify AEs into System Organ Classes
SAEs	52, 104	Defined as in protocol with MEDRA coding used to classify SAEs into System Organ Classes
Rates of severe hypoglycaemia	52, 104	Calculated per participant as total number of severe hypoglycaemia events divided by the total follow-up time, where severe hypoglycaemia is defined as hypoglycaemic episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (i.e., 'severe hypoglycaemic episodes')
Change in heart rate from baseline (beats per minute)	52, 104	Follow-up heart rate – baseline heart rate
Compliance of patient with the treatment		
Compliant with Tier 3 service (completers)	52, 104	Binary indicator of 1 if participant is compliant, 0 otherwise (defined in study database)
Stopped treatment with LIRA 3mg because of adverse effects	52, 104	Binary indicator of 1 if participant stopped treatment with LIRA 3mg because of adverse effects*, 0 otherwise. Only defined for participants in intervention arm who were currently eligible for LIRA 3mg treatment. * This includes main reason of 'adverse event' or 'unable to tolerate drug'.
The adherence of participants with the LIRA	52, 104	Participants will be defined as treatment compliant if they self-administer at least 70% of planned doses. Binary indicator of 1 if participant is compliant, 0 otherwise.

3mg (monitored through specific questionnaire and return of used pens)		Given the change in visits as a result of COVID-19 to allow face-to-face, this will be defined using the questionnaire answers as detailed in Appendix 7. Only defined for participants in intervention arm who were currently eligible for LIRA 3mg treatment.
Stopped LIRA 3mg	16, 32, 52	Binary indicator of 1 if participant stopped treatment with LIRA 3mg at time-point (i.e., due to stopping rules or side effects), 0 otherwise. Only defined for participants in intervention arm who were on LIRA 3mg treatment at the previous time-point.
Completed 52 weeks of the Tier 3 service programme despite stopping LIRA 3mg at 16 weeks	52	Binary indicator of 1 if participant completed 52 weeks of the Tier 3 service programme despite stopping LIRA 3mg at 16 weeks, 0 otherwise. Only defined for participants in intervention arm who stopped LIRA 3mg treatment at 16 weeks.
Completed 52 weeks of Tier 3 service programme despite stopping LIRA 3mg at 32 weeks	52	Binary indicator of 1 if participant completed 52 weeks of the Tier 3 service programme despite stopping LIRA 3mg at 32 weeks, 0 otherwise. Only defined for participants in intervention arm who stopped LIRA 3mg treatment at 32 weeks.
Started on anti-obesity drugs	52, 104	Binary indicator of 1 if participant started on anti-obesity drugs other than LIRA 3mg, 0 otherwise. Defined as a concomitant medication listing of Orlistat.
Physical activity assessment		
International physical activity questionnaire (IPAQ- Long Form; MET-minutes/week)	52, 104	Total MET-minutes/week calculated in line with Appendix 6 and then change from baseline calculated.

[a] Glucose lowering medications are defined as metformin, a sulphonylurea, a thiazolidinedione, or a SGLT-2.

[b] These are also considered safety outcomes.

[c] On the CRF, hypertension is a yes/no tick box with the following wording: "Hypertension treated (antihypertensives with or without diagnosis) or untreated (systolic blood pressure >140 mmHG at two consecutive visits to Tier 3 clinic)." If a definition of anti-hypertensive medications is required for the derivation of any variables then the following medication should be considered as anti-hypertensive: ACE-inhibitors, calcium channel blockers, thiazide diuretics, alpha-blockers (e.g., doxazosin) and beta-blockers.

N.B. CPAP compliance (hours/days) was listed as a secondary outcome in the protocol but will not be reported as it hasn't been captured in the database.

2.3 Subgroups and/or interactions

No subgroup or interaction analyses are planned.

2.4 Compliance

For assessing the impact of compliance on the effectiveness of the intervention, , compliance is defined as:

Participants in the standard care group are defined as treatment compliant if they complete at least 70% of the planned contacts in the Tier 3 service. Participants in the intervention group are defined as treatment compliant if they complete at least 70% of the planned contacts in the Tier 3 service, and take at least 70% of their planned doses of LIRA 3mg as stipulated by the prescribing pathway.

Compliance variables are listed in Section 2.2.
A binary variable of compliant with tier 3 service captures whether a participant has been compliant with the planned contacts in Tier 3 service (see section 3.3.3).

2.5 Other

There are no other variables to be presented in the statistical report which are not outcomes, baseline or demographic variables, or for measuring compliance or safety.

3 Analysis Sets/Populations

3.1 Disposition of participants

Screened patients

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent form.

Treated patients

Treated patients consist of all patients, who have been allocated to one of the two treatment groups, and have at least partially completed the Baseline Visit.

Data from all randomised participants will be used in the study final report and analysis, with data analysed in the group to which the participant was randomised.

3.2 Protocol deviations

The following deviations were captured in the protocol deviation Case Report Form:

Participant ineligible for entry into trial
Participant deviated from randomised treatment group
Participant's visit/assessment not performed as per protocol
Non-permitted treatment
Trial Specific Issues
Other deviation

No protocol deviations will result in systematic exclusion from all statistical analyses. Reasons for exclusion/inclusion in each population are described in 3.3. below.

3.3 Populations

All treated patients will be included in the Intention-To-Treat (ITT) population as a minimum. Patients who were screened, but not treated, will not be included in any of the analysis populations.

3.3.1 Complete Cases Population

The complete cases population is defined as all randomised participants who have data available for the outcome being analysed, according to the study group to which they were randomised at baseline. Participants who had bariatric surgery during the study period will be only be included at time-points prior to their bariatric surgery. They will be excluded from time-points after their bariatric surgery.

3.3.2 Intention-To-Treat Population

The ITT population are all randomised participants and they will be analysed according to the treatment group to which they were randomised at baseline. Missing outcome data will be imputed. Participants who had bariatric surgery during the study period will be included in this population.

Missing primary outcome data will need to be imputed for the ITT analyses; this will be done by assuming that these participants did not achieve ≥15% weight loss at 52 weeks, which is a conservative approach.

3.3.3 Per Protocol Population

The per protocol population is defined as all participants who were compliant with their randomised treatment group, analysed according to the treatment group to which they have randomised at baseline. Participants in the standard care group are defined as treatment compliant if they complete at least 70% of the planned contacts in the Tier 3 service. Participants in the intervention group are defined as treatment compliant if they complete at least 70% of the planned contacts in the Tier 3 service, and take at least 70% of their planned doses of LIRA 3mg as stipulated by the prescribing pathway.

Participants that had Liraglutide 3mg outside of the treatment pathway (i.e. in the control group or in the intervention group after a stopping rule means they should have stopped taking Liraglutide 3mg) will be excluded from the per protocol population. The protocol deviations and in particular deviations from randomised treatment group in the protocol deviations will capture where this has occurred for any individual.

Participants who had bariatric surgery during the study period will be only be included at time-points prior to their bariatric surgery. They will be excluded from time-points after their bariatric surgery.

The binary variable of compliant with tier 3 service at 52 weeks will be used to exclude individuals that did not have 70% of planned visits for outcomes assessed at 52 weeks, likewise for outcomes assessed at 104 weeks the variable at 104 weeks will be used.

Individuals in the intervention arm that did not receive 70% of the doses as determined by the protocol (i.e. in the first 16 weeks or there after whilst continuing to meet the continue rules of the protocolised treatment schedule) will be excluded from the per protocol populations. The number of days taking LIRA and whether this corresponds to 70% of doses is defined in Appendix 7 in section 14. For outcomes at

the 52 week time point the definition in 14.1 should be used; while for outcomes at the 104 week time point the definition in 14.2 should be used.

3.3.4 Responder Population

The Responder population is defined as all participants in the intervention group who achieved ≥15% weight loss at 52 weeks, and all participants in the standard care group. Participants will be analysed according to the treatment group to which they were randomised at baseline.

Participants who had bariatric surgery during the study period will be only be included at time-points prior to their bariatric surgery. They will be excluded from time-points after their bariatric surgery.

3.3.5 Safety Population

All individuals randomised into the trial will be in the safety population. Individuals randomised to the intervention will be analysed in the intervention arm unless they have not receive a dose of LIRA on the prescribed treatment pathway i.e. the protocol deviations and in particular a deviation from randomised treatment group indicates this is the case. Individuals randomised to the control arm will be analysed in the control arm unless they have received a dose of LIRA as part of the prescribed treatment pathway i.e. the protocol deviations and in particular a deviation from randomised treatment group indicates this is the case.

4 General Issues for Statistical Analysis

4.1 Analysis Groups

In all analyses, participants will be analysed in the group to which they were randomised at baseline; importantly, the participants in the intervention group who stop LIRA 3mg, because they meet a pre-specified stopping rule, will still be analysed in the intervention group.

4.2 Missing Data

Attempts will be made to assess the primary outcome on all participants including those who have withdrawn from treatment. The number of missing observations for each outcome will be reported. If missing outcome data are present then the initial analysis will be based on the complete cases. A sensitivity analysis will then be carried out repeating the analyses with the ITT population to assess the possible impact of the missing data on the results produced. Missing primary outcome data will need to be imputed for the ITT analyses; this will be done by assuming that these participants did not achieve ≥15% weight loss at 52 weeks, which is a conservative approach. We will also attempt to address bias by comparing the characteristics of those with missing outcome data to those who have completed follow-up. This strategy for dealing with missing outcome data has been recommended by White et al. (White 2011)

There should be no missing covariate data because site and baseline BMI are used as part of the randomisation process. The other covariate is treatment group which was assigned as part of the randomisation process and will be known for all participants.

Where participants were lost to follow up or missed a study visit, the study team attempted to access primary outcome data from existing hospital, GP or health records, where appropriate consent was in place.

4.3 Derived/ Computed Variables

Analyses will be adjusted for the stratification variables which are study site and body mass index (BMI).

Study site is a non-ordinal, categorical, dummy variable with a unique code for each site.

BMI is a continuous variable calculated as weight in kg divided by height in metres squared. For stratification purposes, baseline BMI was dichotomised based on cut-off values of $\geq$45kg/m^2 and <45kg/m^2. This dichotomised grouping will be included in statistical models.

4.4 Multiple Testing

No corrections will be made for multiple testing. However, due to the large amount of secondary outcomes, statistical models will only be fitted for the most important secondary outcomes to limit the impact of multiple testing. Descriptive summaries will be produced for the other secondary outcomes without multiple testing, as described below.

4.5 Analysis Software

Latest version of Stata, SAS, or other appropriate statistical software.

4.6 Statistical Significance

All statistical tests, p-values, and confidence intervals will be two-sided. Statistical significance will be assessed at the 5% level for main effects. No interaction analyses are planned, however if post-hoc interaction effects are tested then these will be assessed at the 10% level.

4.7 Outliers

Given that the study participants are taking part in this study because of issues around weight control, outliers will not be removed from the dataset as these could feasibly be genuine extremes.

5 Statistical Methodology

5.1 Disposition

A CONSORT diagram showing the flow of participants through the study will be produced, including the number of screened and treated participants. This diagram will also show the number of participants receiving the allocated treatment at each stage of the study, along with the reasons for stopping treatment. In particular, the number who stop LIRA 3mg due to each stopping rule will be clearly stated.

The number (percentage) of participants in each analysis population will be tabulated overall and by treatment group. The type and number (percentage) of protocol deviations will also be tabulated overall and by treatment group in the ITT population.

5.2 Interim analysis

No interim analysis is planned.

5.3 Demographic and Baseline Characteristics

Baseline characteristics of the participants will be summarised by randomisation group and overall using mean (standard deviation) and median (interquartile range) for continuous variables and count (percentage) for categorical variables. There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

Additionally, the baseline characteristics of those with missing primary outcome data will be summarised separately from those with complete primary outcome data using mean (standard deviation) and median (interquartile range) for continuous variables and count (percentage) for categorical variables. These characteristics will be compared using a t-test for normally distributed variables, a Mann-Whitney test for non-normally distributed variables, and a chi-squared test for categorical variables.

5.4 Primary Outcome Analysis

The complete cases, ITT, and per protocol analyses will compare the two groups to demonstrate the effectiveness of the targeted prescribing pathway compared with standard care.

5.4.1 Primary Analysis of Primary Outcome

The primary analysis will compare the proportion of participants achieving ≥15% weight loss at 52 weeks (primary outcome) after randomisation between the two randomisation groups. The primary outcome will be summarised using count and percentage. A logistic regression model will be used with a binary indicator showing whether or not ≥15% weight loss was achieved at 52 weeks as the outcome, randomisation group (intervention or control) as the main covariate, and the stratification factors of site (non-ordinal categorical variable) and baseline BMI ($\geq$45kg/m^2; <45kg/m^2) as additional covariates. The adjusted odds ratio will be presented, 95% confidence interval and p-value comparing the two groups.

The primary analysis will use the complete cases population, therefore missing data will not be imputed.

5.4.2 Secondary Analyses of Primary Outcome

The primary analysis of the primary outcome will be repeated using the ITT and per protocol populations as secondary analyses. Missing primary outcome data will need to be imputed for the ITT analyses; this will be done by assuming that these participants did not achieve ≥15% weight loss at 52 weeks, which is a conservative approach.

5.4.3 Sensitivity Analyses

No sensitivity analyses are planned.

5.4.4 Exploratory Analyses

The per-protocol analysis of the primary outcome will be repeated in the per-protocol population but also excluding individuals had any of the following concomitant medications before their 52 week weight measure was recorded:

- Orlistat
- GLP-1 at glucose lowering dose
- Bupropion/Naltrexone
- SGLT-2 inhibitor which was started after randomisation

5.5 Secondary Outcome Analyses

5.5.1 Primary Analysis of Secondary Outcomes

Secondary anthropometric outcomes will be analysed in a similar way to the primary analysis. These outcomes will be summarised overall and by treatment group.

Categorial outcomes will be summarised using count and percentage. Continuous outcomes will be summarised using mean, standard deviation, median, range, and interquartile range. Binary anthropometric outcomes will be compared between the two treatment arms using logistic regression models with the anthropometric outcome as the outcome and randomisation group and the stratification factors (site, baseline BMI) as covariates. The adjusted odds ratio will be presented along with 95% confidence interval and p-value comparing the two treatment arms. Continuous anthropometric outcomes will be compared using linear regression models with the anthropometric outcome as the outcome and randomisation group and the stratification factors (site, BMI) as covariates. The adjusted mean difference will be estimated along with 95% confidence interval and p-value comparing the two treatment arms. If continuous outcomes are non-normally distributed then they will be transformed or a more suitable regression model will be selected.

No formal statistical testing will take place for the other secondary outcomes due to the large amount of secondary outcomes and to reduce multiple testing. Instead, descriptive analyses will be performed to explore potential patterns in improvements. This will apply to the outcomes relating to obesity-related co-morbidities, referrals to Tier 4 services, treatment satisfaction, treatment compliance, and physical activity. Categorial outcomes will be summarised using count and percentage. Continuous outcomes will be summarised using mean, standard deviation, median, range, and interquartile range. Where it makes sense to do so, for continuous variables the baseline, follow-up, and change values will all be summarised; some outcomes can only be defined at follow-up and so this will not apply to those outcomes.

In all analyses, participants will be analysed in the group to which they were randomised at baseline. Only the complete cases population will be used for the secondary outcomes to reduce the number of models being fitted. Participants who have undergone bariatric surgery during the period of the study will be excluded from these analyses if their bariatric surgery took place before the analysed time-point.

5.5.2 Secondary Analyses of Secondary Outcomes

As additional secondary analyses, we will perform a responder analysis which will repeat the analyses of the secondary anthropometric outcomes with the intervention group restricted to those participants who responded to the targeted prescribing pathway (i.e. had achieved ≥15% weight loss at 52 weeks after randomisation). The purpose of these analyses is to compare the outcomes of "early and good" responders to the targeted prescribing pathway with those who received standard care only.

Therefore, all participants randomised to the standard care group will also be included in these responder analyses.

5.5.3 Sensitivity Analyses

No sensitivity analyses are planned.

5.6 Subgroup Analyses

No subgroup analyses are planned.

5.7 Figures to be produced

Figure	Description
CONSORT diagram	See Section 5.1
Treatment flow	Based on figure in Section 1.2.1 with numbers added to show number of participants at each stage

5.8 Changes to the Planned Analysis

In the protocol, it stated that most secondary outcomes would be subject to formal statistical testing, with some secondary outcomes (safety, treatment compliance, treatment satisfaction) tabulated only, without statistical testing. However, due to the large number of secondary outcomes, it was decided that more secondary outcomes should be tabulated only to reduce the impact of multiple testing. The following outcomes were the ones for which the approach changed: obesity-related co-morbidities, referrals to Tier 4 services, and physical activity.

In the protocol, the majority of the secondary outcomes were listed as absolute values, however the change from baseline will instead be analysed for continuous variables.

In the protocol, it states that ACR will be analysed as a secondary outcome for participants with diabetes. However, ACR was also measured for participants with prediabetes or hypertension and so these have been added to the ACR secondary outcome definition.

In the protocol, it was stated that participants who had bariatric surgery would be excluded from the complete cases, per protocol, and responder populations. However, it is more likely that these individuals will be poor responders and so excluding them could potentially bias the analyses. Therefore, participants who had bariatric surgery during the study period will be only be included at time-points prior to their bariatric surgery. They will be excluded from time-points after their bariatric surgery.

In the protocol, it stated that adjusted proportions or means would be presented by treatment group in the primary and secondary analyses. However, the unadjusted raw values are presented instead.

6 Safety and Adverse events (AEs)

The safety outcomes (including AEs and SAEs) will be summarised overall, by randomisation group, and by whether or not the participant was currently receiving LIRA 3mg treatment using count and percentage. The following information will also be presented:

- Incidence rate (per person-year) of each System Organ Class of AEs by treatment and overall
- Proportion of participants with at least one AE, by System Organ Class type, treatment arm, and overall
- Incidence rate (per person-year) of each expected AE type by treatment and overall
- Proportion of participants with at least one expected AE, by AE type, treatment arm, and overall
- Bar chart of number of AEs per individual, split by treatment
- Proportion of individuals with at least one AE of given severity by treatment and overall
- Proportion of individuals with at least one AE of given 'likelihood related' by treatment and overall.

For System Organ Classes with >0.1 AEs per person-year, the AEs broken down by higher level term.

Additionally, separate listings of all AEs and SAEs will be produced, including 'likelihood related', expectedness, duration, severity, action taken, outcome, and treatment, with sorting by randomisation group, participant ID, then date.

Finally, hypogylcaemia events will be tabulated by Glycaemic status for ADA and Novo Nordisk definition separately.

The safety analyses will use the safety population.

7 References

White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ. **2011**;342:d40.

8 Appendix 1: Scoring for King's College Obesity Staging System

	Stage 0 Normal Health	Stage 1 At risk of disease	Stage 2 Established disease	Stage 3 Advanced disease
Airways	Normal	Snoring	CPAP therapy	Cor pulmonale
BMI	<35kg/m^2	35-40 kg/m^2	40-60 kg/m^2	>60 kg/m^2
Cardiovascular	<10% risk	10-20% risk	Heart disease	Heart failure
Diabetes	Normal	Impaired fasting glucose	Type 2 diabetes	Uncontrolled type 2 diabetes
Economic	Normal	Increased expense for clothes and travel	Workplace discrimination	Unemployment due to obesity
Functional	Can walk three flights of stairs	Can walk one or two flights of stairs	Requires mobility aid	Housebound
Gonadal	Normal	PCOS/erectile dysfunction	Subfertility	Sexual dysfunction leading to relationship breakdown
Health status (perceived)	Normal	Low mood or QoL	Depression or poor QoL	Severe depression
Image (body)	Normal	Dislikes body	Body image dysphoria	Eating disorder

Abbreviations: CPAP, Continuous Positive Airway Pressure; PCOS, Polycystic Ovarian Syndrome; QoL, Quality of Life.

9 Appendix 2: Scoring for PHQ-9 Questionnaire

PHQ-9* Questionnaire for Depression Scoring and Interpretation Guide

For physician use only

Scoring:
Count the number (#) of boxes checked in a column. Multiply that number by the value indicated below, then add the subtotal to produce a total score. The possible range is 0-27. Use the table below to interpret the PHQ-9 score.

Not at all (#) _____ x 0 = _____
Several days (#) _____ x 1 = _____
More than half the days (#) _____ x 2 = _____
Nearly every day (#) _____ x 3 = _____

Total score: _____

Interpreting PHQ-9 Scores

Diagnosis	Total Score	For Score	Action
Minimal depression	0-4	≤ 4	The score suggests the patient may not need depression treatment
Mild depression	5-9	5 - 14	Physician uses clinical judgment about treatment, based on patient's duration of symptoms and functional impairment
Moderate depression	10-14		
Moderately severe depression	15-19	> 14	Warrants treatment for depression, using antidepressant, psychotherapy and/or a combination of treatment.
Severe depression	20-27		

10 Appendix 3: Scoring for Epworth Sleepiness Scale

How Sleepy Are You?
How likely are you to doze off or fall asleep in the following situations? You should rate your chances of dozing off, not just feeling tired. Even if you have not done some of these things recently try to determine how they would have affected you.

For each situation, decide whether or not you would have:

· No chance of dozing =0
· Slight chance of dozing =1
· Moderate chance of dozing =2
· High chance of dozing =3

Write down the number corresponding to your choice in the right-hand column. Total your score below.

Situation Chance of Dozing
Sitting and reading ·
Watching TV ·
Sitting inactive in a public place (e.g., a theater or a meeting) ·
As a passenger in a car for an hour without a break ·
Lying down to rest in the afternoon when circumstances permit ·
Sitting and talking to someone ·
Sitting quietly after a lunch without alcohol ·
In a car, while stopped for a few minutes in traffic ·
Total Score = _____

Analyze Your Score
Interpretation:
≥10: Requires referral for sleep apnoea studies as indicates above average daily sleepiness.

11 Appendix 4: Scoring for Stop Bang Questionnaire

1.	Do you **Snore** loudly? Louder than talking or loud enough to be heard through a closed door	Yes	No
2.	Has anybody **Observed** you stop breathing during your sleep?	Yes	No
3.	Do you often feel **Tired**, fatigued, or sleepy during the daytime?	Yes	No
4.	High Blood **Pressure?** – do you have it or are you on treatment?	Yes	No
5.	**Gender:** Are you male or female?	M	F
6.	Is your **Age** above 50?	Yes	No

Clinic/nursing staff to complete:					
Neck Circumference – collar size		cm / inches	Neck circumference >40cm?	Yes	No
Weight		kg	-	-	-
Height		m	-	-	-
BMI		kg/m2	BMI > 35 kg/m2	Yes	No
Total STOP-BANG Score:				/ 8	

If the **STOP-BANG score is 5 or more**, consideration should be given to referral to the Sleep Service for investigation and treatment of possible Obstructive Sleep Apnoea (OSA).

· A score of 3 or more is sensitive for moderate-severe OSA but is not very specific, there is a high false positive rate.

· A score of 5-8 is far more specific and indicates a high probability of moderate-severe OSA.

12 Appendix 5: Definitions of hypoglycaemia

A hypoglycaemic episode will be defined as treatment emergent if the onset of the episode is on or after the first day of randomised treatment and no later than 14 days after the last day of randomised treatment. Hypoglycaemic events will be defined as nocturnal if the time onset is between 00:01 and 05:59 (both included).

A hypoglycaemic episode form and an Adverse Event (AE) form must be filled in for all hypoglycaemic episodes. Hypoglycaemic episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (i.e., 'severe hypoglycaemic episodes') will be qualified as an event of special interest.

A different definition of hypoglycaemia will apply for patients with type 2 diabetes and a different definition will apply for patients without diabetes.

Classification of hypoglycaemia for participants with type 2 diabetes

All participants with diabetes will be supplied with a glucose meter and a diabetes diary for recording of hypoglycaemia, symptomatic episodes and routine blood glucose monitoring. Plasma glucose should always be measured from all participants with diabetes when there is the suspicion of a hypoglycaemic episode.

All plasma glucose values ≤3.1 mmol/L (56mg/dL), as well as values >3.1 mmol/L (56mg/dL) when hypoglycaemic symptoms have occurred should be recorded by the participants in the diaries. Hypoglycaemic episodes will be recorded by the participant in his/her diary throughout the trial and must be transcribed into the CRF by the Investigator at each site visit throughout the trial.

Hypoglycaemic episodes will be summarised based on the American Diabetes Association (ADA) classification and Novo Nordisk's definition.

Novo Nordisk definition

In normal physiology, hypoglycaemia symptoms occur at a blood glucose level of approximately < 2.8 mmol/L (50 mg/dL)/plasma glucose level < 3.1 mmol/L (56 mg/dL). Therefore, Novo Nordisk has used this cut-off value to define minor hypoglycaemia.

Minor hypoglycaemic episode is defined as:

- An episode with symptoms consistent with hypoglycaemia with confirmation by plasma glucose < 3.1 mmol/L (56 mg/dL), or full blood glucose < 2.8 mmol/L (50 mg/dL) and which is handled by the subject himself/herself

- Or any asymptomatic plasma glucose value < 3.1 mmol/L (56 mg/dL) or full blood glucose value < 2.8 mmol/L (50 mg/dL). Minor hypoglycaemic episodes will be summarised according to this definition, and can be subject to additional analysis.

ADA hypoglycaemia classification

According to ADA the definition of a hypoglycaemic episode is categorised as:

Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤3.9 mmol/L.

Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentrations ≤3.9 mmol/L.

Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤3.9mmol/L).

Relative hypoglycaemia: An episode during which the participant reports any of the typical symptoms of hypoglycaemia and interprets those as indicative of hypoglycaemia, but with a measured plasma glucose concentration >3.9 mmol/L.

Classification of hypoglycaemia for participants without diabetes

Participants without diabetes will not be routinely provided with blood glucose meters or diaries; hence blood glucose will not be measured in case of symptoms of hypoglycaemia unless it coincides with a clinic visit.

The hypoglycaemia events for participants without diabetes will be reported spontaneously i.e., symptoms of hypoglycaemia (not biochemically confirmed) occurring outside of visits to the clinic; severe hypoglycaemia will be defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. In the event of severe or symptomatic hypoglycaemia patients will be given a glucose monitor and asked to record their blood glucose whenever they feel symptomatic.

13 Appendix 6: IPAQ scoring system

Further details including data processing rules can be found here:
https://sites.google.com/site/theipaq/scoring-protocol

Continuous Score

Data collected with the IPAQ long form can be reported as a continuous measure and reported as median MET-minutes. Median values and interquartile ranges can be computed for walking (W), moderate-intensity activities (M), and vigorous-intensity activities (V) within each domain using the formulas below. Total scores may also be calculated for walking (W), moderate-intensity activities (M), and vigorous-intensity activities (V); for each domain (work, transport, domestic and garden, and leisure) and for an overall grand total.

MET Values and Formula for Computation of MET-minutes

Work Domain

Walking MET-minutes/week at work = 3.3 * walking minutes * walking days at work
Moderate MET-minutes/week at work= 4.0 * moderate-intensity activity minutes * moderate-intensity days at work
Vigorous MET-minutes/week at work= 8.0 * vigorous-intensity activity minutes * vigorous-intensity days at work
Total Work MET-minutes/week =sum of Walking + Moderate + Vigorous MET-minutes/week scores at work.

Active Transportation Domain

Walking MET-minutes/week for transport = 3.3 * walking minutes * walking days for transportation
Cycle MET-minutes/week for transport= 6.0 * cycling minutes * cycle days for transportation
Total Transport MET-minutes/week = sum of Walking + Cycling MET-minutes/week scores for transportation.

Domestic and Garden [Yard Work] Domain

Vigorous MET-minutes/week yard chores= 5.5 * vigorous-intensity activity minutes * vigorous-intensity days doing yard work (Note: the MET value of 5.5 indicates that vigorous garden/yard work should be considered a moderate-intensity activity for scoring and computing total moderate intensity activities.)
Moderate MET-minutes/week yard chores= 4.0 * moderate-intensity activity minutes * moderateintensity days doing yard work

Moderate MET-minutes/week inside chores= 3.0* moderate-intensity activity minutes * moderateintensity days doing inside chores.
Total Domestic and Garden MET-minutes/week =sum of Vigorous yard + Moderate yard + Moderate inside chores MET-minutes/week scores.

Leisure-Time Domain
Walking MET-minutes/week leisure = 3.3 * walking minutes * walking days in leisure
Moderate MET-minutes/week leisure = 4.0 * moderate-intensity activity minutes * moderate-intensity days in leisure
Vigorous MET-minutes/week leisure = 8.0 * vigorous-intensity activity minutes * vigorous-intensity days in leisure
Total Leisure-Time MET-minutes/week = sum of Walking + Moderate + Vigorous MET-minutes/week scores in leisure.

Total Scores for all Walking, Moderate and Vigorous Physical Activities
Total Walking MET-minutes/week = Walking MET-minutes/week (at Work + for Transport + in Leisure)
Total Moderate MET-minutes/week total = Moderate MET-minutes/week (at Work + Yard chores + inside chores + in Leisure time) + Cycling Met-minutes/week for Transport + Vigorous Yard chores MET-minutes/week
Total Vigorous MET-minutes/week = Vigorous MET-minutes/week (at Work + in Leisure)

Note: Cycling MET value and Vigorous garden/yard work MET value fall within the coding range of moderate-intensity activities.

Total Physical Activity Scores
An overall total physical activity MET-minutes/week score can be computed as: Total physical activity MET-minutes/week = sum of Total (Walking + Moderate + Vigorous) METminutes/week scores.

This is equivalent to computing: Total physical activity MET-minutes/week = sum of Total Work + Total Transport + Total Domestic and Garden + Total Leisure-Time MET-minutes/week scores.

As there are no established thresholds for presenting MET-minutes, the IPAQ Research Committee proposes that these data are reported as comparisons of median values and interquartile ranges for different populations.

14 Appendix 7 Definitions for adherence of participants with the LIRA 3mg

Individuals that didn't receive 70% of the doses as determined by the protocol (i.e. in the first 16 weeks or there after whilst continuing to meet the continue rules of the protocolised treatment schedule) will be classed as not adhering with the LIRA 3mg pathway.

Defining days taking LIRA

The number of days taking LIRA will be calculated as the time from first dose dispensed (normally at baseline visit) to the last known date of individuals taking the LIRA. Where individuals are recorded as not completing the trial due to stopping the LIRA, the date of last dose of LIRA in the completion form will be used; if this is not recorded then the date of first visit at which individuals say they are not happy to continue taking LIRA will be used; and where neither of these are recorded the date of the last visit that individuals said they are happy to continue LIRA will be used.

14.1 52 weeks

Individuals will then be assessed for whether they have received 70% as per table below.

Stopping rule on protocolised treatment schedule	Did not receive 70% of planned doses	Did receive 70% of planned doses
Did not meet rule to continue on Lira at 16 weeks (either <5% weight loss or not measured)	If days taking LIRA is <70% of days between baseline and Week 16. Or, if Week 16 date missing, if days taking LIRA is ≤ 78.	If days taking LIRA is ≥70% of days between baseline and Week 16. Or, if Week 16 date missing, if days taking LIRA is >78
Did meet rule to continue Lira (≥5% weight loss) at 16 weeks but did not meet rule to continue Lira at 32 weeks (either <10% weight loss or not measured)	If days taking LIRA is <70% of days between baseline and Week 32. Or, if Week 32 date missing, if days taking LIRA is ≤156.	If days taking LIRA is ≥70% of days between baseline and Week 32. Or, if Week 32 date missing, if days taking LIRA is >156.
Did meet rule to continue Lira (≥5% weight loss) at 16 weeks and did meet rule to continue Lira at 32 weeks (≥10% weight loss)	If days taking LIRA is <70% of days between baseline and week 52. Or, if week 52 date missing, if days taking LIRA is ≤254.	If days taking LIRA is ≥70% of days between baseline and week 52. Or, if week 52 date is missing, if days taking LIRA is >254.

14.2 104 weeks

Individuals will then be assessed for whether they have received 70% as per table below.

Stopping rule on protocolised treatment schedule	Did not receive 70% of planned doses	Did receive 70% of planned doses
Did not meet rule to continue on Lira at 16 weeks (either <5% weight loss or not measured)	If days taking LIRA is <70% of days between baseline and Week 16. Or, if Week 16 date missing, if days taking LIRA is ≤ 78.	If days taking LIRA is ≥70% of days between baseline and Week 16. Or, if Week 16 date missing, if days taking LIRA is >78
Did meet rule to continue Lira (≥5% weight loss) at 16 weeks but did not meet rule to continue Lira at 32 weeks (either <10% weight loss or not measured)	If days taking LIRA is <70% of days between baseline and Week 32. Or, if Week 32 date missing, if days taking LIRA is ≤156.	If days taking LIRA is ≥70% of days between baseline and Week 32. Or, if Week 32 date missing, if days taking LIRA is >156.
Did meet rule to continue Lira (≥5% weight loss) at 16 weeks, did meet rule to continue Lira at 32 weeks (≥10% weight loss) and did not meet rule to continue Lira at 52 weeks (either <15% weight loss or not measured)	If days taking LIRA is <70% of days between baseline and week 52. Or, if Week 52 date missing, if days taking LIRA is ≤254.	If days taking LIRA is ≥70% of days between baseline and week 52. Or, if Week 52 date missing, if days taking LIRA is >254.
Did meet rule to continue Lira (≥5% weight loss) at 16 weeks, did meet rule to continue Lira at 32 weeks (≥10% weight loss) and did meet rule to continue Lira at 52 weeks (≥15% weight loss)	If days taking LIRA is <70% of days between baseline and week 104. Or, if Week 104 date missing, if days taking LIRA is ≤510.	If days taking LIRA is ≥70% of days between baseline and week 104. Or, if Week 104 date missing, if days taking LIRA is >510.

15 Appendix 8: Baseline and follow-up Glycaemic Status Definitions

15.1 Baseline Glycaemic Status

Individuals are classified as having diabetes remission status if all of the following is the satisfied:

- HbA1C <6.5%, not on glucose lowering medication and have a previous medical history of diabetes

Individuals are classified as having diabetes status if one of the following is the satisfied:

- HbA1C ≥6.5%
- Have previous medical history of diabetes and they are on any glucose lowering medication (including Metformin)
- Are on any glucose-lowering medication except of Metformin (with or without past medical history of diabetes).

Individuals are classified as having pre-diabetes status if one of the following is the satisfied:

- HbA1C 6.0-6.4%, without a previous medical history of diabetes and not on any glucose-lowering medication.
- HbA1C 6.0-6.4%, without a previous medical history of diabetes and only on Metformin from glucose-lowering medications.
- HbA1C <6.0%, with a previous medical history of pre-diabetes (but without a previous medical history of diabetes) and only on Metformin from glucose-lowering medications.

Individuals are classified as having Normoglycaemia if one of the following is satisfied:

- HbA1C <6.0%, without a previous medical history of diabetes and not on any glucose-lowering medication.
- HbA1C <6.0%, without a previous medical history of diabetes or pre-diabetes and only on Metformin from glucose-lowering medications.

15.2 Follow-up Glycaemic Status

Individuals are classified as having diabetes remission status if all the following is satisfied:

- Follow-up HbA1C <6.5%, not on glucose lowering medication for ≥ 3months, have a previous medical history of diabetes and have NOT being on LIRA 3mg within the last 3 months

Individuals are classified as having diabetes status if one of the following is the satisfied:

- Follow-up HbA1C ≥6.5%
- Have previous medical history of diabetes and they are on any glucose lowering medication (including Metformin) within the last 3 months and/or have being on LIRA 3mg within the last 3 months
- Are on any glucose-lowering medication except of Metformin (LIRA 3mg is considered obesity medication, not glucose-lowering)

Individuals are classified as having pre-diabetes status if one of the following is the satisfied:

- Follow-up HbA1C 6.0-6.4%, without previous medical history of diabetes and not on any glucose-lowering medication (but they can be on LIRA 3mg).
- Follow-up HbA1C 6.0-6.4%, without previous medical history of diabetes and only on Metformin from glucose lowering agents (and they can also be on LIRA 3mg).
- Follow-up HbA1C <6.0%, with a previous medical history of pre-diabetes (but without a previous medical history of diabetes) and only on Metformin from glucose-lowering agents (and they can also be on LIRA 3mg).

Individuals are classified as having Normoglycaemia if one of the following is the satisfied:

- Follow-up HbA1C <6.0%, without a previous medical history of diabetes and not on any glucose-lowering medication (but they can be on LIRA 3mg).
- Follow-up HbA1C <6.0%, without a previous medical history of diabetes or pre-diabetes and only on Metformin from glucose-lowering medications (and they can also be on LIRA 3mg).

16 Appendix 9: Templates for Tables

16.1 Disposition

Population	Control group (n =)		Intervention group (n =)		Total population (n =)	
	Number	Percentage	Number	Percentage	Number	Percentage
Complete cases						
Intention-to-treat						
Of whom, those who had bariatric surgery						
Per protocol						
Responder						

16.2 Protocol deviations

Type of protocol deviation	Control group (n =)		Intervention group (n =)		Total population (n =)	
	Number	Percentage	Number	Percentage	Number	Percentage
[TBC]						
[TBC]						
[TBC]						
[TBC]						

16.3 Summary of continuous baseline characteristics

Baseline characteristic	Control group (n =)					Intervention group (n =)					Total population (n =)				
	N missing	Mean	SD	Median	IQR	N missing	Mean	SD	Median	IQR	N missing	Mean	SD	Median	IQ
Age, years															
Weight, kg															
Body mass index, kg/m^2															
Heart rate, beats/minute															
Waist circumference, cm															
HbA1c, mmol/mol															
HbA1c, %															
Albumin-creatinine ratio, mg/mmol															
Systolic blood pressure, mmHg															
Diastolic blood pressure, mmHg															
LDL cholesterol, mmol/L															

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Baseline characteristic	Control group (n =)					Intervention group (n =)					Total population (n =)				
	N missing	Mean	SD	Median	IQR	N missing	Mean	SD	Median	IQR	N missing	Mean	SD	Median	IQ
HDL cholesterol, mmol/L															
Total cholesterol, mmol/L															
Triglycerides, mmol/L															
Average total MET-minutes/week															

Abbreviations: IQR, Interquartile Range; N, Number; SD, Standard Deviation.

16.4 Summary of categorical baseline characteristics

Baseline characteristic	Control group (n =)		Intervention group (n =)		Total population (n =)	
	Number	Percentage	Number	Percentage	Number	Percentage
Sex						
Men						
Women						
Missing						
Ethnicity						
[TBC]						
[TBC]						
[TBC]						
Missing						
Smoking status						
Never smoker						
Ex-smoker						
Current smoker						
Missing						
Glycaemic Status						
Normoglycaemia						
Prediabetes						
Diabetes						
Diabetes remission						
Missing						
Hypertension status						
No						
Yes						
Missing						
Sleep apnoea status						
No						
Yes						
Missing						
Total number of medications						
0						
1						

Baseline characteristic	Control group (n =)		Intervention group (n =)		Total population (n =)	
	Number	Percentage	Number	Percentage	Number	Percentage
2						
≥3						
Missing						
Number of diabetes medications						
0						
1						
2						
≥3						
Missing						
Type of diabetes medication						
SGLT-2						
Metformin						
Sulphonylureas						
Glitazones						
Missing						
Number of antihypertensive medications						
0						
1						
2						
≥3						
Missing						
CPAP use						
No						
Yes						
Missing						
Statin use						
No						
Yes						
Missing						

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16.5 Comparison of continuous baseline characteristics between those with and without primary outcome data

Baseline characteristic	Missing primary outcome data (n =)					Non-missing primary outcome data (n =)					P-value[a]
	N missing	Mean	SD	Median	IQR	N missing	Mean	SD	Median	IQR	
Age, years											
Weight, kg											
Body mass index, kg/m^2											
Waist circumference, cm											
Heart rate, beats/minute											
HbA1c, mmol/mol											
HbA1c, %											
Albumin-creatinine ratio, mg/mmol											
Systolic blood pressure, mmHg											
Diastolic blood pressure, mmHg											
LDL cholesterol, mmol/L											
HDL cholesterol, mmol/L											
Total cholesterol, mmol/L											
Triglycerides, mmol/L											

Baseline characteristic	Missing primary outcome data (n =)					Non-missing primary outcome data (n =)					P-value[a]
	N missing	Mean	SD	Median	IQR	N missing	Mean	SD	Median	IQR	
Average total MET-minutes/week											

Abbreviations: IQR, Interquartile Range; N, Number; SD, Standard Deviation.

[a] P-values were estimated using a t-test for normally distributed variables and a Mann-Whitney test for non-normally distributed variables.

16.6 Comparison of categorical baseline characteristics between those with and without primary outcome data

Baseline characteristic	Missing primary outcome data (n =)		Non-missing primary outcome data (n =)		P-value[a]
	Number	Percentage	Number	Percentage	
Sex					
Men					
Women					
Missing					
Ethnicity					
[TBC]					
[TBC]					
[TBC]					
Missing					
Smoking status					
Never smoker					
Ex-smoker					
Current smoker					
Missing					
Glycaemic Status					
Normoglycaemia					
Prediabetes					
Diabetes					
Diabetes remission					
Missing					
Hypertension status					
No					
Yes					
Missing					
Sleep apnoea status					
No					
Yes					
Missing					
Total number of medications					
0					
1					

Baseline characteristic	Missing primary outcome data (n =)		Non-missing primary outcome data (n =)		P-value[a]
	Number	Percentage	Number	Percentage	
2					
≥3					
Missing					
Number of diabetes medications					
0					
1					
2					
≥3					
Missing					
Type of diabetes medication					
SGLT-2					
Metformin					
Sulphonylureas					
Glitazones					
Missing					
Number of antihypertensive medications					
0					
1					
2					
≥3					
Missing					
CPAP use					
No					
Yes					
Missing					
Statin use					
No					
Yes					
Missing					

[a] P-values were estimated using a chi-squared test.

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16.7 Analysis of primary outcome

Population	Control			Intervention			Adjusted difference between the two groups[a]	
	N with data	N with outcome	% with outcome	N with data	N with outcome	% with outcome	OR (95% CI)	P-value
Complete cases[b]								
Intention-to-treat								
Per protocol								
Responder								

Abbreviations: CI, Confidence Interval; OR, Odds Ratio.

[a] Estimates are adjusted for the stratification variables: site and baseline body mass index ($\geq$45kg/m^2; <45kg/m^2).

[b] Primary analysis

16.8 Analysis of secondary categorical anthropometric outcomes

Outcome	Control			Intervention			Adjusted difference between the two groups[a]	
	N with data	N with outcome	% with outcome	N with data	N with outcome	% with outcome	OR (95% CI)	P-value
Weight loss of ≥5%								
16 weeks								
32 weeks								
52 weeks								
104 weeks								
Weight loss of ≥10%								
16 weeks								
32 weeks								
52 weeks								
104 weeks								
Weight loss of ≥15%								
16 weeks								
32 weeks								
52 weeks[b]								
104 weeks								
Maintenance of weight loss of ≥15% among those								

Outcome	Control			Intervention			Adjusted difference between the two groups[a]	
	N with data	N with outcome	% with outcome	N with data	N with outcome	% with outcome	OR (95% CI)	P-value
who lost ≥15% at 52 weeks								
104 weeks								

Abbreviations: CI, Confidence Interval; OR, Odds Ratio.

[a] Estimates are adjusted for the stratification variables: site and baseline body mass index (≥45kg/m^2; <45kg/m^2).

[b] Primary analysis.

16.9 Analysis of secondary continuous anthropometric outcomes

	Baseline		Follow-up		Change from baseline		Difference in change from baseline	
Outcome	Control	Intervention	Control	Intervention	Control	Intervention	Adjusted mean difference (95% CI)[a]	P-value
Absolute weight (kg) at 16 weeks								
Number								
Mean								
SD							-	-
Median							-	-
Range							-	-
Interquartile range							-	-
Absolute weight (kg) at 32 weeks								
Number								
Mean								
SD							-	-
Median							-	-
Range							-	-
Interquartile range							-	-
Absolute weight (kg) at 52 weeks								
Number								
Mean								
SD							-	-

Outcome	Baseline		Follow-up		Change from baseline		Difference in change from baseline	
	Control	Intervention	Control	Intervention	Control	Intervention	Adjusted mean difference (95% CI)[a]	P-value
Median							-	-
Range							-	-
Interquartile range							-	-
Absolute weight (kg) at 104 weeks								
Number								
Mean								
SD							-	-
Median							-	-
Range							-	-
Interquartile range							-	-
Relative change in weight (%) at 16 weeks								
Number								
Mean	-	-	-	-				
SD	-	-	-	-			-	-
Median	-	-	-	-			-	-
Range	-	-	-	-			-	-
Interquartile range	-	-	-	-			-	-
Relative change in weight (%) at 32 weeks								
Number								
Mean	-	-	-	-				

Outcome	Baseline		Follow-up		Change from baseline		Difference in change from baseline	
	Control	Intervention	Control	Intervention	Control	Intervention	Adjusted mean difference (95% CI)[a]	P-value
SD	-	-	-	-			-	-
Median	-	-	-	-			-	-
Range	-	-	-	-			-	-
Interquartile range	-	-	-	-			-	-
Relative change in weight (%) at 52 weeks								
Number								
Mean	-	-	-	-				
SD	-	-	-	-			-	-
Median	-	-	-	-			-	-
Range	-	-	-	-			-	-
Interquartile range	-	-	-	-			-	-
Relative change in weight (%) at 104 weeks								
Number								
Mean	-	-	-	-				
SD	-	-	-	-			-	-
Median	-	-	-	-			-	-
Range	-	-	-	-			-	-
Interquartile range	-	-	-	-			-	-
Absolute BMI (kg/m^2) at 52 weeks								
Number								

Outcome	Baseline		Follow-up		Change from baseline		Difference in change from baseline	
	Control	Intervention	Control	Intervention	Control	Intervention	Adjusted mean difference (95% CI)[a]	P-value
Mean								
SD							-	-
Median							-	-
Range							-	-
Interquartile range							-	-
Absolute BMI (kg/m^2) at 104 weeks								
Number								
Mean								
SD							-	-
Median							-	-
Range							-	-
Interquartile range							-	-
Absolute waist circumference (cm) at 52 weeks								
Number								
Mean								
SD							-	-
Median							-	-
Range							-	-
Interquartile range							-	-
Absolute change in waist circumference (cm) at 104 weeks								

Outcome	Baseline		Follow-up		Change from baseline		Difference in change from baseline	
	Control	Intervention	Control	Intervention	Control	Intervention	Adjusted mean difference (95% CI)[a]	P-value
Number								
Mean								
SD							-	-
Median							-	-
Range							-	-
Interquartile range							-	-

Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; OR, Odds Ratio.

[a] Estimates are adjusted for the stratification variables: site and baseline body mass index ($\geq$45kg/m^2; <45kg/m^2).

16.10 Summary of other categorical secondary outcomes

Outcome	N (%) at baseline		N (%) at follow-up	
	Control	Intervention	Control	Intervention
King's College Obesity Staging System at 52 weeks				
Normal health				
At risk of disease				
Established disease				
Advanced disease				
Missing				
King's College Obesity Staging System at 104 weeks				
Normal health				
At risk of disease				
Established disease				
Advanced disease				
Missing				
Patient health questionnaire-9 at 52 weeks				
Minimal depression				
Mild depression				
Moderate depression				
Moderately severe depression				
Severe depression				
Missing				
Patient health questionnaire-9 at 104 weeks				
Minimal depression				
Mild depression				
Moderate depression				
Moderately severe depression				
Severe depression				
Missing				
Epworth sleepiness scale at 52 weeks				
No OSA				
Possible OSA				
Missing				
Epworth sleepiness scale at 104 weeks				
No OSA				
Possible OSA				
Missing				
Stop bang questionnaire at 52 weeks				

Outcome	N (%) at baseline		N (%) at follow-up	
	Control	Intervention	Control	Intervention
No OSA				
Possible OSA				
Likely OSA				
Missing				
Stop bang questionnaire at 104 weeks				
No OSA				
Possible OSA				
Likely OSA				
Missing				
On CPAP at 52 weeks				
No				
Yes				
Missing				
On CPAP at 104 weeks				
No				
Yes				
Missing				
Glycaemic Status at 52 weeks				
Normoglycaemia				
Prediabetes				
Diabetes				
Diabetes remission				
Missing				
Glycaemic Status at 104 weeks				
Normoglycaemia				
Prediabetes				
Diabetes				
Diabetes remission				
Missing				
Hypertension at 52 weeks				
No				
Yes				
Missing				
Hypertension at 104 weeks				
No				
Yes				
Missing				
Referred to Tier 4 for bariatric surgery by 104 weeks				

Outcome	N (%) at baseline		N (%) at follow-up	
	Control	Intervention	Control	Intervention
No				
Yes				
Missing				

Abbreviations: CPAP, XX; N, Number; OSA, Obstructive Sleep Apnoea.

16.11 Summary of other secondary continuous outcomes

	Baseline		Follow-up		Change from ba	
Outcome	Control	Intervention	Control	Intervention	Control	Interv
EQ5D – Mobility at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – Mobility at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – Self-care at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – Self-care at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – Usual activities at 52 weeks						
Number						
Mean						
SD						
Median						
Range						

	Baseline		Follow-up		Change from ba	
Outcome	Control	Intervention	Control	Intervention	Control	Interv
Interquartile range						
EQ5D – Usual activities at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – Pain/discomfort at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – Pain/discomfort at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – Anxiety/depression at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – Anxiety/depression at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – VAS at 52 weeks						

	Baseline		Follow-up		Change from ba	
Outcome	Control	Intervention	Control	Intervention	Control	Interv
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
EQ5D – VAS at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Impact of Weight on Quality of Life-Lite at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Impact of Weight on Quality of Life-Lite at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Patient Health Questionnaire-9 at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Patient Health Questionnaire-9 at 104 weeks						
Number						

Outcome	Baseline		Follow-up		Change from ba	
	Control	Intervention	Control	Intervention	Control	Interv
Mean						
SD						
Median						
Range						
Interquartile range						
Epworth Sleepiness Scale at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Epworth Sleepiness Scale at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Stop Bang score at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Stop Bang score at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
CPAP compliance – Average hours per day at 52 weeks						
Number						
Mean						

Outcome	Baseline		Follow-up		Change from ba	
	Control	Intervention	Control	Intervention	Control	Interv
SD						
Median						
Range						
Interquartile range						
CPAP compliance – Average hours per day at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
HbA1c (mmol/mol) at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
HbA1c (mmol/mol) at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
HbA1c (%) at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
HbA1c (%) at 104 weeks						
Number						
Mean						
SD						

Outcome	Baseline		Follow-up		Change from ba	
	Control	Intervention	Control	Intervention	Control	Interv
Median						
Range						
Interquartile range						
Total number of agents for diabetes at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Total number of agents for diabetes at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Albumin-creatinine ratio (mg/mmol) at 52 weeks[a]						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Albumin-creatinine ratio (mg/mmol) at 104 weeks[a]						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Systolic blood pressure (mmHg) at 52 weeks						
Number						
Mean						
SD						
Median						

Outcome	Baseline		Follow-up		Change from ba	
	Control	Intervention	Control	Intervention	Control	Interv
Range						
Interquartile range						
Systolic blood pressure (mmHg) at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Diastolic blood pressure (mmHg) at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Diastolic blood pressure (mmHg) at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Total number of agents for hypertension at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Total number of agents for hypertension at 104 weeks						
Number						
Mean						
SD						
Median						
Range						

Outcome	Baseline		Follow-up		Change from ba	
	Control	Intervention	Control	Intervention	Control	Interv
Interquartile range						
LDL cholesterol (mmol/L) at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
LDL cholesterol (mmol/L) at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
HDL cholesterol (mmol/L) at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
HDL cholesterol (mmol/L) at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Total cholesterol (mmol/L) at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Total cholesterol (mmol/L) at 104 weeks						

	Baseline		Follow-up		Change from ba	
Outcome	Control	Intervention	Control	Intervention	Control	Interv
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Triglycerides (mmol/L) at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Triglycerides (mmol/L) at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Total number of agents for dyslipidaemia at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Total number of agents for dyslipidaemia at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Treatment Satisfaction Questionnaire for Medication (TSQM) at 52 weeks						
Number						

Outcome	Baseline		Follow-up		Change from ba	
	Control	Intervention	Control	Intervention	Control	Interv
Mean						
SD						
Median						
Range						
Interquartile range						
Treatment Satisfaction Questionnaire for Medication (TSQM) at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Total MET-minutes/week at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Total MET-minutes/week at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						

Abbreviations: VAS, Visual Analogue Scale.

[a] Only defined for participants with diabetes, prediabetes, or hypertension.

16.12 Summary of categorical safety outcomes

Outcome	N (%) at baseline		N (%) at follow-up	
	Control	Intervention	Control	Intervention
Gastrointestinal symptoms within 52 weeks				
No				
Yes				
Missing				
Gastrointestinal symptoms within 104 weeks				
No				
Yes				
Missing				

16.13 Summary of continuous safety outcomes

Outcome	Baseline		Follow-up		Change from ba	
	Control	Intervention	Control	Intervention	Control	Interv
Overall hypoglycaemia rate – ADA definition at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Overall hypoglycaemia rate – ADA definition at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Overall hypoglycaemia rate – Novo Nordisk definition at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Overall hypoglycaemia rate – Novo Nordisk definition at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Overall adverse event rate at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						

Outcome	Baseline		Follow-up		Change from ba	
	Control	Intervention	Control	Intervention	Control	Interv
Overall adverse event rate at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Overall serious adverse event rate at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Overall serious adverse event rate at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Overall severe hypoglycaemia event rate at 52 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Overall severe hypoglycaemia event rate at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						
Heart rate (beats per minute) at 52 weeks						
Number						

Outcome	Baseline		Follow-up		Change from ba	
	Control	Intervention	Control	Intervention	Control	Interv
Mean						
SD						
Median						
Range						
Interquartile range						
Heart rate (beats per minute) at 104 weeks						
Number						
Mean						
SD						
Median						
Range						
Interquartile range						

16.14 Summary of categorical compliance outcomes

Outcome	N (%) at baseline		N (%) at follow-up	
	Control	Intervention	Control	Intervention
Attended at least 70% of scheduled Tier 3 appointments at 52 weeks				
No				
Yes				
Missing				
Attended at least 70% of scheduled Tier 3 appointments at 104 weeks				
No				
Yes				
Missing				
Stopped treatment with LIRA 3mg due to adverse effects at 52 weeks				
No				
Yes				
Missing				
Stopped treatment with LIRA 3mg due to adverse effects at 104 weeks				
No				
Yes				
Missing				
Compliant with LIRA 3mg treatment at 52 weeks				
No				
Yes				
Missing				
Compliant with LIRA 3mg treatment at 104 weeks				
No				
Yes				
Missing				
Stopped LIRA 3mg treatment at 16 weeks				
No				
Yes				
Missing				
Stopped LIRA 3mg treatment at 32 weeks				
No				
Yes				
Missing				
Stopped LIRA 3mg treatment at 52 weeks				
No				
Yes				

Outcome	N (%) at baseline		N (%) at follow-up	
	Control	Intervention	Control	Intervention
Missing				
Completed 52 weeks of the Tier 3 programme despite stopping LIRA 3mg at 16 weeks				
No				
Yes				
Missing				
Completed 52 weeks of the Tier 3 programme despite stopping LIRA 3mg at 32 weeks				
No				
Yes				
Missing				
Started on anti-obesity drugs at 52 weeks				
No				
Yes				
Missing				
Started on anti-obesity drugs at 104 weeks				
No				
Yes				
Missing				

16.15 Summary of Adverse events by MEDRA and expected adverse event terms

Incidence rate (per person year) of each System Organ Class of AEs by treatment and Overall

System Organ Class	Standard N	Standard Incidence	Liraglutide N	Liraglutide Incidence	Overall N	Overall Incidence	Incidence Rate Ratio
Blood and lymphatic system disorders							
Cardiac disorders							
Congenital, familial and genetic disorders							
Ear and labyrinth disorders							
Endocrine disorders							
....							

Proportion of patients with at least one AE, by SOC type, treatment arm and overall

System Organ Class	Standard N	Standard %	Liraglutide N	Liraglutide %	Overall N	Overall %
Blood and lymphatic system disorders						
Cardiac disorders						
Congenital, familial and genetic disorders						
Ear and labyrinth disorders						
Endocrine disorders						
....						

Incidence rate (per person year) of each Expected AE Type by treatment and Overall

Expected AE Type	Standard N	Standard Incidence	Liraglutide N	Liraglutide Incidence	Overall N	Overall Incidence	Incidence Rate Ratio
N/A							
Anaphylactic reaction							
Hypoglycaemia							
Dehydration							
Dizziness							
Nausea							
.....							

Proportion of patients with at least one expected AE, by AE type, treatment arm and overall

Expected AE Type	Standard N	Standard %	Liraglutide N	Liraglutide %	Overall N	Overall %
N/A						
Anaphylactic reaction						
Hypoglycaemia						
Dehydration						
Dizziness						
Nausea						
.....						

Proportion of individuals with at least one AE of given Severity by treatment and overall

	Standard		Liraglutide		Overall	
Severity	N	%	N	%	N	%
Mild						
Moderate						
Severe						
Fatal						

Proportion of individuals with at least one AE of given Likelihood Related by treatment and overall

	Standard		Liraglutide		Overall	
Likelihood Related	N	%	N	%	N	%
Not Related						
Unlikely						
Possible						
Probable						
Definite						

Incidence rate (per person year) of each System Organ Class of SAEs by treatment and Overall

System Organ Class	Standard		Liraglutide		Overall		
	N	Incidence	N	Incidence	N	Incidence	Incidence Rate Ratio
Blood and lymphatic system disorders							
Cardiac disorders							
Congenital, familial and genetic disorders							
Ear and labyrinth disorders							
Endocrine disorders							
....							

Proportion of patients with at least one SAE, by SOC type, treatment arm and overall

	Standard		Liraglutide		Overall	
System Organ Class	N	%	N	%	N	%
Blood and lymphatic system disorders						
Cardiac disorders						
Congenital, familial and genetic disorders						
Ear and labyrinth disorders						
Endocrine disorders						
....						

Incidence rate (per person year) of each Expected SAE Type by treatment and Overall

Expected AE Type	Standard N	Standard Incidence	Liraglutide N	Liraglutide Incidence	Overall N	Overall Incidence	Incidence Rate Ratio
N/A							
Anaphylactic reaction							
Hypoglycaemia							
Dehydration							
Dizziness							
Nausea							
.....							

Proportion of patients with at least one expected SAE, by AE type, treatment arm and overall

Expected AE Type	Standard N	Standard %	Liraglutide N	Liraglutide %	Overall N	Overall %
N/A						
Anaphylactic reaction						
Hypoglycaemia						
Dehydration						
Dizziness						
Nausea						
.....						

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