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# Rationale and design of an open-label, real-world, randomised controlled trial examining the effectiveness and cost of integrating a pragmatic pathway for prescribing liraglutide 3.0 mg in obesity services (STRIVE study).

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## Abstract

### Introduction

In the UK and Ireland, severe and complex obesity is managed in specialist weight management services (SWMS), which provide multicomponent lifestyle interventions to support weight loss, and use of medication if available. Liraglutide 3mg (LIRA 3mg) is an effective weight-loss medication, but weight loss in individual patients is variable, and its efficacy has not been assessed in SWMS. This study aims to investigate whether a targeted prescribing pathway for LIRA 3mg with multiple pre-specified stopping rules could help people with severe obesity and established complications achieve ≥15% weight loss in order to determine whether this could be considered a clinically effective and cost-effective strategy for managing severe and complex obesity in SWMS.

### Methods and analysis

In this two year, multicentre, open-label, real-world randomised controlled trial, 384 adults with severe and complex obesity (defined as BMI ≥35kg/m$^2$ plus either prediabetes, type 2 diabetes, hypertension or sleep apnoea) will be randomised via a 2:1 ratio to receive either standard SWMS care (n=128) or standard SWMS care plus a targeted prescribing pathway for LIRA 3mg with pre-specified stopping rules at 16, 32 and 52 weeks (n=256).

The primary outcome is to compare the proportion of participants achieving a weight loss of ≥15% at 52 weeks with a targeted prescribing pathway vs. standard care. Secondary outcomes include a comparison of a) the weight loss maintenance at 104 weeks and b) the budget impact and cost-effectiveness between the two groups in a real-world setting.

### Ethics and dissemination

The study will be performed and monitored according to the Good Clinical Practice – International Conference on Harmonisation regulations and conducted according to the principles of Helsinki. The Medicines and Healthcare products Regulatory Authority in UK, the Health Products Regulatory Authority in Ireland, the local research ethics committees, and the Health Research Authority have approved the study.

### Trial registration number

ClinicalTrials.gov – Identifier: NCT03036800

European Clinical Trials Database – Identifier: EudraCT Number 2017-002998-20

## Article Summary

### Strengths and limitations of this study

- Large, multicentre, real world, randomised controlled trial
- Assessment of the clinical effectiveness and cost-effectiveness of a targeted prescribing pathway with three stopping rules for LIRA 3mg to optimise its use in obesity services.
- The study will include only patients with severe and complex obesity (BMI ≥35 kg/m$^2$ plus either prediabetes, type 2 diabetes, hypertension or sleep apnoea) referred to a specialist weight management service.
- Some participants will stop using LIRA 3mg due to the 2$^{nd}$ and 3$^{rd}$ stopping rule despite achieving clinically significant weight loss and metabolic benefits.

## INTRODUCTION

Obesity is a complex disease characterised by increased hunger and reduced satiety.[1] Severe and complex obesity is defined as a BMI ≥35kg/m$^2$ with at least one major obesity-related complication.[2] Around 10% of the adult population in England has a BMI ≥35kg/m$^2$,[3] and many have established complications such as type 2 diabetes (T2D),[4] hypertension [5] and sleep apnoea,[4] imposing colossal direct and indirect healthcare costs.[6]

Lifestyle interventions are considered cornerstones for the management of obesity.[7] Despite the impressive results from intensive lifestyle interventions in Look Ahead study,[8] and more recently the DIRECT and Counterweight-Plus studies,[9, 10] which used intensive and structured weight management programmes to achieve weight loss and diabetes remission in real-life community settings, lifestyle interventions still commonly only achieve an average of 5% weight loss[11, 12] and long-term weight maintenance remains a challenge.[13, 14] Although weight loss as little as 5% does produce metabolic improvements, it is not enough to make a difference to the lives of most people with severe and complex obesity. Maximal benefits for the treatment of obesity-associated complications are obtained with weight loss above 15%.[15] Pharmacotherapy for obesity can support some people to achieve these results,[16-18] but currently it is not used frequently enough to be considered a cornerstone treatment.[7]

Severe and complex obesity is managed in specialist weight management services (SWMS) in UK and Ireland.[7, 11, 19, 20] SWMS consist of a multidisciplinary team typically led by a medical clinician with expertise in obesity management and/or a specialist dietician and supported by specialist physiotherapists, psychologists and nurses; these services offer intensive lifestyle interventions with similar components to those used by DIRECT and Look Ahead studies, and can be supported by pharmacotherapy.[7] Orlistat is the only weight loss medication approved by the National Institute for Health and Care Excellence (NICE) for use in SWMS, however its side effects and limited effectiveness [18, 21] have reduced the penetrance of it usage. SWMS support is usually required for up to 1 year, before patients may be offered bariatric surgery.[11]

Liraglutide 3.0mg (LIRA 3mg), a Glucagon Like Peptide-1 (GLP-1) receptor analogue, was approved in 2015 by the European Medicines Agency (EMA) for the treatment of obesity in

combination with lifestyle intervention after multiple, large, phase 3 randomised controlled trials demonstrated its safety and efficacy for weight loss, weight maintenance and improvement of obesity-related complications.[17, 22-24]

The average weight loss in SCALE Obesity and Prediabetes trial at 1 year after initiation of treatment with LIRA 3mg was 8.0±6.7% compared to 2.6±5.7% for patients in the placebo group.[22] The same data also suggests that after 1 year of therapy, LIRA 3mg can result in ≥15% weight loss in 14% of patients, compared with 3.5% of patients treated with placebo.[22] Nevertheless, SCALE trials were placebo-controlled, included patients with BMI as low as 27 kg/m$^2$, and typically combined LIRA 3mg with moderate-intensity lifestyle interventions.[17, 22-24, 25] These limitations make it difficult to predict the clinical effectiveness of LIRA 3mg for the treatment of severe and complex obesity in SWMS. Addressing these limitations, Wadden et al. in a pragmatic, single centre, open-label study demonstrated that by intensifying the diet and behaviour therapy in combination with LIRA 3mg, 28% of participants were able to achieve ≥15% weight loss at 12 months compared to 12% with intensive behavioural therapy alone.[26] Therefore, the current evidence suggests that LIRA 3mg could help a number of patients with severe and complex obesity referred to SWMS to achieve significant weight reduction, and this is highly likely to generate substantial health benefits and long-term cost-savings, especially if weight loss can be maintained, as demonstrated at the 3-year results of the SCALE Prediabetes study.[25]

Currently, LIRA 3mg has not been approved by NICE for use in management of severe and complex obesity in the UK. NICE guidelines take into account both the clinical and the cost effectiveness of treatment. EMA has approved LIRA 3mg with a single stopping rule of 5% weight loss at 16 weeks after initiation of treatment, based on a post-hoc analysis of the SCALE trials demonstrated that "early responders" (defined as those achieved ≥4% weight loss after 16 weeks of LIRA 3mg) were more likely to achieve clinically significant weight loss at 1 year compared to "early non-responders" (10.8% vs 3.0% mean weight loss in those without T2D and 8.5% vs 3.1% mean weight loss in those with T2D).[27] Based on the EMA single stopping rule, it is estimated that 62-77% of patients with obesity referred to SWMS will be suitable to continue long-term on LIRA 3mg.[27] However, only 9-21% of those who achieve 5% weight loss at 16 weeks will obtain maximal benefit (≥15% weight loss) from LIRA 3mg.[27] Taking into account the cost of the medication, it is unlikely that NICE or other equivalent organisations will approve long-term treatment with LIRA 3mg for all patients who currently present for obesity treatment in SWMS and achieve the single EMA

stopping rule. A different and more pragmatic use of LIRA 3mg in SWMS is needed in order for the medication to be targeted to those who will benefit most from using it.

In this paper, we describe the rationale and methodology of a study investigating a targeted prescribing pathway with multiple pre-specified stopping rules, designed specifically to provide a more pragmatic approach towards the use of LIRA 3mg in a SWMS for the treatment of severe and complex obesity. The targeted prescribing pathway aims to stratify the use of LIRA 3mg in "early" responders (in accordance with the EMA stopping rule) to the lifestyle intervention plus LIRA 3mg as well as identifying patients who are most likely to benefit more from continued long-term prescription of LIRA 3mg (i.e. those who are able to achieve ≥15% weight loss at 1 year). This approach aims to optimise the use of this medication to patients with severe and complex obesity that will have substantial benefit from it, and at the same time to optimise the health economic outcomes (cost-effectiveness and budget impact of SWMS) associated with the use of LIRA 3mg.

**Aim and objectives**

The aim of the present study is to compare the clinical effectiveness, the cost-effectiveness and the budget impact (on SWMS) of a targeted prescribing pathway for LIRA 3mg (with pre-specified stopping rules) plus SWMS standard care versus the SWMS standard care alone.

The primary objective will be to compare the proportion of participants with severe and complex obesity achieving weight loss ≥15% at 52 weeks using a targeted prescribing pathway (use of LIRA 3mg according to a pre-specified protocol) in combination with SWMS standard care versus SWMS standard care alone.

The secondary objectives (see also Supplementary Material, Appendix 1) are to compare the targeted prescribing pathway plus SWMS standard care vs SWMS standard care alone in terms of:

1. improving obesity-related complications (prediabetes, diabetes, hypertension, obstructive sleep apnoea, dyslipidaemia, depression)
2. referral rates to other obesity interventions
3. long-term weight 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 SWMS
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 and quality of life

## METHODS AND ANALYSIS

The protocol of this clinical trial follows the Standard Protocol Items: Recommendations for Inteventional Trials (SPIRIT) guidelines.[28]

### Study design (Figure 1)

The STRIVE study is a phase 4, investigator-initiated, two year, parallel, two group, multicentre, open-label, real-world, randomised controlled trial taking place in UK and Ireland. The total duration of participation will be 104 weeks (±2 weeks). In total, 384 patients with severe and complex obesity who are referred to a SWMS will be randomised through a validated online system (sealedenvelope.com) provided through the Leicester Clinical Trials Unit (LCTU) in a 2:1 fashion (2 intervention: 1 control) to either the intervention (SWMS standard care plus targeted prescribing pathway) or control arm (SWMS standard care). Randomisation will be stratified by centre and BMI (≥45kg/m$^2$; <45kg/m$^2$).

The study is intentionally designed to reflect a pragmatic "real-world" scenario and each SWMS provider may require a different number of visits for their programme. However, study appointments for data collection, medication titration reviews, application of the stopping rules of LIRA 3mg, and dispensing of the medication will be standardised for all of the study sites.

The first 52 weeks of the study will determine whether using the targeted prescribing pathway of LIRA 3mg plus standard care in a SWMS setting will result in more participants achieving ≥15% weight loss compared with standard care alone. The second 52 weeks of the study will assess whether patients who lose ≥15% of their baseline weight by the first 52

weeks are more likely to maintain ≥15% weight loss for another 52 weeks in the targeted prescribing pathway plus standard care compared with standard care alone. Further measurements on budget impact of SWMS and cost-effectiveness for both treatment groups will be assessed and compared.

**Control (Standard Care)**

Across the UK and Ireland, each region has a SWMS. This service includes a clinician led multidisciplinary team approach, potentially including a specialist physician, dietitian, nurse, psychologist and physiotherapist/physical activity physiologist.

Participants in the control group will follow the best medical care provided by the SWMS at the relevant site. This typically involves dietary advice to reduce energy intake (and may include a period using formula-diet meal replacement or total diet 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 SWMS at each site. Clinician input will include the medical assessment of participants for severe and complex obesity and the prescription of anti-obesity drugs (i.e. orlistat) as per local SWMS policy. Participants will remain in the SWMS 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 SWMS Multidisciplinary Team.

**Intervention (Targeted Prescribing Pathway plus Standard Care)**

Participants in the intervention arm will receive the same SWMS care with the control arm. Additionally, at baseline, LIRA 3mg will be prescribed to all of the participants in the intervention arm. Dose escalation of liraglutide will occur in accordance with the Summary of Product Characteristics (SPC) from 0.6 mg to a maximum of 3.0 mg. Participants will be withdrawn from receiving LIRA 3mg if the doses are not tolerated during or following the titration period.

Participants will also be informed about the pre-specified weight loss criteria in order to continue receiving treatment with LIRA 3mg. Participants in the targeted prescribing pathway will be prescribed LIRA 3mg for the duration of the study, unless they do not meet the pre-defined weight loss targets at each stopping point (after 16, 32 and 52 weeks).

Targeted Prescribing Pathway Stopping Rules (Figure 1)

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.

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.

3rd stopping rule:

After 52 weeks (±14 days) on the medication, 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 fail to reach the thresholds to continue LIRA 3mg treatment, or who have withdrawn from LIRA 3mg due to intolerance, adverse effects or inability to titrate up to a maximum dose of LIRA 3mg, will continue to be offered the standard care provided by the relevant SWMS. The conditions for participants' withdrawal from the study as well as for temporary and/or permanent treatment discontinuation for LIRA 3mg (outside prespecified stopping rules) are described in Supplementary Material, Appendix 2.

**Study Outcomes**

**Primary Outcome**

The primary outcome is the proportion (%) of participants with severe and complex obesity achieving weight loss ≥15% of baseline weight at 52 weeks after randomisation with the standard care provided in SWMS versus a targeted prescribing pathway of LIRA 3mg with pre-specified stopping rules plus the standard care provided in SWMS.

**Secondary measurements and outcomes**

A range of secondary outcomes including anthropometrics, weight maintenance, obesity associated comorbidities, budget impact, cost-effectiveness, safety/adverse events, compliance of patients with treatment and referrals to other obesity interventions between the two groups will be measured and assessed throughout the study. These are listed in Supplementary Material, Appendix 1.

**Study population**

Five culturally and racially diverse sites in different geographical areas (Dublin, Glasgow, Leicester, Liverpool and London) will be used to reflect typical SWMS settings across UK and Ireland.

Potentially eligible patients who have agreed to participate in the SWMS will be identified by the clinical care team and invited for screening. Patients will be allowed at least 24 hours to consider their participation to the study. Full inclusion and exclusion criteria are listed in Box 1. Each site will plan to recruit up to 77 subjects over the 24 months recruitment period.

**Study procedures (Figure 2 and Supplementary Material, Appendix 3)**

**Study visits**

A participant flowchart is demonstrated in Figure 2 and the study visit outline and measurement plan for each visit is included in Supplementary Material, Appendix 3, Table 1. Participants in both groups will attend 13 visits during the two-year trial. Participants in the intervention group who continue on LIRA 3mg during the second year of the study, will attend 2 additional visits for safety, monitoring of side effects, compliance and medication supply.

**Screening and Consent Visit (Day -42 to -1)**

A study clinician will determine the eligibility of potential participants and obtain written informed consent. Following this, demographics, medical and surgical history, anthropometrics (height, weight, waist circumference), blood pressure and pulse rate, a comprehensive clinical examination and routine laboratory investigations will be performed (see Supplementary Material, Appendix 3, Table 1). Female participants of childbearing potential will undergo a urine pregnancy test. Urine albumin creatinine ratio (ACR) will be analysed for participants with prediabetes, diabetes and hypertension.

All participants will undergo an assessment with the King's College Obesity Staging System (see Supplementary Material, Appendix 4, Table 2), STOP-Bang questionnaire and Epworth sleepiness score. Participants at risk of undiagnosed OSA (defined by STOP-Bang score of ≥ 5) will be referred to sleep clinic for further investigation. Participants with established OSA on CPAP therapy will have their notes reviewed to determine compliance with CPAP therapy and whether it was a "successful" treatment according to the following criteria: a. CPAP

usage ≥ 4 hrs/night = successful, b. CPAP usage < 4 hrs/night = struggling, c. CPAP usage ≤ 1 hr/night = failure.

**Data Collection and Safety Visits (Baseline, Weeks 52 and 104)**

During the baseline visit, eligibility will be confirmed by the study clinician at each site based on the results and investigations from screening visit. Following this, only eligible participants will be randomised and allocated into either group (open label study). Participants allocated to the targeted prescribing pathway plus standard care (intervention group), will be prescribed LIRA 3mg and reminded of the prescribing pathway medication stopping rules at weeks 16, 32 and 52. Participants will receive training to confidently administer the Investigational Medical Product (IMP). Female participants of childbearing potential will be reminded to use effective contraception throughout the study.

A full description of the outcome measures and the procedures during baseline visit, week 52 and week 104 is shown in Supplementary Material, Appendix 3, Table 1. Serious Adverse Events (SAE) and Adverse Events (AE) as well as changes in medication or diseases will be recorded during every visit from consent to the end of study. Moreover, participant adherence to the SWMS programme will be monitored (completers will be defined as those who attended >70% of scheduled visits in the SWMS during the first 52 weeks).

At weeks 52 and 104, blood tests for biochemical outcomes will be performed for all participants in the study as well as urine ACR for participants with diabetes, prediabetes and hypertension.

At week 104, the study clinician will evaluate all the participants who experience significant weight regain in either treatment group and may consider a recommendation to Tier 4 service for bariatric surgery. For 'responders' on LIRA 3 mg, the clinician will recommend that the participant's GP may consider prescribing LIRA 3mg long-term, depending on the local prescribing practice.

**Clinical Review Visits (safety and retention) (Weeks 2, 4, 8, 12, 16, 20, 32, 40 and 78)**

Participant's eligibility and consent for continuation in the study will be confirmed. Measurements of outcomes during these visits including reporting potential AEs/SAEs are detailed in Supplementary Material, Appendix 3, Table 1. Participants on LIRA 3mg will be given advice on dose titration (at weeks 2 and 4) as per SPC and will be monitored for any possible side effects and adherence with the daily injection (by examining medication

returns).

At week 32, blood tests for biochemical outcomes will be performed for all participants in the study as well as urine ACR for participants with diabetes, prediabetes and hypertension.

**Additional Clinical Review (safety and retention) Visits for LIRA 3mg group (Weeks 65 and 91)**

Two additional visits will take place only for participants in the intervention group who remain eligible and continue to be offered treatment with LIRA 3mg in the second year. The visits will be identical to the other Clinical Review visits as described above, with the intention to provide participants with a new prescription of LIRA 3mg, discuss adherence with the treatment and record any AE/SAEs.

**Treatment of Trial participants**

**Study Medication**

Participants randomised to LIRA 3mg group will be instructed to take daily subcutaneous injection of liraglutide (Saxenda) whilst continuing their usual medication. Participants will be given specific instructions to adhere to the titration policy of LIRA 3mg in accordance with the SpC. LIRA 3mg will be prescribed to participants for a maximum of 106 weeks (4 weeks dose titration, 100 weeks maintenance dose, ±2 weeks visit window).

*Compliance and Accountability*: Participants will be asked to return all unused investigational products and vials/packages to the pharmacy at each study visit. Compliance and concordance with LIRA 3mg will be evaluated and discussed at each study visit based upon tolerability and returned vials of medication. Participants will be defined as treatment compliant if they self-administer at least 70% of planned doses.

**Harms**

Throughout the STRIVE study, all the reported AEs, SAEs and other unintended effects of trial interventions or trial conduct will be collected, assessed, reported and managed according to the Good Clinical Practice – International Conference of Harmonisation (GCP-ICH) guidelines.

**Data collection, management and confidentiality**

Details on data collection, management and confidentiality for the STRIVE study are provided in Supplementary Material, Appendix 5.

## Statistics

### Sample Size

Based on previous studies, it is anticipated that at one year approximately 5% of the participants in the standard care group will have achieved ≥15% weight loss (likely range: 3%-5%).[17,22] An achievable target for ≥15% weight loss at 52 weeks in the intervention group (standard care plus LIRA 3mg with pre-specified stopping rules) is 16% (likely range: 14%-20%).[17,22] Accounting for 25% drop out, 5% alpha and a 2:1 randomisation ratio with higher proportion of participants being randomised to the intervention group; we would need to recruit 384 participants (256 intervention group; 128 standard care) to have 80% power to detect a significant difference between the groups in participants achieving ≥15% weight loss at one year.

### Statistical methods and analysis

The primary analysis will compare the proportion of participants achieving ≥15% weight loss at 52 weeks (primary outcome) after randomisation between the two study arms using a logistic regression model with adjustment for stratification factors (site and BMI). The adjusted proportion (95% confidence interval) of participants achieving ≥15% weight loss will be estimated by group. The primary analysis will be based upon the complete case population. This 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.

The secondary analyses of the primary outcome will be based upon intention to treat (ITT) and per protocol analyses. The ITT population is defined as all randomised participants in the study and the per protocol population is defined as all randomised participants who were compliant with their treatment group. Treatment compliance for the control group is defined as completion at least 70% of the planned contacts in the SWMS. Participants in the intervention group are defined as treatment compliant if they complete at least 70% of the planned contacts in the SWMS, and take at least 70% of their planned doses of LIRA 3mg as stipulated by the prescribing pathway. In all analyses, participants will be analysed within the treatment arm to which they were allocated at baseline. More specifically, participants within the intervention group who were taken off LIRA 3mg due to pre-specified stopping rule will remain in the intervention group. Participants who have undergone bariatric surgery during the first 52 weeks of the study will be excluded from the analysis for the primary outcome. Missing primary outcome data will be imputed for the ITT analyses; categorically we will

classify those participants as "non-responders" (did not achieve ≥15% weight loss at 52 weeks). The characteristics of those with missing outcome data will be compared to those who have completed follow-up.

Secondary outcomes measured at 52 and 104 weeks will be analysed based upon the complete cases population. Binary outcomes will be analysed using logistic regression models and summarised using proportion (95% confidence interval). Continuous outcomes will be compared using linear regression models and summarised as mean with standard deviation (95% confidence interval). If continuous outcomes are non-normally distributed, the most suitable regression model will be selected. Only the complete cases population will be used for the secondary outcomes to reduce the number of models. Data on treatment adherence, safety (including adverse events), and treatment satisfaction will be summarised and tabulated.

In addition, we will perform a responder analysis which will repeat the analyses of the secondary outcomes with the intervention group restricted to those participants who responded to the targeted prescribing pathway (those achieving ≥15% weight loss at 52 weeks after randomisation). This allows us to statistically compare the outcomes of "super" responders within the targeted prescribing pathway to all the participants who received standard care in the control group.

**Health Economic Input**

A state-transition Markov cohort model has been developed for the cost-effectiveness analysis, with health states encompassing the possible co-morbidities associated with obesity and documented to respond to weight loss. A thorough review of the literature was conducted to identify such conditions and inform transition probabilities in the model.

**Patient and public involvement**

Patients and public were not involved in the development of the research questions or the design of this study. However, on completion of the study, all participants will be informed for the results of the study.

## ETHICS AND DISSEMINATION

**Ethical issues**

Approval for the protocol (and any subsequent substantial amendments) has been obtained

from the Medicines and Healthcare products Regulatory Agency (MHRA, UK Competent authority) and Health Products Regulatory Authority (HRPA, Irish Competent Authority). This protocol has been approved by the Health Research Authority (HRA) and ethical approval as a Clinical Trial of an Investigational Medicinal Product (CTIMP) study was granted by the North West Deanery National Research Ethics Service (NRES) committee (17/NW/0517) in UK (29 September 2017) and from the St Vincent's University Hospital European Research Ethics Committee (EUREC) (2017-002998-20) in Ireland. This manuscript details the 4th version of the protocol approved on 8th of June 2018.

The study is conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, as well as in full conformity with the International Conference of Harmonisation (ICH) Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996. Ethical and research governance approval has been obtained for this study through the HRA, appropriate regulatory bodies and National Health Service (NHS) Trust prior to any participant activity.

**Protocol amendments**

All changes to the study protocol were reviewed by the North West Deanery NRES committee in UK and from the St Vincent's Hospital EUREC in Ireland and then reported to the sponsor and funder. The participating sites and co-investigators were sent regular emails with updates on the study recruitment timeline and any major protocol changes during the enrolment period. All significant protocol changes were noted in ClinicalTrials.gov.

**Trial oversight and governance**

The study sponsor is the University of Leicester (UK) and the study is managed by the LCTU and is overseen by trial steering committee (TSC) comprised of independent chair and a group of experts. This study is registered at the http://www.clinicaltrials.gov (NCT03036800) as well as on the European Clinical Trials Database (EudraCT Number 2017-002998-20) before the enrolment of the first participant and monitored by the University of Leicester.

Safety of the participants will be independently monitored by the Data monitoring and Ethics Committee (DMEC), which will make recommendations to the TSC for appropriate action in the interest of the participants.

## Current status and time scale

Recruitment started in December 2017 and the last patient last visit should complete by December 2021. To date, 340 patients have been screened and consented, of which 311 were eligible to participate and 302 have been randomised to the study.

## Publication policy

The results of the study will be submitted for publication to the relevant Obesity/General Medical peer-reviewed journals. Acknowledgement of any supporting organisations, including funders, University of Leicester and the LCTU, will be included.

**Author contributions:** DP: coinvestigator at University of Leicester, trial coapplicant, primary author of manuscript, co-author of the approved study protocol. WA-N: coauthor at University College Dublin, contributed to writing the manuscript and approved the final version. JZML: coauthor at University of Liverpool, contributed to writing the manuscript and approved the final version. JC: provided critical appraisal of current manuscript and approved final version. ML: principal investigator at University of Glasgow, trial coapplicant, coauthor for approved study protocol, contributed to trial set-up and design, provided critical appraisal of the manuscript and approved the final version. CWLR: principal investigator at University of Dublin, coauthor of the approved study protocol, contributed to trial set-up and design, provided critical appraisal of the manuscript and approved the final version. BM: principal investigator at Guy's and St Thomas' NHS Foundation Trust, trial coapplicant, coauthor for approved study protocol, contributed to trial set-up and design, provided critical appraisal of the manuscript and approved the final version. DO'S: principal investigator at University of Dublin, trial coapplicant, coauthor for approved study protocol, provided critical appraisal of the manuscript and approved the final version. DRW: principal investigator at University of Leicester, trial coapplicant, contributed to trial set-up and design, coauthor for approved study protocol, provided critical appraisal of the manuscript and approved the final version. JPHW: principal investigator at University of Liverpool, trial coapplicant, contributed to trial set-up and design, coauthor for approved study protocol, provided critical appraisal of the manuscript and approved the final version. MJD: chief investigator, trial coapplicant, contributed to trial set-up and design, coauthor for approved study protocol, corresponding author, provided critical appraisal of the manuscript and approved the final version.

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**Competing interests statement:** DP is funded from an NIHR Clinical Lectureship and reports grants from the Novo Nordisk UK Research Foundation outside submitted work; WA-N is funded by the Irish Research Council's Postdoctoral Enterprise Partnership Scheme and reports personal fees from Novo Nordisk outside the submitted work; JZML has nothing to disclose; JC reports participation at the Novo Nordisk Emerging Obesity Leaders Programme which included registration and travel expenses to the European Congress of Obesity 2019, Glasgow, funded by Novo Nordisk; CWLR reports grants from Science Foundation Ireland, grants from Health Research Board, during the conduct of the study; other from Novo Nordisk, other from GI Dynamics, personal fees from Eli Lilly, grants and personal fees from Johnson and Johnson, personal fees from Sanofi Aventis, personal fees from Astra Zeneca, personal fees from Janssen, personal fees from Bristol-Myers Squibb, personal fees from Boehringer-Ingelheim, outside the submitted work; BM reports grants from Novo Nordisk, during the conduct of the study; grants and personal fees from Novo Nordisk , personal fees from Sanofi, personal fees from Boheringher Ingelheim, personal fees from MSD, outside the submitted work; DRW has nothing to disclose; JPHW reports grants from Novo Nordisk, during the conduct of the study; grants, personal fees and other from AstraZeneca, other from Astellas, personal fees and other from Boehringer Ingelheim, other from Janssen, personal fees and other from Mundipharma, personal fees and other from Napp, personal fees and other from Lilly, personal fees and other from Sanofi, other from Wilmington Healthcare, outside the submitted work; MJD reports grants from Novo Nordisk, during the conduct of the study; personal fees from Novo Nordisk, personal fees from Sanofi-Aventis, personal fees from Lilly, personal fees from Merck Sharp & Dohme, personal fees from Boehringer Ingelheim, personal fees from AstraZeneca, personal fees from Janssen, personal fees from Servier, personal fees from Mitsubishi Tanabe Pharma Corporation, personal fees from Takeda Pharmaceuticals International Inc., grants from Sanofi-Aventis, grants from Lilly, grants from Boehringer Ingelheim, grants from Janssen, outside the submitted work.

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## Box 1. Inclusion and exclusion criteria

**Inclusion criteria:**

- 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 Specialist Weight Management 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, type 2 diabetes (T2D), 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)
  - type 2 diabetes [defined as established diagnosis of T2D 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 sodium-glucose co-tranporter-2 (SGLT-2) inhibitors]
  - 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 Specialist Weight Management Service clinic),
  - obstructive sleep apnoea (on CPAP or established diagnosis of Apnoea Hypopnoea Index ≥15 at sleep studies during the last 12 months).

**Exclusion criteria:**

- Diagnosis of Type 1 diabetes
- T2D with treatment on DPP-IV or insulin currently
- Treatment with Glucagon Like Peptide-1 (GLP-1) receptor agonists within the last 6 months and/or have a history of GLP-1 receptor agonist intolerance.
- Treatment with anti-obesity drugs within 12 weeks prior to randomisation
- eGFR ≤30ml/min/1.73m$^2$ on serum testing over the last 26 weeks
- Females referred to the clinic because of fertility problem
- Females of child bearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using or willing to use adequate contraceptive methods during the study period
- Have terminal illness
- Are not primarily responsible for their own care
- Any other significant disease or disorder which in the opinion of the investigator, may either put the participants at risk or may influence the result of the study or the participant's ability to participate
- Untreated or uncontrolled hypothyroidism/hyperthyroidism defined as thyroid-stimulating hormone >6 mIU/litre or <0.4 mIU/litre
- Family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC)
- Personal history of non-familial medullary thyroid carcinoma
- History of chronic pancreatitis or idiopathic acute pancreatitis
- Amylase levels three times higher than the upper normal range
- Obesity induced by other endocrinologic disorders (e.g. Cushing's Syndrome)
- Current or history of treatment with medications that may cause significant weight gain, within 12 weeks prior to randomisation, including systemic corticosteroids (except for a short course of treatment, i.e. 7−10 days), atypical antipsychotic and mood stabilizers (e.g. clozapine, olanzapine, valproic acid and its derivatives, and lithium)
- Initiation of antidepressants during the last 12 weeks
- Previous surgical treatment for obesity (excluding liposuction if performed >1 year before trial entry)
- History of other severe psychiatric disorders
- History of known or suspected abuse of alcohol and/or narcotics
- History of major depressive episode during the last 2 years
- Simultaneous participation in other clinical trials of investigational drugs, lifestyle or physical activity interventions. Patients will only be able to take part following participation in a previous clinical trial after a wash-out period of 16 weeks.

**Figure 1. Study design**

**Figure 2. Participant flowchart**

**Figure 1.**

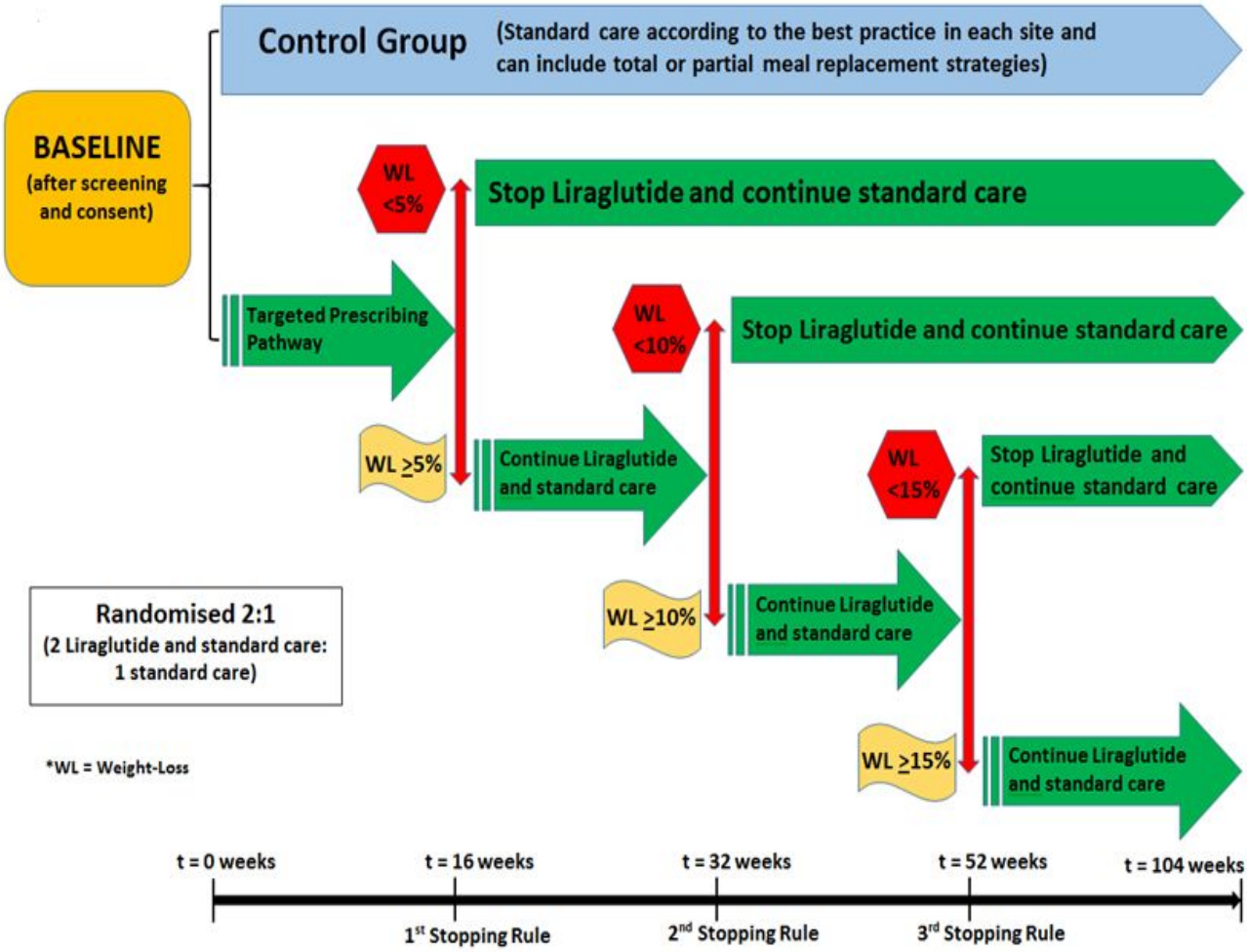
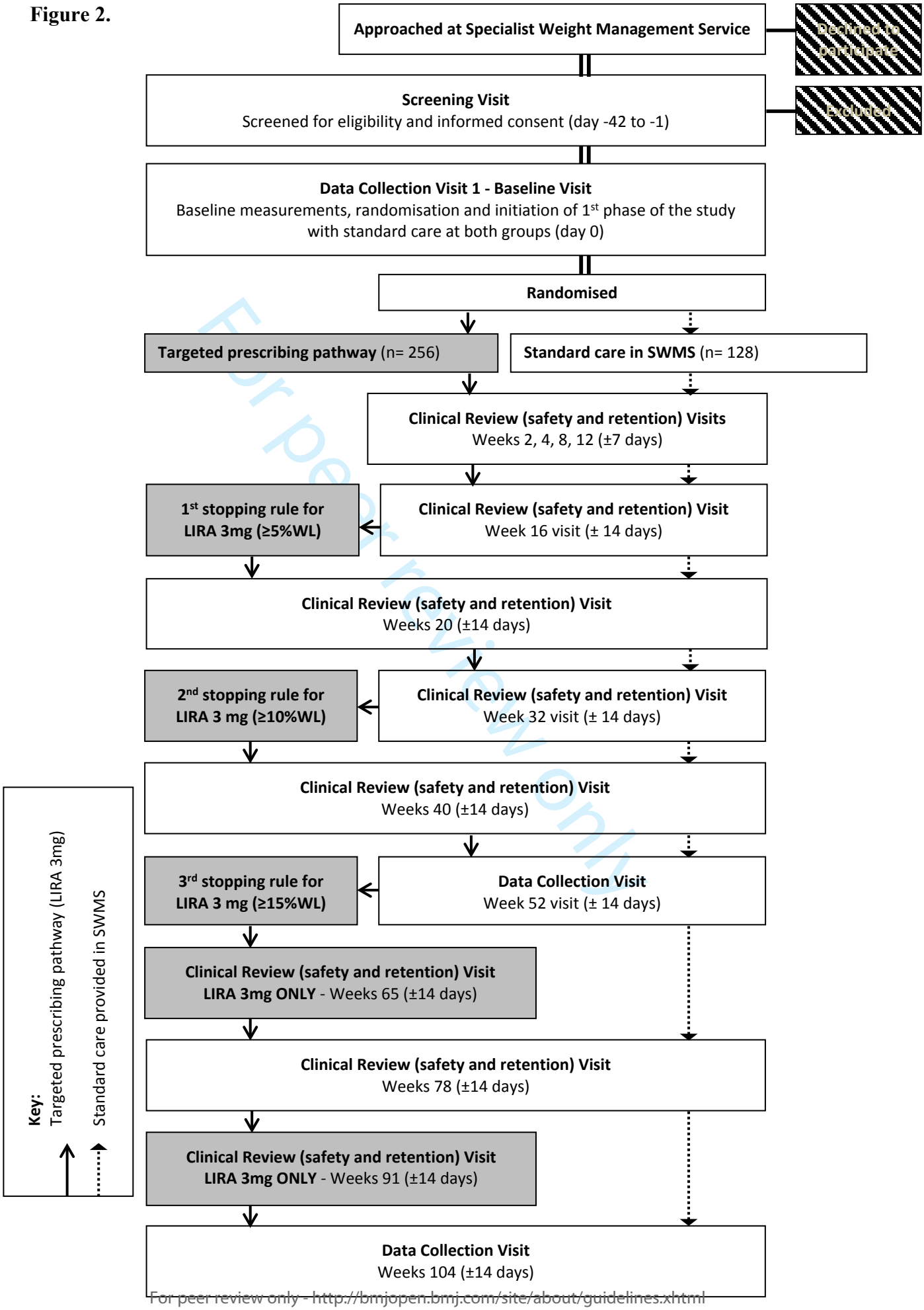


**Figure 2.**



## Appendix 1. Secondary Outcomes

Unless stated otherwise, the secondary outcomes listed below will be assessed at 52 and 104 weeks.

### Anthropometric Outcomes

- Weight (kg), from which these secondary outcomes will be derived (also at 16 and 32 weeks):
  - Absolute change in weight (kg) from baseline
  - Relative change in weight (%) from baseline
  - Proportion of participants reaching weight loss of ≥5%, ≥10% and ≥15%
  - 104 weeks only: Proportion of participants maintaining weight loss of ≥15% among those who lost ≥15% at 52 weeks
- Height (cm), from which this secondary outcome will be derived:
  - Change in BMI ($kg/m^2$) from baseline
- Waist circumference (cm)

### Obesity-related co-morbidities and their treatments (General)

- King's College Obesity Staging System assessment (a system to assess multiple co-morbidities related to obesity and their severity, see Appendix 1)
- Quality of life (EQ5D)
- Impact of Weight on Quality of Life-Lite (IWQOL-Lite)
- Patient Health Questionnaire-9 (PHQ9)

### Obesity-related co-morbidities and their treatments (Prediabetes/Diabetes)

- HbA1C
- Proportion of participants with normoglycaemia (defined as HbA1C <42.0 mmol/mol without glucose lowering medications)
- Proportion of participants with prediabetes (defined as HbA1C 42.0-47.9 mmol/mol without glucose lowering medications)
- Proportion of participants with diabetes (defined as HbA1C ≥48 mmol/mol or on glucose lowering medications)
- Dose, class of medication, and number of agents for diabetes
- Monitoring of microvascular complications for patients with diabetes [Albumin-Creatinine Ratio (ACR)]

### Obesity-related co-morbidities and their treatments (Hypertension)

- Blood pressure
- Proportion of participants with hypertension (defined as patients on antihypertensive medications or systolic blood pressure>140mmHg)
- Dose, class of medication, and number of agents for hypertension

### Obesity-related co-morbidities and their treatments (Obstructive Sleep Apnoea)

- Epworth score for all participants to determine levels of daytime sleepiness

- Stop Bang questionnaire for all participants to identify undetected OSA - it will be administered by research team or taken from medical notes
- Proportion of participants on CPAP
- CPAP pressures for patients on variable pressures CPAP
- Apnoea Hypopnea Index (AHI) for participants with sleep apnoea who cannot tolerate CPAP or for participants on fixed pressures CPAP
- Oxygen desaturation index for participants with sleep apnoea who cannot tolerate CPAP or for participants on fixed pressures CPAP

**Obesity-related co-morbidities and their treatments (Dyslipidaemia)**

- Lipids
- Dose, class of medication, and number of agents for dyslipidaemia

**Number of participants referred for other obesity intervention**

- Number of participants referred to Tier 4 for bariatric surgery over the 104 weeks study period

**Direct healthcare cost**

- Frequency and cost of contact with General Practitioner (GP) (type and duration of contact will be recorded to enable use of Tariff prices from http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php?file=full to calculate accurate costings – accessed 21/07/2017)
- Frequency and cost of contact with Healthcare Professionals (HCP) (type and duration of contact will be recorded to enable use of Tariff prices from http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php?file=full to calculate accurate costings)
- Frequency of admissions, length of stay and cost of admissions to the hospital
- Frequency and cost of outpatient appointments with the hospital
- Prescription medication costs
- Health Service and Resources Use Questionnaire (HSRUQ)

**Budget impact of Specialist Weight Management Service**

- Cost of the proposed LIRA 3mg (as per protocol - e.g. actual dose taken = number of days taking study drug x daily cost of drug, or cost of total amount of study drug used)
- Cost of visits to clinician for assessment and medication prescription during Specialist Weight Management Service programme
- Cost of visits to dietician during Specialist Weight Management Service programme
- Cost of visits to psychologist during Specialist Weight Management Service programme
- Cost of physical activity physiologist/physiotherapist during Specialist Weight Management Service programme (if applicable)

- Cost of Multidisciplinary Team (MDT) discussion in Specialist Weight Management Service
- Cost of blood tests in Specialist Weight Management Service
- Cost of consumables and goods
- Cost of referral into Tier 4

**Estimated cost-effectiveness of treatment over 2 years**

- Length of treatment with LIRA 3mg
- Daily dose of LIRA 3mg (based on actual doses taken)

**Safety/adverse events**

- Gastrointestinal symptoms (nausea, vomiting)
- Overall hypoglycaemia rate
- Overall AE/SAE rate
- Rates of severe hypoglycaemia
- Heart rate
- Blood pressure

**Treatment satisfaction**

- Treatment Satisfaction Questionnaire for Medication (TSQM)

**Compliance of patient with the treatment and patient related outcomes**

- The number of participants who did or did not attend at least 70% of the scheduled appointments with the Specialist Weight Management Service (completers)
- The number of participants who had to stop treatment with LIRA 3mg because of adverse effects
- The adherence of participants with the LIRA 3mg (monitored through specific questionnaire and return of used pens)
- The number of participants who stopped LIRA 3mg at 16 weeks after randomisation
- The number of participants who stopped LIRA 3mg at 32 weeks after randomisation
- The number of participants who stopped LIRA 3mg at 52 weeks after randomisation
- The number of participants who completed 52 weeks of the Specialist Weight Management Service programme despite stopping LIRA 3mg at 16 weeks
- The number of participants who completed the 52 weeks of the Specialist Weigth Management Service programme despite stopping LIRA 3mg at 32 weeks
- The number of participants in the treatment group who had to stop treatment with LIRA 3mg because of side effects
- The number of participants started on anti-obesity drugs

**Physical activity assessment**

- International physical activity questionnaire (IPAQ- Long Form)

## Appendix 2: Withdrawal of participants from the study, temporary and permanent treatment discontinuation for LIRA 3mg (outside prespecified stopping rules)

### Withdrawal of participants from the study

Participants may withdraw consent from the study before study completion if they decide to do so, at any time and for any reason.

Participants will be withdrawn from this study by the research team as agreed by the Principal Investigator (PI) if: i) they are diagnosed with a terminal illness, ii) the PI, Sponsor and/or study clinician deem it unsafe for their continuation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations or Good Clinical Practice (GCP), iii) they are considered to be lost to follow up as deemed by the clinician, iv) they have lost their capacity during participation in research, v) they receive treatment with medications which the PI determines to require permanent withdrawal from the study (e.g. systemic corticosteroids).

It will be emphasised to participants who withdraw from the study that their standard care will not be affected and that they will return to standard care.

Attempts will be made to assess the primary outcome on all participants whether or not they were compliant and in those who have who have discontinued the treatment (including those participants who have stopped the treatment outside of the pre-specified stopping rules).

### Temporary treatment discontinuation for LIRA 3mg (outside of the pre-specified stopping rules)

Temporary discontinuation of LIRA 3mg may be considered by the Principal Investigator (PI) because of suspected Adverse Events (AEs).

Re-initiation of LIRA 3mg at a lower dose, under close and appropriate clinical and/or laboratory monitoring maybe considered at discretion of the PI and if the inclusion and exclusion criteria for the study are still met.

### Permanent treatment discontinuation (outside of the pre-specified stopping rules)

Permanent treatment discontinuation is any treatment discontinuation associated with a definitive decision from the PI or the participant not to re-expose the participant to LIRA 3mg treatment. This definition is different to treatment discontinuation due to a participant not meeting the weight-loss targets at the pre-specified stopping rules as per the protocol.

Factors leading to permanent discontinuation of LIRA 3mg include i) pregnancy, ii) episode

of acute pancreatitis and breast malignancy, iii) repeat violation or non-compliance with the protocol, iv) participant being unable to tolerate LIRA 3mg doses and/or v) any other contraindication to the study medication which the PI determines to require permanent treatment discontinuation.

Key:
Stopping rules apply
Extra visits for LIRA 3mg group only
End of study

## Appendix 3.

### Table 1. Outcome measures and planned visits during the enrolment and control visits.

| WEEKS | -6 to -1/52 | 0/52 | 2/52 | 4/52 | 8/52 | 12 /52 | 16 /52 | 20 /52 | 32 /52 | 40 /52 | 52 /52 | 65 /52* | 78 /52 | 91 /52* | 104/52 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VISIT WINDOW | Screening^^ | Base-line | +/- 3dys | +/- 3dys | +/- 7dys | +/- 7dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys |
| Visit No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12* | 13* /12 | 14* | 15* /13 |
| **STUDY PROCEDURES** | | | | | | | | | | | | | | | |
| Inclusion/ exclusion criteria | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Informed consent | X | | | | | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | | | | | |
| Injection training* | | X | | | | | | | | | | | | | |
| Titration/ Review Visit* (dose$) /or telephone call)$$ | | X 0.6$ 1.2$$ | X 1.8$ 2.4$$ | X 3.0$ | | | | | | | | | | | |
| Other HCP | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Glucose self-monitoring training/ education | | X | | | | | | | | | | | | | |
| Dispensing (or unsched visit)### | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **DATA COLLECTION** | | | | | | | | | | | | | | | |
| Subject demography | X | | | | | | | | | | | | | | |
| Medical/Surgical history | X | | | | | | | | | | | | | | |
| Medication history | X | | | | | | | | | | | | | | |
| Concomitant medication | X | | | | | | | | | | | | | | |
| Changes in med/diseases | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | |
| BMI | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Waist Circumference | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood Pressure | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pulse rate | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liver function tests | X | | | | | | | | X | | X | | | | X |
| Renal function tests | X | | | | | | | | X | | X | | | | X |
| Thyroid function tests | X | | | | | | | | X | | X | | | | X |
| Haematology profile | X | | | | | | | | X | | X | | | | X |
| Lipids | X | | | | | | | | X | | X | | | | X |
| HbA1C | X | | | | | | | | X | | X | | | | X |
| Amylase | X | | | | | | | | X* | | X* | | | | X* |

| WEEKS | -6 to -1/52 | 0/52 | 2/52 | 4/52 | 8/52 | 12 /52 | 16 /52 | 20 /52 | 32 /52 | 40 /52 | 52 /52 | 65 /52* | 78 /52 | 91 /52* | 104/52 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **VISIT WINDOW** | Screening^^ | Base-line | +/- 3dys | +/- 3dys | +/- 7dys | +/- 7dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys |
| **Visit No.** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12* | 13* /12 | 14* | 15* /13 |
| King's Obesity Staging System | X | | | | | | | | | | X | | | | X |
| Epworth score | X | | | | | | | | | | X | | | | X |
| Stop Bang Questionnaire | X | | | | | | | | | | X | | | | X |
| Sleep Study (home based ambulatory sleep monitor)** | X | | | | | | | | | | X | | | | X |
| Apnoea Hypopnoea Index** | X | | | | | | | | | | X | | | | X |
| Oxygen desaturation index** | X | | | | | | | | | | X | | | | X |
| CPAP pressures** | X | | | | | | | | | | X | | | | X |
| Pregnancy test | X | X | X* | X* | X* | X* | X* | X* | X* | X* | X | X* | X* | X* | X |
| ACR*** | X | | | | | | | | X | | X | | | | X |
| AE/SAE recording | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adherence with injection* | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adherence with other anti-obesity medications# | | | | | | | X | | X | | X | | | | X |
| Adherence to Specialist Weight Management Service (SWMS) | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Contacts with GP/HCP | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Inpatient and Outpatient apt's | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medications cost | | X | | | | | | | | | X | | | | X |
| **QUESTIONNAIRES** | | | | | | | | | | | | | | | |
| HSRUQ | | X | | | | | | | | | X | | | | X |
| TSQM### | | X | | | | | | | | | X | | | | X |
| EQ-5D | | X | | | | | | | | | X | | | | X |
| IWQOL-Lite | | X | | | | | | | | | X | | | | X |
| IPAQ-Long | | X | | | | | | | | | X | | | | X |
| PHQ-9 | | X | | | | | | | | | X | | | | X |

*Only for participants at the LIRA 3mg group who are on active treatment

$Titrated dose participant will leave on at the end of the visit. $$Optional Telephone calls to check tolerance and up-titrate at weeks 1, 3 & 5.

**As required for participants with identified risk OSA of or current OSA based on CPAP use and type of CPAP (variable or fixed pressures CPAP)

*** Only for prediabetic, diabetic and hypertensive individuals

# Only for participants in the standard care group on treatment with anti-obesity drugs

##Only for participants with diagnosis of T2DM

### For participants on treatment either with LIRA 3mg or other anti-obesity medication

^ Only participants who report problems with injection and/or side-effects may be reviewed by study clinician

^^A repeat screening visit may take place to assess eligibility

Drug dispensing unscheduled visits may occur at any point within the study period for participants in LIRA3 mg group as required (not depicted above)

**Appendix 4.**

**Table 2.** 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 |

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

## Appendix 5

## Data collection, management and confidentiality

### Data collection

Paper Case Report Forms (CRF) and study questionnaires are the primary data collection instruments and treated as source data. All data requested in the CRF will be recorded. All missing data will be explained. Data captured in the paper CRFs will then be entered into a validated web based database under the management of LCTU. On-entry validation checks will be applied where required and data entered will be checked for completeness, accuracy and timeliness by the study team/trial manager/data manager. All study visits and AEs will be recorded in the hospital notes.

### Data management

All study documentation containing identifiable patient data will be managed in accordance with ICH-GCP, the UK Policy Framework for Health and Social Care Research and the Data Protection Act (or its subsequent legislation) and made available for inspection, monitoring or audit purposes by the Sponsor, host, regulatory authorities or the funder. All electronic data will be stored in secure network drives, to which only the relevant study staff have access. All study documents and data will be kept for 15 years or the minimum determined by the regulatory authorities, whichever is the longer.

### Data confidentiality

Each participant will be assigned a unique identification number upon recruitment. Participant's contact details will be held on database separate to the study visit data and used to arrange data collection visits. The database will be password protected and only researchers collecting data will have access. All data collected during the study will be stored anonymously on a separate database. Again access will be password protected and restricted to relevant members of the research team. Paper copies of the CRFs and questionnaires will be stored in a locked filing cabinet in the relevant research office. The study research team will comply with the Data Protection Policy of the University of Leicester and local NHS Trusts.

# *Reporting checklist for protocol of a clinical trial.*

*Based on the SPIRIT guidelines.*

## *Instructions to authors*

*Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.*

*Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.*

*Upload your completed checklist as an extra file when you submit to a journal.*

*In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:*

*Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207*

| | | *Reporting Item* | *Page Number* |
|---|---|---|---|
| ***Administrative information*** | | | |
| *Title* | *#1* | *Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym* | *1* |
| *Trial registration* | *#2a* | *Trial identifier and registry name. If not yet registered, name of intended registry* | *2, 15* |
| *Trial registration: data set* | *#2b* | *All items from the World Health Organization Trial Registration Data Set* | *N/A* |
| *Protocol version* | *#3* | *Date and version identifier* | *15* |
| *Funding* | *#4* | *Sources and types of financial, material, and other support* | *17* |
| *Roles and responsibilities: contributorship* | *#5a* | *Names, affiliations, and roles of protocol contributors* | *1, 16* |
| *Roles and responsibilities: sponsor contact information* | *#5b* | *Name and contact information for the trial sponsor* | *15* |
| *Roles and responsibilities: sponsor and funder* | *#5c* | *Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over* | *17* |

| | | | |
|---|---|---|---|
| | | *any of these activities* | |
| *Roles and responsibilities: committees* | *#5d* | *Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)* | *15* |
| ***Introduction*** | | | |
| *Background and rationale* | *#6a* | *Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention* | *4-6* |
| *Background and rationale: choice of comparators* | *#6b* | *Explanation for choice of comparators* | *5, 6* |
| *Objectives* | *#7* | *Specific objectives or hypotheses* | *6, 7* |
| *Trial design* | *#8* | *Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)* | *7* |
| ***Methods: Participants, interventions, and outcomes*** | | | |
| *Study setting* | *#9* | *Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained* | *10* |
| *Eligibility criteria* | *#10* | *Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)* | *10 (Box 1)* |
| *Interventions: description* | *#11a* | *Interventions for each group with sufficient detail to allow replication, including how and when they will be administered* | *8, 9* |
| *Interventions: modifications* | *#11b* | *Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)* | *9 (Appendix 2)* |
| *Interventions: adherance* | *#11c* | *Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)* | *11, 12* |
| *Interventions: concomitant care* | *#11d* | *Relevant concomitant care and interventions that are permitted or prohibited during the trial* | *10 (Box 1), 11, 12* |
| *Outcomes* | *#12* | *Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,* | *9 (Appendix 1)* |

| | | | |
|---|---|---|---|
| | | *final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended* | |
| *Participant timeline* | *#13* | *Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)* | *10-12, (Figure 2 and Appendix 3)* |
| *Sample size* | *#14* | *Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations* | *13* |
| *Recruitment* | *#15* | *Strategies for achieving adequate participant enrolment to reach target sample size* | *10* |
| ***Methods: Assignment of interventions (for controlled trials)*** | | | |
| *Allocation: sequence generation* | *#16a* | *Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions* | *7* |
| *Allocation concealment mechanism* | *#16b* | *Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned* | *7* |
| *Allocation: implementation* | *#16c* | *Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions* | *7, 11* |
| *Blinding (masking)* | *#17a* | *Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how* | *N/A* |
| *Blinding (masking): emergency unblinding* | *#17b* | *If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial* | *N/A* |
| ***Methods: Data collection, management, and analysis*** | | | |
| *Data collection plan* | *#18a* | *Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol* | *10, 11 (Appendix 3), 12, (Appendix 5)* |
| *Data collection plan: retention* | *#18b* | *Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from* | *9 (Appendix 1), 9 (Appendix 2),* |

| | | | |
|---|---|---|---|
| | | *intervention protocols* | *12 (Appendix 5)* |
| *Data management* | *#19* | *Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol* | *12 (Appendix 5)* |
| *Statistics: outcomes* | *#20a* | *Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol* | *13, 14* |
| *Statistics: additional analyses* | *#20b* | *Methods for any additional analyses (eg, subgroup and adjusted analyses)* | *13, 14* |
| *Statistics: analysis population and missing data* | *#20c* | *Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)* | *13, 14* |
| ***Methods: Monitoring*** | | | |
| *Data monitoring: formal committee* | *#21a* | *Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed* | *15* |
| *Data monitoring: interim analysis* | *#21b* | *Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial* | *15* |
| *Harms* | *#22* | *Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct* | *12* |
| *Auditing* | *#23* | *Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor* | *12 (Appendix 5)* |
| ***Ethics and dissemination*** | | | |
| *Research ethics approval* | *#24* | *Plans for seeking research ethics committee / institutional review board (REC / IRB) approval* | *14, 15* |
| *Protocol amendments* | *#25* | *Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)* | *15* |
| *Consent or assent* | *#26a* | *Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)* | *10* |
| *Consent or assent:* | *#26b* | *Additional consent provisions for collection and use of participant data and* | *10* |

| | | | |
|---|---|---|---|
| *ancillary studies* | | *biological specimens in ancillary studies, if applicable* | |
| *Confidentiality* | *#27* | *How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial* | *12 (Appendix 5)* |
| *Declaration of interests* | *#28* | *Financial and other competing interests for principal investigators for the overall trial and each study site* | *17* |
| *Data access* | *#29* | *Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators* | *12 (Appendix 5), 15* |
| *Ancillary and post trial care* | *#30* | *Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation* | *11, 12* |
| *Dissemination policy: trial results* | *#31a* | *Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions* | *16* |
| *Dissemination policy: authorship* | *#31b* | *Authorship eligibility guidelines and any intended use of professional writers* | *16* |
| *Dissemination policy: reproducible research* | *#31c* | *Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code* | *N/A* |
| ***Appendices*** | | | |
| *Informed consent materials* | *#32* | *Model consent form and other related documentation given to participants and authorised surrogates* | *N/A* |
| *Biological specimens* | *#33* | *Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable* | *N/A* |

BMJ Open

# Effectiveness and cost of integrating a pragmatic pathway for prescribing liraglutide 3.0 mg in obesity services (STRIVE study): Study protocol of an open-label, real-world, randomised, controlled trial.



| | |
|---|---|
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| | |

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# Effectiveness and cost of integrating a pragmatic pathway for prescribing liraglutide 3.0 mg in obesity services (STRIVE study): Study protocol of an open-label, real-world, randomised, controlled trial.

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**Key words: complex obesity, Liraglutide 3mg, Saxenda, weight loss, specialist weight management services**

**Word Count (manuscript): 4776 words**

## Abstract

**Introduction**

In the UK and Ireland, severe and complex obesity is managed in specialist weight management services (SWMS), which provide multicomponent lifestyle interventions to support weight loss, and use of medication if available. Liraglutide 3mg (LIRA 3mg) is an effective weight-loss medication, but weight loss in individual patients is variable, and its efficacy has not been assessed in SWMS. This study aims to investigate whether a targeted prescribing pathway for LIRA 3mg with multiple pre-specified stopping rules could help people with severe obesity and established complications achieve ≥15% weight loss in order to determine whether this could be considered a clinically effective and cost-effective strategy for managing severe and complex obesity in SWMS.

**Methods and analysis**

In this two year, multicentre, open-label, real-world randomised controlled trial, 384 adults with severe and complex obesity (defined as BMI ≥35kg/m$^2$ plus either prediabetes, type 2 diabetes, hypertension or sleep apnoea) will be randomised via a 2:1 ratio to receive either standard SWMS care (n=128) or standard SWMS care plus a targeted prescribing pathway for LIRA 3mg with pre-specified stopping rules at 16, 32 and 52 weeks (n=256).

The primary outcome is to compare the proportion of participants achieving a weight loss of ≥15% at 52 weeks with a targeted prescribing pathway vs. standard care. Secondary outcomes include a comparison of a) the weight loss maintenance at 104 weeks and b) the budget impact and cost-effectiveness between the two groups in a real-world setting.

**Ethics and dissemination**

The Health Research Authority and the Medicines and Healthcare products Regulatory Authority in UK, the Health Products Regulatory Authority in Ireland, the North West Deanery Research Ethics Committee (UK) and the St Vincent's University Hospital European Research Ethics Committee (Ireland) have approved the study. The findings of the study will be published in peer-reviewed journals.

**Trial registration number**

ClinicalTrials.gov – Identifier: NCT03036800

European Clinical Trials Database – Identifier: EudraCT Number 2017-002998-20

**Article Summary**

**Strengths and limitations of this study**

- Large, multicentre, real world, randomised controlled trial
- Assessment of the clinical effectiveness and cost-effectiveness of a targeted prescribing pathway with three stopping rules for LIRA 3mg to optimise its use in obesity services.
- The study will include only patients with severe and complex obesity (BMI ≥35 kg/m$^2$ plus either prediabetes, type 2 diabetes, hypertension or sleep apnoea) referred to a specialist weight management service.
- Some participants will stop using LIRA 3mg due to the 2$^{nd}$ and 3$^{rd}$ stopping rule despite achieving clinically significant weight loss and metabolic benefits.
- The study has been deliberately designed as open-label, however randomization to control (standard care) group, without the opportunity to receive LIRA 3mg, may be a disincentive to adherence to the SWMS program and attendance to study visits for some participants.



## INTRODUCTION

Obesity is a complex disease characterised by increased hunger and reduced satiety.[1] Severe and complex obesity is defined as a BMI ≥35kg/m$^2$ with at least one major obesity-related complication.[2] Around 10% of the adult population in England has a BMI ≥35kg/m$^2$,[3] and many have established complications such as type 2 diabetes (T2D),[4] hypertension [5] and sleep apnoea,[4] imposing colossal direct and indirect healthcare costs.[6]

Lifestyle interventions are considered cornerstones for the management of obesity.[7] Despite the impressive results from intensive lifestyle interventions in Look Ahead study,[8] and more recently the DIRECT and Counterweight-Plus studies,[9, 10] which used intensive and structured weight management programmes to achieve weight loss and diabetes remission in real-life community settings, lifestyle interventions still commonly only achieve an average of 5% weight loss[11, 12] and long-term weight maintenance remains a challenge.[13, 14] Although weight loss as little as 5% does produce metabolic improvements, it is not enough to make a difference to the lives of most people with severe and complex obesity. Maximal benefits for the treatment of obesity-associated complications are obtained with weight loss above 15%.[15] Pharmacotherapy for obesity can support some people to achieve these results,[16-18] but currently it is not used frequently enough to be considered a cornerstone treatment.[7]

Severe and complex obesity is managed in specialist weight management services (SWMS) in UK and Ireland.[7, 11, 19, 20] SWMS consist of a multidisciplinary team typically led by a medical clinician with expertise in obesity management and/or a specialist dietician and supported by specialist physiotherapists, psychologists and nurses; these services offer intensive lifestyle interventions with similar components to those used by DIRECT and Look Ahead studies, and can be supported by pharmacotherapy.[7] Orlistat is the only weight loss medication approved by the National Institute for Health and Care Excellence (NICE) for use in SWMS, however its side effects and limited effectiveness [18, 21] have reduced the penetrance of its usage. SWMS support is usually required for up to 1 year, before patients may be offered bariatric surgery.[11]

Liraglutide 3.0mg (LIRA 3mg), a Glucagon Like Peptide-1 (GLP-1) receptor analogue, was approved in 2015 by the European Medicines Agency (EMA) for the treatment of obesity in combination with lifestyle intervention after multiple, large, phase 3 randomised controlled

trials demonstrated its safety and efficacy for weight loss, weight maintenance and improvement of obesity-related complications.[17, 22-24]

The average weight loss in SCALE Obesity and Prediabetes trial at 1 year after initiation of treatment with LIRA 3mg was 8.0±6.7% compared to 2.6±5.7% for patients in the placebo group.[22] The same data also suggests that after 1 year of therapy, LIRA 3mg can result in ≥15% weight loss in 14% of patients, compared with 3.5% of patients treated with placebo.[22] Nevertheless, SCALE trials were placebo-controlled, included patients with BMI as low as 27 kg/m$^2$, and typically combined LIRA 3mg with moderate-intensity lifestyle interventions.[17, 22-24, 25] These limitations make it difficult to predict the clinical effectiveness of LIRA 3mg for the treatment of severe and complex obesity in SWMS. Addressing these limitations, Wadden et al. in a pragmatic, single centre, open-label study demonstrated that by intensifying the diet and behaviour therapy in combination with LIRA 3mg, 28% of participants were able to achieve ≥15% weight loss at 12 months compared to 12% with intensive behavioural therapy alone.[26] Therefore, the current evidence suggests that LIRA 3mg could help a number of patients with severe and complex obesity referred to SWMS to achieve significant weight reduction, and this is highly likely to generate substantial health benefits and long-term cost-savings, especially if weight loss can be maintained, as demonstrated at the 3-year results of the SCALE Prediabetes study.[25]

Currently, LIRA 3mg has not been approved by NICE for use in management of severe and complex obesity in the UK. NICE guidelines take into account both the clinical and the cost effectiveness of treatment. EMA has approved LIRA 3mg with a single stopping rule of 5% weight loss at 16 weeks after initiation of treatment, based on a post-hoc analysis of the SCALE trials demonstrated that "early responders" (defined as those achieved ≥4% weight loss after 16 weeks of LIRA 3mg) were more likely to achieve clinically significant weight loss at 1 year compared to "early non-responders" (10.8% vs 3.0% mean weight loss in those without T2D and 8.5% vs 3.1% mean weight loss in those with T2D).[27] Based on the EMA single stopping rule, it is estimated that 62-77% of patients with obesity referred to SWMS will be suitable to continue long-term on LIRA 3mg.[27] However, only 9-21% of those who achieve ≥5% weight loss at 16 weeks will obtain maximal benefit (≥15% weight loss) from LIRA 3mg.[27] Taking into account the cost of the medication, it is unlikely that NICE or other equivalent organisations will approve long-term treatment with LIRA 3mg for all patients who currently present for obesity treatment in SWMS and achieve the single EMA stopping rule. A different

and more pragmatic use of LIRA 3mg in SWMS is needed in order for the medication to be targeted to those who will benefit most from using it.

In this paper, we describe the rationale and methodology of a study investigating the effectiveness and cost of a targeted prescribing pathway (with multiple pre-specified stopping rules) for the use of LIRA 3mg in SWMS settings for treatment of severe and complex obesity. The targeted prescribing pathway aims to optimise the use of LIRA 3mg in "early responders" (in accordance with the EMA stopping rule) to the combination of lifestyle intervention plus LIRA 3mg as well as identifying patients who are most likely to benefit more from continued long-term prescription of LIRA 3mg (i.e. those who are able to achieve ≥15% weight loss at 1 year). This approach aims to direct the use of this medication to patients with severe and complex obesity that will have substantial benefit from it, and at the same time to optimise the health economic outcomes (cost-effectiveness and budget impact of SWMS) associated with the use of LIRA 3mg.

**Aim and objectives**

The aim of the present study is to compare the clinical effectiveness, the cost-effectiveness and the budget impact (on SWMS) of a targeted prescribing pathway for LIRA 3mg (with pre-specified stopping rules) plus SWMS standard care versus the SWMS standard care alone.

The primary objective will be to compare the proportion of participants with severe and complex obesity achieving weight loss ≥15% at 52 weeks using a targeted prescribing pathway (use of LIRA 3mg according to a pre-specified protocol) in combination with SWMS standard care versus SWMS standard care alone.

The secondary objectives (see also Supplementary Material, Appendix 1) are to compare the targeted prescribing pathway plus SWMS standard care vs SWMS standard care alone in terms of:

1. improving obesity-related complications (prediabetes, diabetes, hypertension, obstructive sleep apnoea, dyslipidaemia, depression) at 52 and 104 weeks
2. referral rates to other obesity interventions at 52 and 104 weeks
3. long-term weight 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 SWMS at 52 and 104 weeks
5. estimated cost-effectiveness of treatment over 104 weeks
6. direct healthcare costs in terms of admissions, frequency, and cost of appointments at 52 and 104 weeks
7. safety-related outcomes at 52 and 104 weeks
8. adherence to treatment at 16, 32, 52 and 104 weeks.
9. patient satisfaction and quality of life at 52 and 104 weeks

## METHODS AND ANALYSIS

The protocol of this clinical trial follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[28]

### Study design

The STRIVE study is a phase 4, investigator-initiated, two year, parallel, two group, multicentre, open-label, real-world, randomised controlled trial taking place in UK and Ireland. The total duration of participation will be 104 weeks (±2 weeks). In total, 384 patients with severe and complex obesity who are referred to a SWMS will be randomised through a validated online system (sealedenvelope.com) provided through the Leicester Clinical Trials Unit (LCTU) in a 2:1 fashion (2 intervention: 1 control) to either the intervention (SWMS standard care plus targeted prescribing pathway) or control arm (SWMS standard care) (see also Figure 1). Randomisation will be stratified by centre and BMI (≥45kg/m$^2$; <45kg/m$^2$).

The study is intentionally designed to reflect a pragmatic "real-world" scenario and each SWMS provider may require a different number of visits for their programme. However, study appointments for data collection, medication titration reviews, application of the stopping rules of LIRA 3mg, and dispensing of the medication will be standardised for all of the study sites.

The first 52 weeks of the study will determine whether using the targeted prescribing pathway of LIRA 3mg plus standard care in a SWMS setting will result in more participants achieving ≥15% weight loss compared with participants in the control group (standard care alone). The second 52 weeks of the study will assess whether patients who lose ≥15% of their baseline weight by the first 52 weeks with the targeted prescribing pathway plus standard care are more

likely to maintain ≥15% weight loss for another 52 weeks compared with patients in the control group (standard care alone) who were also able to achieve ≥15% weight loss by the first 52 weeks. Further measurements on budget impact of SWMS and cost-effectiveness for both treatment groups will be assessed and compared.

**Control (Standard Care)**

Across the UK and Ireland, each region has a SWMS. This service includes a clinician led multidisciplinary team approach, potentially including a specialist physician, dietitian, nurse, psychologist and physiotherapist/physical activity physiologist. The accessibility and the workflow of the SWMS are broadly similar for all the five participating sites in this study.

Participants in the control group will follow the best medical care provided by the SWMS at the relevant site. This typically involves dietary advice to reduce energy intake (and may include a period using formula-diet meal replacement or total diet 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 SWMS at each site. Clinician input will include the medical assessment of participants for severe and complex obesity and the prescription of anti-obesity drugs (i.e. orlistat) as per local SWMS policy. Participants will remain in the SWMS 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 SWMS Multidisciplinary Team.

**Intervention (Targeted Prescribing Pathway plus Standard Care)**

Participants in the intervention arm will receive the same SWMS care with the control arm. Additionally, at baseline, LIRA 3mg will be prescribed to all of the participants in the intervention arm. Dose escalation of liraglutide will occur in accordance with the Summary of Product Characteristics (SPC) from 0.6 mg to a maximum of 3.0 mg. Participants will be withdrawn from receiving LIRA 3mg if the doses are not tolerated during or following the titration period.

Participants will also be informed about the pre-specified weight loss criteria in order to continue receiving treatment with LIRA 3mg. Participants in the targeted prescribing pathway will be prescribed LIRA 3mg for the duration of the study, unless they do not meet the pre-defined weight loss targets at each stopping point (after 16, 32 and 52 weeks, see also Figure 1).

Targeted Prescribing Pathway Stopping Rules

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.

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.

3rd stopping rule:

After 52 weeks (±14 days) on the medication, 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 fail to reach the thresholds to continue LIRA 3mg treatment, or who have withdrawn from LIRA 3mg due to intolerance, adverse effects or inability to titrate up to a maximum dose of LIRA 3mg, will continue to be offered the standard care provided by the relevant SWMS. The conditions for participants' withdrawal from the study as well as for temporary and/or permanent treatment discontinuation for LIRA 3mg (outside prespecified stopping rules) are described in Supplementary Material, Appendix 2.

**Study Outcomes**

**Primary Outcome**

The primary outcome is the proportion (%) of participants with severe and complex obesity achieving weight loss ≥15% of baseline weight at 52 weeks after randomisation with the standard care provided in SWMS versus a targeted prescribing pathway of LIRA 3mg with pre-specified stopping rules plus the standard care provided in SWMS.

**Secondary measurements and outcomes**

A range of secondary outcomes including anthropometrics, weight maintenance, obesity associated comorbidities, budget impact, cost-effectiveness, safety/adverse events, compliance of patients with treatment and referrals to other obesity interventions between the two groups will be measured and assessed throughout the study. These are listed in Supplementary Material, Appendix 1.

**Study population**

Five culturally and racially diverse sites in different geographical areas (Dublin, Glasgow, Leicester, Liverpool and London) will be used to reflect typical SWMS settings across UK and Ireland.

Potentially eligible patients who have agreed to participate in the SWMS will be identified by the clinical care team and invited for screening. Patients will be allowed at least 24 hours to consider their participation to the study. Full inclusion and exclusion criteria are listed in Box 1. Each site will plan to recruit up to 77 subjects over the 24 months recruitment period.

**Study procedures**

**Study visits**

A participant flowchart is demonstrated in Figure 2 and the study visit outline and measurement plan for each visit is included in Supplementary Material, Appendix 3, Table 1. Participants in both groups will attend 13 visits during the two-year trial. Participants in the intervention group who continue on LIRA 3mg during the second year of the study, will attend 2 additional visits for safety, monitoring of side effects, compliance and medication supply.

**Screening and Consent Visit (Day -42 to -1)**

A study clinician will determine the eligibility of potential participants and obtain written informed consent (see Supplementary Material Appendix 4). Following this, demographics, medical and surgical history, anthropometrics (height, weight, waist circumference), blood pressure and pulse rate, a comprehensive clinical examination and routine laboratory investigations will be performed (see Supplementary Material, Appendix 3, Table 1). Female participants of childbearing potential will undergo a urine pregnancy test. Urine albumin creatinine ratio (ACR) will be analysed for participants with prediabetes, diabetes and hypertension.

All participants will undergo an assessment with the King's College Obesity Staging System (see Supplementary Material, Appendix 5, Table 1), STOP-Bang questionnaire and Epworth sleepiness score. Participants at risk of undiagnosed OSA (defined by STOP-Bang score of ≥ 5) will be referred to sleep clinic for further investigation. Participants with established OSA on CPAP therapy will have their notes reviewed to determine compliance with CPAP therapy and whether it was a "successful" treatment according to the following criteria: a. CPAP usage

≥ 4 hrs/night = successful, b. CPAP usage < 4 hrs/night = struggling, c. CPAP usage ≤ 1 hr/night = failure.

**Data Collection and Safety Visits (Baseline, Weeks 52 and 104)**

During the baseline visit, eligibility will be confirmed by the study clinician at each site based on the results and investigations from screening visit. Following this, only eligible participants will be randomised and allocated into either group (open label study). Participants allocated to the targeted prescribing pathway plus standard care (intervention group), will be prescribed LIRA 3mg and reminded of the prescribing pathway medication stopping rules at weeks 16, 32 and 52. Participants will receive training to confidently administer the Investigational Medical Product (IMP). Female participants of childbearing potential will be reminded to use effective contraception throughout the study.

A full description of the outcome measures and the procedures during baseline visit, week 52 and week 104 is shown in Supplementary Material, Appendix 3, Table 1. Serious Adverse Events (SAE) and Adverse Events (AE) as well as changes in medication or diseases will be recorded during every visit from consent to the end of study. Moreover, participant adherence to the SWMS programme will be monitored (completers will be defined as those who attended >70% of scheduled visits in the SWMS during the first 52 weeks).

At weeks 52 and 104, blood tests for biochemical outcomes will be performed for all participants in the study as well as urine ACR for participants with diabetes, prediabetes and hypertension.

At week 104, the study clinician will evaluate all the participants who experience significant weight regain in either treatment group and may consider a recommendation to Tier 4 service for bariatric surgery. For 'responders' on LIRA 3 mg, the clinician will recommend that the participant's GP may consider prescribing LIRA 3mg long-term, depending on the local prescribing practice.

**Clinical Review Visits (safety and retention) (Weeks 2, 4, 8, 12, 16, 20, 32, 40 and 78)**

Participant's eligibility and consent for continuation in the study will be confirmed. Measurements of outcomes during these visits including reporting potential AEs/SAEs are detailed in Supplementary Material, Appendix 3, Table 1. Participants on LIRA 3mg will be given advice on dose titration (at weeks 2 and 4) as per SPC and will be monitored for any possible side effects and adherence with the daily injection (by examining medication returns).

At week 32, blood tests for biochemical outcomes will be performed for all participants in the study as well as urine ACR for participants with diabetes, prediabetes and hypertension.

**Additional Clinical Review (safety and retention) Visits for LIRA 3mg group (Weeks 65 and 91)**

Two additional visits will take place only for participants in the intervention group who remain eligible and continue to be offered treatment with LIRA 3mg in the second year. The visits will be identical to the other Clinical Review visits as described above, with the intention to provide participants with a new prescription of LIRA 3mg, discuss adherence with the treatment and record any AE/SAEs.

**Treatment of Trial participants**

**Study Medication**

Participants randomised to LIRA 3mg group will be instructed to take daily subcutaneous injection of liraglutide (Saxenda) whilst continuing their usual medication. Participants will be given specific instructions to adhere to the titration policy of LIRA 3mg in accordance with the SpC. LIRA 3mg will be prescribed to participants for a maximum of 106 weeks (4 weeks dose titration, 100 weeks maintenance dose, ±2 weeks visit window).

*Compliance and Accountability*: Participants will be asked to return all unused investigational products and vials/packages to the pharmacy at each study visit. Compliance and concordance with LIRA 3mg will be evaluated and discussed at each study visit based upon tolerability and returned vials of medication. Participants will be defined as treatment compliant if they self-administer at least 70% of planned doses.

**Harms**

Throughout the STRIVE study, all the reported AEs, SAEs and other unintended effects of trial interventions or trial conduct will be collected, assessed, reported and managed according to the Good Clinical Practice – International Conference of Harmonisation (GCP-ICH) guidelines.

**Data collection, management and confidentiality**

Details on data collection, management and confidentiality for the STRIVE study are provided in Supplementary Material, Appendix 6.

## Statistics

### Sample Size

Based on previous studies, it is anticipated that at one year approximately 5% of the participants in the standard care group will have achieved ≥15% weight loss (likely range: 3%-5%).[17,22] An achievable target for ≥15% weight loss at 52 weeks in the intervention group (standard care plus LIRA 3mg with pre-specified stopping rules) is 16% (likely range: 14%-20%).[17,22] Accounting for 25% drop out, 5% alpha and a 2:1 randomisation ratio with higher proportion of participants being randomised to the intervention group; we would need to recruit 384 participants (256 intervention group; 128 standard care) to have 80% power to detect a significant difference between the groups in participants achieving ≥15% weight loss at one year.

### Statistical methods and analysis

The primary analysis will compare the proportion of participants achieving ≥15% weight loss at 52 weeks (primary outcome) after randomisation between the two study arms using a logistic regression model with adjustment for stratification factors (site and BMI). The adjusted proportion (95% confidence interval) of participants achieving ≥15% weight loss will be estimated by group. The primary analysis will be based upon the complete case population. This 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.

The secondary analyses of the primary outcome will be based upon intention to treat (ITT) and per protocol analyses. The ITT population is defined as all randomised participants in the study and the per protocol population is defined as all randomised participants who were compliant with their treatment group. Treatment compliance for the control group is defined as completion at least 70% of the planned contacts in the SWMS. Participants in the intervention group are defined as treatment compliant if they complete at least 70% of the planned contacts in the SWMS, and take at least 70% of their planned doses of LIRA 3mg as stipulated by the prescribing pathway. In all analyses, participants will be analysed within the treatment arm to which they were allocated at baseline. More specifically, participants within the intervention group who were taken off LIRA 3mg due to pre-specified stopping rule will remain in the intervention group. Participants who have undergone bariatric surgery during the first 52 weeks of the study will be excluded from the complete cases population analysis (primary analysis) and the per protocol analysis for the primary outcome (but they will be included at the ITT analysis). Missing primary outcome data will be imputed for the ITT analyses; categorically

we will classify those participants as "non-responders" (did not achieve ≥15% weight loss at 52 weeks). The characteristics of those with missing outcome data will be compared to those who have completed follow-up.

Secondary outcomes measured at 52 and 104 weeks will be analysed based upon the complete cases population. Binary outcomes will be analysed using logistic regression models and summarised using proportion (95% confidence interval). Continuous outcomes will be compared using linear regression models and summarised as mean with standard deviation (95% confidence interval). If continuous outcomes are non-normally distributed, the most suitable regression model will be selected. Only the complete cases population will be used for the secondary outcomes to reduce the number of models. Participants who have undergone bariatric surgery during the first 52 weeks of the study will be excluded from the analyses for secondary outcomes at 52 weeks. Moreover, participants who have undergone bariatric surgery during the study period will be excluded from the analyses for secondary outcomes at 104 weeks. Data on treatment adherence, safety (including adverse events), and treatment satisfaction will be summarised and tabulated.

In addition, we will perform a responder analysis which will repeat the analyses of the secondary outcomes with the intervention group restricted to those participants who responded to the targeted prescribing pathway (those achieving ≥15% weight loss at 52 weeks after randomisation). This allows us to statistically compare the outcomes of "super" responders within the targeted prescribing pathway to all the participants who received standard care in the control group.

**Health Economic Input**

A state-transition Markov cohort model has been developed for the cost-effectiveness analysis, with health states encompassing the possible co-morbidities associated with obesity and documented to respond to weight loss. A thorough review of the literature was conducted to identify such conditions and inform transition probabilities in the model.

The model projects development of T2DM, myocardial infarction, stroke, asthma cancer or mortality in the long term (up to lifetime horizon) based on short term effects of interventions in surrogate outcomes – BMI, systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol and (for patients with T2D) glycated haemoglobin (HbA1c).

Effects on surrogate outcomes are translated into lifetime risks through risk-prediction models.

Treatment effects are applied incrementally to the efficacy of the targeted prescribing pathway group. Effect on weight, in terms of BMI % reduction, is applied at every subsequent cycle starting from 3 months after treatment start for as long as the cohort remains on treatment and over the predefined catch-up time post-treatment. Note that a natural increase in weight is applied each year to all interventions considered, including no treatment.

Treatment can be discontinued at 16 weeks, 32 weeks or at 52 weeks (based on the pre-specified stopping rule). Discontinuation causes the cohort to receive the standard care provided via the SWMS at the control group. Thus, if the discontinuation is allowed at 16 weeks, "non-responders" will have the same effect of the cohort in the control group, and "responders" will have the effect of the targeted prescribing pathway in the clinical trial.

Discontinuation of treatment beyond 52 weeks causes BMI, and other cardio-metabolic risk factors, to revert to the levels projected under the no treatment option. Reversal takes place over a given number of cycles (years). Costs and quality of life outcomes are applied to the health state in which the cohort resides at each particular moment in time or once-off to events. Costs and health benefits (life years, quality-adjusted life-years, years T2D free, years cancer free etc.) are summed-up for the time horizon of the model and results reported as incremental cost-effectiveness ratios. The risk of acquiring obesity-related co-morbidities have been taken from published epidemiological studies.

### Patient and public involvement

Patients and public were not involved in the development of the research questions or the design of this study. However, on completion of the study, all participants will be informed for the results of the study.

## ETHICS AND DISSEMINATION

### Ethical issues

Approval for the protocol (and any subsequent substantial amendments) has been obtained from the Medicines and Healthcare products Regulatory Agency (MHRA, UK Competent authority) and Health Products Regulatory Authority (HRPA, Irish Competent Authority). This protocol has been approved by the Health Research Authority (HRA) and ethical approval as

a Clinical Trial of an Investigational Medicinal Product (CTIMP) study was granted by the North West Deanery National Research Ethics Service (NRES) committee (17/NW/0517) in UK (29 September 2017) and from the St Vincent's University Hospital European Research Ethics Committee (EUREC) (2017-002998-20) in Ireland. This manuscript details the 4th version of the protocol approved on 8th of June 2018.

The study is conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, as well as in full conformity with the International Conference of Harmonisation (ICH) Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996. Ethical and research governance approval has been obtained for this study through the HRA, appropriate regulatory bodies and National Health Service (NHS) Trust prior to any participant activity.

**Protocol amendments**

All changes to the study protocol were reviewed by the North West Deanery NRES committee in UK and from the St Vincent's Hospital EUREC in Ireland and then reported to the sponsor and funder. The participating sites and co-investigators were sent regular emails with updates on the study recruitment timeline and any major protocol changes during the enrolment period. All significant protocol changes were noted in ClinicalTrials.gov.

**Trial oversight and governance**

The study sponsor is the University of Leicester (UK) and the study is managed by the LCTU and is overseen by trial steering committee (TSC) comprised of independent chair and a group of experts. This study is registered at the http://www.clinicaltrials.gov (NCT03036800) as well as on the European Clinical Trials Database (EudraCT Number 2017-002998-20) before the enrolment of the first participant and monitored by the University of Leicester.

Safety of the participants will be independently monitored by the Data monitoring and Ethics Committee (DMEC), which will make recommendations to the TSC for appropriate action in the interest of the participants.

**Current status and time scale**

Recruitment started in November 2017 and the last patient last visit should complete by December 2021. To date, 380 patients have been screened and consented, of which 351 were eligible to participate and 337 have been randomised to the study.

**Dissemination plan**

The results of the study will be presented in national and international meetings and will be submitted for publication to the relevant Obesity/General Medical peer-reviewed journals. Acknowledgement of any supporting organisations, including funders, University of Leicester and the LCTU, will be included.

**Author contributions:** DP: coinvestigator at University of Leicester, trial coapplicant, primary author of manuscript, co-author of the approved study protocol. WA-N: coauthor at University College Dublin, contributed to writing the manuscript and approved the final version. JL: coauthor at University of Liverpool, contributed to writing the manuscript and approved the final version. JC: provided critical appraisal of current manuscript and approved final version. ML: principal investigator at University of Glasgow, trial coapplicant, coauthor for approved study protocol, contributed to trial set-up and design, provided critical appraisal of the manuscript and approved the final version. CLR: principal investigator at University of Dublin, coauthor of the approved study protocol, contributed to trial set-up and design, provided critical appraisal of the manuscript and approved the final version. BM: principal investigator at Guy's and St Thomas' NHS Foundation Trust, trial coapplicant, coauthor for approved study protocol, contributed to trial set-up and design, provided critical appraisal of the manuscript and approved the final version. DO'S: principal investigator at University of Dublin, trial coapplicant, coauthor for approved study protocol, provided critical appraisal of the manuscript and approved the final version. DW: principal investigator at University of Leicester, trial coapplicant, contributed to trial set-up and design, coauthor for approved study protocol, provided critical appraisal of the manuscript and approved the final version. JW: principal investigator at University of Liverpool, trial coapplicant, contributed to trial set-up and design, coauthor for approved study protocol, provided critical appraisal of the manuscript and approved the final version. MJD: chief investigator, trial coapplicant, contributed to trial set-up and design, coauthor for approved study protocol, corresponding author, provided critical appraisal of the manuscript and approved the final version.

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**Data availability statement:** De-identified participant data will be made available after publication of the main paper of the study by application to the corresponding author and after assenting to a data access agreement.

**Competing interests statement:** DP is funded from an NIHR Clinical Lectureship and reports grants from the Novo Nordisk UK Research Foundation outside submitted work; WA-N is funded by the Irish Research Council's Postdoctoral Enterprise Partnership Scheme and reports personal fees from Novo Nordisk outside the submitted work; JL has nothing to disclose; JC reports participation at the Novo Nordisk Emerging Obesity Leaders Programme which included registration and travel expenses to the European Congress of Obesity 2019, Glasgow, funded by Novo Nordisk; ML reports grants and personal fees from Novo Nordisk, personal fees from Sanofi, personal fees from Eli Lilly, personal fees from Counterweight Ltd, personal fees from Roche, outside the submitted work; CLR reports grants from Science Foundation Ireland, grants from Health Research Board, during the conduct of the study; other from Novo Nordisk, other from GI Dynamics, personal fees from Eli Lilly, grants and personal fees from Johnson and Johnson, personal fees from Sanofi Aventis, personal fees from Astra Zeneca, personal fees from Janssen, personal fees from Bristol-Myers Squibb, personal fees from Boehringer-Ingelheim, outside the submitted work; BM reports grants from Novo Nordisk, during the conduct of the study; grants and personal fees from Novo Nordisk , personal fees from Sanofi, personal fees from Boheringher Ingelheim, personal fees from MSD, outside the submitted work; DO'S has nothing to disclose; DW has nothing to disclose; JW reports grants from Novo Nordisk, during the conduct of the study; grants, personal fees and other from AstraZeneca, other from Astellas, personal fees and other from Boehringer Ingelheim, other from Janssen, personal fees and other from Mundipharma, personal fees and other from Napp, personal fees and other from Lilly, personal fees and other from Sanofi, other from Wilmington Healthcare, outside the submitted work; MJD reports grants from Novo Nordisk, during the conduct of the study; personal fees from Novo Nordisk, personal fees from Sanofi-Aventis, personal fees from Lilly, personal fees from Merck Sharp & Dohme, personal fees from Boehringer Ingelheim, personal fees from AstraZeneca, personal fees from Janssen, personal fees from Servier, personal fees from Mitsubishi Tanabe Pharma Corporation, personal fees from Takeda Pharmaceuticals International Inc., grants from Sanofi-Aventis, grants from Lilly, grants from Boehringer Ingelheim, grants from Janssen, outside the submitted work.

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## Box 1. Inclusion and exclusion criteria

**Inclusion criteria:**

- 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 Specialist Weight Management 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, type 2 diabetes (T2D), 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)
  - type 2 diabetes [defined as established diagnosis of T2D 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 sodium-glucose co-tranporter-2 (SGLT-2) inhibitors]
  - 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

**Figure 1. Study design**

**Figure 2. Participant flowchart**

**Figure 1.**

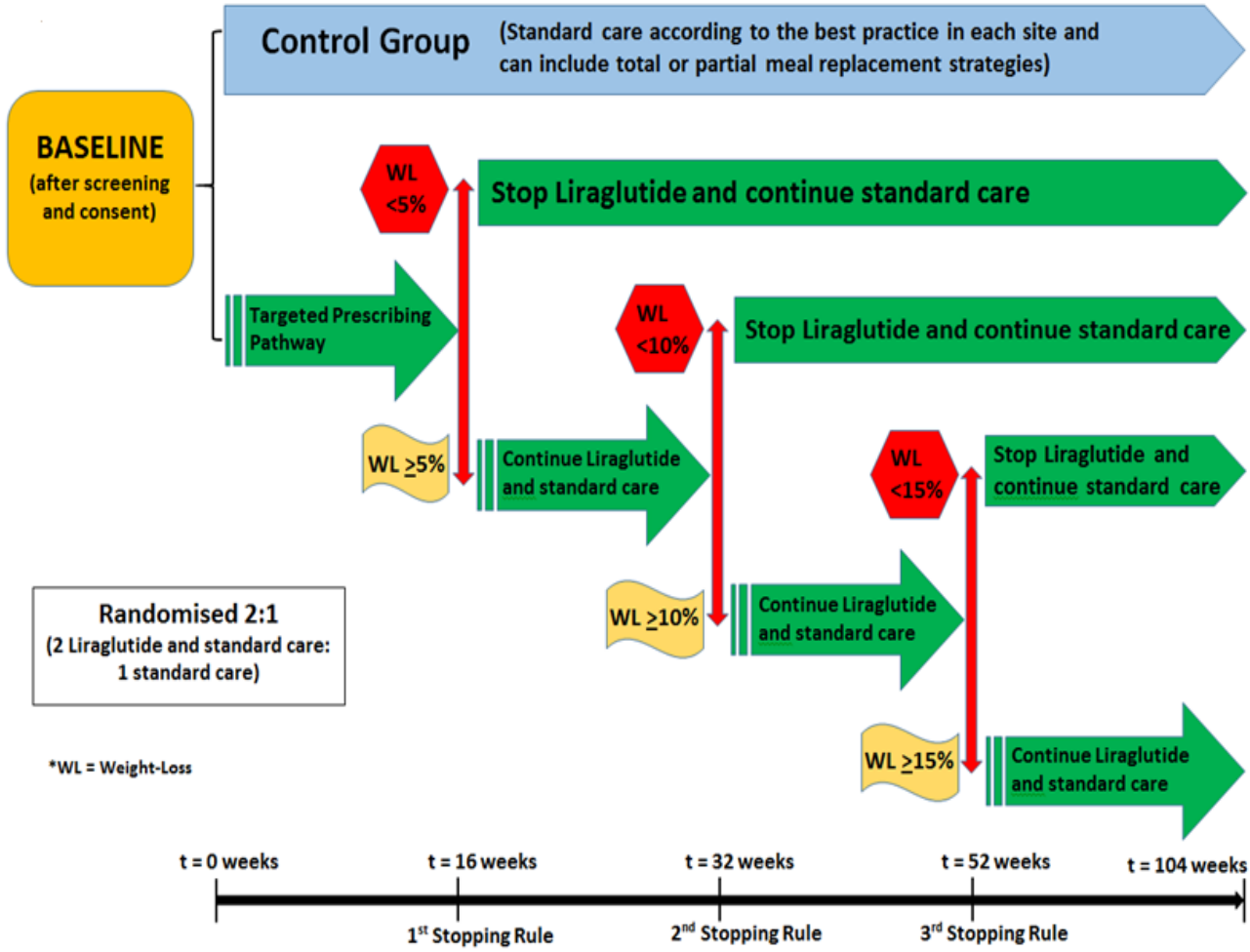
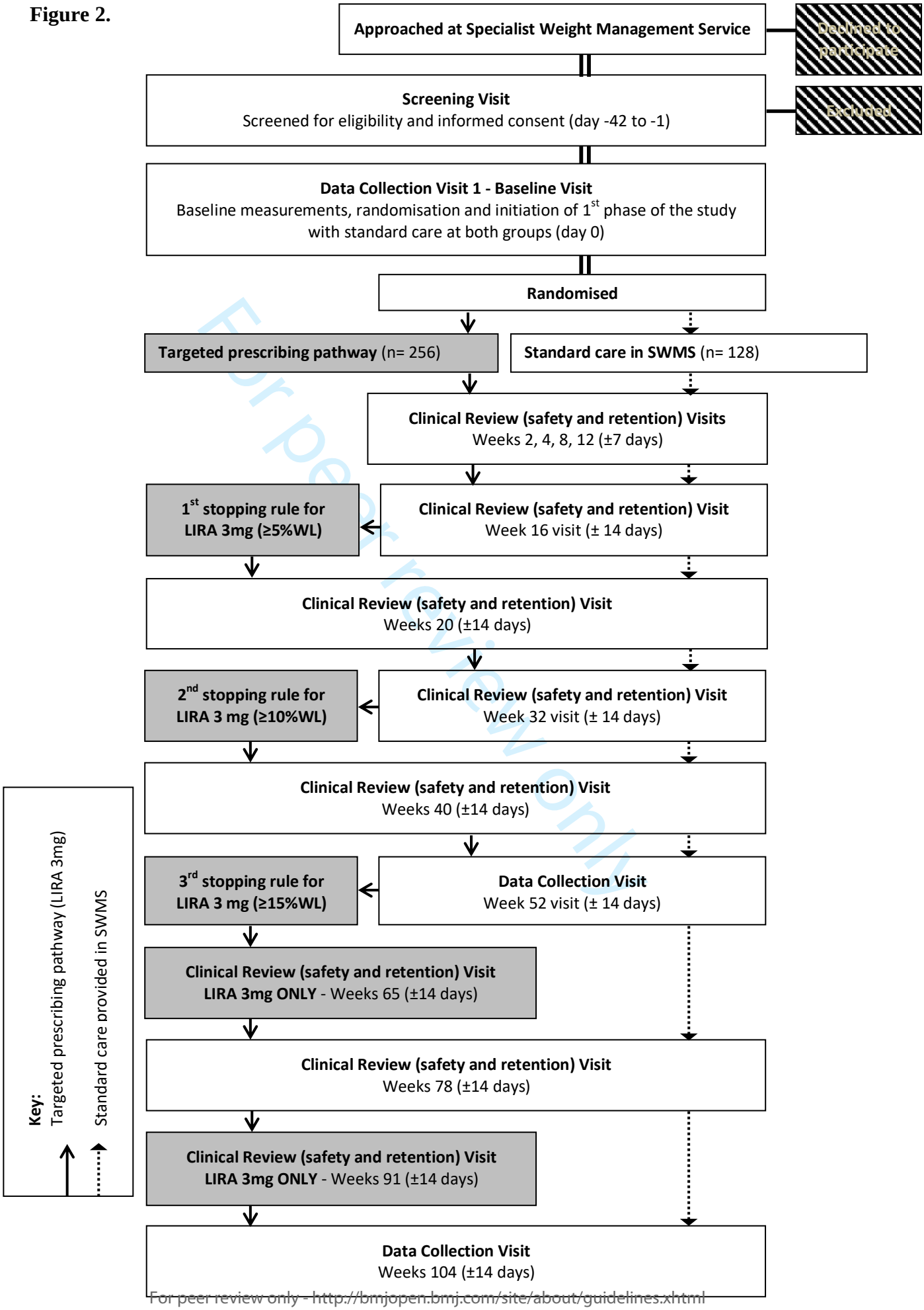


**Figure 2.**



## Appendix 1. Secondary Outcomes

Unless stated otherwise, the secondary outcomes listed below will be assessed at 52 and 104 weeks.

### Anthropometric Outcomes

- Weight (kg), from which these secondary outcomes will be derived (also at 16 and 32 weeks):
  - Absolute change in weight (kg) from baseline
  - Relative change in weight (%) from baseline
  - Proportion of participants reaching weight loss of ≥5%, ≥10% and ≥15%
  - 104 weeks only: Proportion of participants maintaining weight loss of ≥15% among those who lost ≥15% at 52 weeks
- Height (cm), from which this secondary outcome will be derived:
  - Change in BMI ($kg/m^2$) from baseline
- Waist circumference (cm)

### Obesity-related co-morbidities and their treatments (General)

- King's College Obesity Staging System assessment (a system to assess multiple co-morbidities related to obesity and their severity, see Appendix 1)
- Quality of life (EQ5D)
- Impact of Weight on Quality of Life-Lite (IWQOL-Lite)
- Patient Health Questionnaire-9 (PHQ9)

### Obesity-related co-morbidities and their treatments (Prediabetes/Diabetes)

- HbA1C
- Proportion of participants with normoglycaemia (defined as HbA1C <42.0 mmol/mol without glucose lowering medications)
- Proportion of participants with prediabetes (defined as HbA1C 42.0-47.9 mmol/mol without glucose lowering medications)
- Proportion of participants with diabetes (defined as HbA1C ≥48 mmol/mol or on glucose lowering medications)
- Dose, class of medication, and number of agents for diabetes
- Monitoring of microvascular complications for patients with diabetes [Albumin-Creatinine Ratio (ACR)]

### Obesity-related co-morbidities and their treatments (Hypertension)

- Blood pressure
- Proportion of participants with hypertension (defined as patients on antihypertensive medications or systolic blood pressure>140mmHg)
- Dose, class of medication, and number of agents for hypertension

### Obesity-related co-morbidities and their treatments (Obstructive Sleep Apnoea)

- Epworth score for all participants to determine levels of daytime sleepiness

- Stop Bang questionnaire for all participants to identify undetected OSA - it will be administered by research team or taken from medical notes
- Proportion of participants on CPAP
- CPAP pressures for patients on variable pressures CPAP
- Apnoea Hypopnea Index (AHI) for participants with sleep apnoea who cannot tolerate CPAP or for participants on fixed pressures CPAP
- Oxygen desaturation index for participants with sleep apnoea who cannot tolerate CPAP or for participants on fixed pressures CPAP

**Obesity-related co-morbidities and their treatments (Dyslipidaemia)**

- Lipids
- Dose, class of medication, and number of agents for dyslipidaemia

**Number of participants referred for other obesity intervention**

- Number of participants referred to Tier 4 for bariatric surgery over the 104 weeks study period

**Direct healthcare cost**

- Frequency and cost of contact with General Practitioner (GP) (type and duration of contact will be recorded to enable use of Tariff prices from http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php?file=full to calculate accurate costings – accessed 21/07/2017)
- Frequency and cost of contact with Healthcare Professionals (HCP) (type and duration of contact will be recorded to enable use of Tariff prices from http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php?file=full to calculate accurate costings)
- Frequency of admissions, length of stay and cost of admissions to the hospital
- Frequency and cost of outpatient appointments with the hospital
- Prescription medication costs
- Health Service and Resources Use Questionnaire (HSRUQ)

**Budget impact of Specialist Weight Management Service**

- Cost of the proposed LIRA 3mg (as per protocol - e.g. actual dose taken = number of days taking study drug x daily cost of drug, or cost of total amount of study drug used)
- Cost of visits to clinician for assessment and medication prescription during Specialist Weight Management Service programme
- Cost of visits to dietician during Specialist Weight Management Service programme
- Cost of visits to psychologist during Specialist Weight Management Service programme
- Cost of physical activity physiologist/physiotherapist during Specialist Weight Management Service programme (if applicable)

- Cost of Multidisciplinary Team (MDT) discussion in Specialist Weight Management Service
- Cost of blood tests in Specialist Weight Management Service
- Cost of consumables and goods
- Cost of referral into Tier 4

**Estimated cost-effectiveness of treatment over 2 years**

- Length of treatment with LIRA 3mg
- Daily dose of LIRA 3mg (based on actual doses taken)

**Safety/adverse events**

- Gastrointestinal symptoms (nausea, vomiting)
- Overall hypoglycaemia rate
- Overall AE/SAE rate
- Rates of severe hypoglycaemia
- Heart rate
- Blood pressure

**Treatment satisfaction**

- Treatment Satisfaction Questionnaire for Medication (TSQM)

**Compliance of patient with the treatment and patient related outcomes**

- The number of participants who did or did not attend at least 70% of the scheduled appointments with the Specialist Weight Management Service (completers)
- The number of participants who had to stop treatment with LIRA 3mg because of adverse effects
- The adherence of participants with the LIRA 3mg (monitored through specific questionnaire and return of used pens)
- The number of participants who stopped LIRA 3mg at 16 weeks after randomisation
- The number of participants who stopped LIRA 3mg at 32 weeks after randomisation
- The number of participants who stopped LIRA 3mg at 52 weeks after randomisation
- The number of participants who completed 52 weeks of the Specialist Weight Management Service programme despite stopping LIRA 3mg at 16 weeks
- The number of participants who completed the 52 weeks of the Specialist Weigth Management Service programme despite stopping LIRA 3mg at 32 weeks
- The number of participants in the treatment group who had to stop treatment with LIRA 3mg because of side effects
- The number of participants started on anti-obesity drugs

**Physical activity assessment**

- International physical activity questionnaire (IPAQ- Long Form)

## Appendix 2: Withdrawal of participants from the study, temporary and permanent treatment discontinuation for LIRA 3mg (outside prespecified stopping rules)

### Withdrawal of participants from the study

Participants may withdraw consent from the study before study completion if they decide to do so, at any time and for any reason.

Participants will be withdrawn from this study by the research team as agreed by the Principal Investigator (PI) if: i) they are diagnosed with a terminal illness, ii) the PI, Sponsor and/or study clinician deem it unsafe for their continuation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations or Good Clinical Practice (GCP), iii) they are considered to be lost to follow up as deemed by the clinician, iv) they have lost their capacity during participation in research, v) they receive treatment with medications which the PI determines to require permanent withdrawal from the study (e.g. systemic corticosteroids).

It will be emphasised to participants who withdraw from the study that their standard care will not be affected and that they will return to standard care.

Attempts will be made to assess the primary outcome on all participants whether or not they were compliant and in those who have who have discontinued the treatment (including those participants who have stopped the treatment outside of the pre-specified stopping rules).

### Temporary treatment discontinuation for LIRA 3mg (outside of the pre-specified stopping rules)

Temporary discontinuation of LIRA 3mg may be considered by the Principal Investigator (PI) because of suspected Adverse Events (AEs).

Re-initiation of LIRA 3mg at a lower dose, under close and appropriate clinical and/or laboratory monitoring maybe considered at discretion of the PI and if the inclusion and exclusion criteria for the study are still met.

### Permanent treatment discontinuation (outside of the pre-specified stopping rules)

Permanent treatment discontinuation is any treatment discontinuation associated with a definitive decision from the PI or the participant not to re-expose the participant to LIRA 3mg treatment. This definition is different to treatment discontinuation due to a participant not meeting the weight-loss targets at the pre-specified stopping rules as per the protocol.

Factors leading to permanent discontinuation of LIRA 3mg include i) pregnancy, ii) episode

of acute pancreatitis and breast malignancy, iii) repeat violation or non-compliance with the protocol, iv) participant being unable to tolerate LIRA 3mg doses and/or v) any other contraindication to the study medication which the PI determines to require permanent treatment discontinuation.

Key:
Stopping rules apply
Extra visits for LIRA 3mg group only
End of study

## Appendix 3.

### Table 1. Outcome measures and planned visits during the enrolment and control visits.

| WEEKS | -6 to -1/52 | 0/52 | 2/52 | 4/52 | 8/52 | 12 /52 | 16 /52 | 20 /52 | 32 /52 | 40 /52 | 52 /52 | 65 /52* | 78 /52 | 91 /52* | 104/52 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VISIT WINDOW | Screening^^ | Base-line | +/- 3dys | +/- 3dys | +/- 7dys | +/- 7dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys |
| Visit No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12* | 13* /12 | 14* | 15* /13 |
| **STUDY PROCEDURES** | | | | | | | | | | | | | | | |
| Inclusion/ exclusion criteria | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Informed consent | X | | | | | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | | | | | |
| Injection training* | | X | | | | | | | | | | | | | |
| Titration/ Review Visit* (dose$) /or telephone call)$$ | | X 0.6$ | 1.2$$ X 1.8$ | 2.4$$ X 3.0$ | | | | | | | | | | | |
| Other HCP | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Glucose self-monitoring training/ education | | X | | | | | | | | | | | | | |
| Dispensing (or unsched visit)### | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **DATA COLLECTION** | | | | | | | | | | | | | | | |
| Subject demography | X | | | | | | | | | | | | | | |
| Medical/Surgical history | X | | | | | | | | | | | | | | |
| Medication history | X | | | | | | | | | | | | | | |
| Concomitant medication | X | | | | | | | | | | | | | | |
| Changes in med/diseases | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | |
| BMI | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Waist Circumference | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood Pressure | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pulse rate | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liver function tests | X | | | | | | | | X | | X | | | | X |
| Renal function tests | X | | | | | | | | X | | X | | | | X |
| Thyroid function tests | X | | | | | | | | X | | X | | | | X |
| Haematology profile | X | | | | | | | | X | | X | | | | X |
| Lipids | X | | | | | | | | X | | X | | | | X |
| HbA1C | X | | | | | | | | X | | X | | | | X |
| Amylase | X | | | | | | | | X* | | X* | | | | X* |

| WEEKS | -6 to -1/52 | 0/52 | 2/52 | 4/52 | 8/52 | 12 /52 | 16 /52 | 20 /52 | 32 /52 | 40 /52 | 52 /52 | 65 /52* | 78 /52 | 91 /52* | 104/52 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **VISIT WINDOW** | Screening^^ | Base-line | +/- 3dys | +/- 3dys | +/- 7dys | +/- 7dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys | +/- 14dys |
| **Visit No.** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12* | 13* /12 | 14* | 15* /13 |
| King's Obesity Staging System | X | | | | | | | | | | X | | | | X |
| Epworth score | X | | | | | | | | | | X | | | | X |
| Stop Bang Questionnaire | X | | | | | | | | | | X | | | | X |
| Sleep Study (home based ambulatory sleep monitor)** | X | | | | | | | | | | X | | | | X |
| Apnoea Hypopnoea Index** | X | | | | | | | | | | X | | | | X |
| Oxygen desaturation index** | X | | | | | | | | | | X | | | | X |
| CPAP pressures** | X | | | | | | | | | | X | | | | X |
| Pregnancy test | X | X | X* | X* | X* | X* | X* | X* | X* | X* | X | X* | X* | X* | X |
| ACR*** | X | | | | | | | | X | | X | | | | X |
| AE/SAE recording | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adherence with injection* | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adherence with other anti-obesity medications# | | | | | | | X | | X | | X | | | | X |
| Adherence to Specialist Weight Management Service (SWMS) | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Contacts with GP/HCP | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Inpatient and Outpatient apt's | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medications cost | | X | | | | | | | | | X | | | | X |
| **QUESTIONNAIRES** | | | | | | | | | | | | | | | |
| HSRUQ | | X | | | | | | | | | X | | | | X |
| TSQM### | | X | | | | | | | | | X | | | | X |
| EQ-5D | | X | | | | | | | | | X | | | | X |
| IWQOL-Lite | | X | | | | | | | | | X | | | | X |
| IPAQ-Long | | X | | | | | | | | | X | | | | X |
| PHQ-9 | | X | | | | | | | | | X | | | | X |

*Only for participants at the LIRA 3mg group who are on active treatment

$Titrated dose participant will leave on at the end of the visit. $$Optional Telephone calls to check tolerance and up-titrate at weeks 1, 3 & 5.

**As required for participants with identified risk OSA of or current OSA based on CPAP use and type of CPAP (variable or fixed pressures CPAP)

*** Only for prediabetic, diabetic and hypertensive individuals

# Only for participants in the standard care group on treatment with anti-obesity drugs

##Only for participants with diagnosis of T2DM

### For participants on treatment either with LIRA 3mg or other anti-obesity medication

^ Only participants who report problems with injection and/or side-effects may be reviewed by study clinician

^^A repeat screening visit may take place to assess eligibility

Drug dispensing unscheduled visits may occur at any point within the study period for participants in LIRA3 mg group as required (not depicted above)

UNIVERSITY OF LEICESTER

<INSERT LOCAL HEADERS>

# Effectiveness and Cost of Integrating a Protocol with use of Liraglutide 3.0 Mg into an Obesity Service (STRIVE Study)

## INFORMED CONSENT FORM

**Local Principal Investigator:**

**PARTICIPANT ID No:** SN __ __ __ __ __ __

<Insert Local investigator name – single line>
<Insert local Site details/address – single line>

**Please initial each statement**

1. I have read the Participant Information Leaflet (v5 08/06/2018) of the above study and have been given a copy to keep. I have had the opportunity to ask questions about the study and I am satisfied with the information I have been given. ☐
2. I agree that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I agree to undergo the tests and investigations as described in the Participant Information Leaflet. The nature of the tests and investigations and any possible risks have been explained. ☐
4. I agree to my medical history from my GP being accessed by the research team should it be relevant to my taking part in the study ☐
5. I agree to my GP and any other doctor treating me to being informed of my participation in this study. ☐
6. I agree that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the regulatory authorities, NHS Trust, Sponsor, host organisation, funder, or study team, where it is relevant to my taking part in this research. I give my permission for these individuals to have access to my records. ☐
7. I agree to being contacted with the details of future research and for my contact details to be stored securely on a computer database by the local study team. ☐
8. I agree that my anonymised data and personal information may be Transferred and stored between university and NHS trust computers using secure encrypted methods. ☐
9. I agree that my data may be used for other ethically approved research. It will be stored at the University Hospitals of Leicester or other academic partners if it is anonymised. ☐

| | Yes | N/A |
|---|---|---|
| 10. **FEMALE PARTICIPANTS ONLY:** I agree to being withdrawn from the study if I become pregnant and for the funder to be informed of this withdrawal. | ☐ | ☐ |
| 11. I agree to take part in the above study. | ☐ | |

| Name of patient | Date | Signature |
|---|---|---|
| | | |

| Name of person taking consent | Date | Signature |
|---|---|---|
| | | |

**Appendix 5.**

**Table 1.** 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 |

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

## Appendix 6

## Data collection, management and confidentiality

### Data collection

Paper Case Report Forms (CRF) and study questionnaires are the primary data collection instruments and treated as source data. All data requested in the CRF will be recorded. All missing data will be explained. Data captured in the paper CRFs will then be entered into a validated web based database under the management of LCTU. On-entry validation checks will be applied where required and data entered will be checked for completeness, accuracy and timeliness by the study team/trial manager/data manager. All study visits and AEs will be recorded in the hospital notes.

### Data management

All study documentation containing identifiable patient data will be managed in accordance with ICH-GCP, the UK Policy Framework for Health and Social Care Research and the Data Protection Act (or its subsequent legislation) and made available for inspection, monitoring or audit purposes by the Sponsor, host, regulatory authorities or the funder. All electronic data will be stored in secure network drives, to which only the relevant study staff have access. All study documents and data will be kept for 15 years or the minimum determined by the regulatory authorities, whichever is the longer.

### Data confidentiality

Each participant will be assigned a unique identification number upon recruitment. Participant's contact details will be held on database separate to the study visit data and used to arrange data collection visits. The database will be password protected and only researchers collecting data will have access. All data collected during the study will be stored anonymously on a separate database. Again access will be password protected and restricted to relevant members of the research team. Paper copies of the CRFs and questionnaires will be stored in a locked filing cabinet in the relevant research office. The study research team will comply with the Data Protection Policy of the University of Leicester and local NHS Trusts.

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |

| | | | |
|---|---|---|---|
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2, 16 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | N/A |
| Protocol version | #3 | Date and version identifier | 16 |
| Funding | #4 | Sources and types of financial, material, and other support | 18 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 1, 17 |
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 16 |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 18 |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and | 16 |

| | | | |
|---|---|---|---|
| | | other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4-6 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 5, 6 |
| Objectives | #7 | Specific objectives or hypotheses | 6, 7 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 7, 8 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites | 10 |

| | | | |
|---|---|---|---|
| | | can be obtained | |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 10 (Box 1) |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8, 9 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | 9 (Appendix 2) |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 11, 12 |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10 (Box 1), 11, 12 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 9 ,10 (Appendix 1) |

| | | | |
|---|---|---|---|
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 10-12, (Figure 2 and Appendix 3) |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 13 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 10 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 7 |
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to | 7 |

| | | | |
|---|---|---|---|
| | | conceal the sequence until interventions are assigned | |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 7, 11 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 10, 11 (Appendix 3), 12, 13 (Appendix 6) |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be | 10 (Appendix 1), 9 |

| | | | |
|---|---|---|---|
| | | collected for participants who discontinue or deviate from intervention protocols | (Appendix 2), 13 (Appendix 6) |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13 (Appendix 6) |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 13-15 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 13-15 |
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 13, 14 |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further | 16 |

| | | | |
|---|---|---|---|
| | | details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 16 |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 12 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 13 (Appendix 6) |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 15, 16 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | 16 |

| | | | |
|---|---|---|---|
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 10 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 10 |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 13 (Appendix 6) |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 18, 19 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 13 (Appendix 6), 16 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 11, 12 |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication | 17 |

| | | | |
|---|---|---|---|
| | | restrictions | |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 17 |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | 10 (Appendix 4) |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N/A |