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

STRIVE STUDY

Sponsor Reference No:	UNOLE 0626
Ethics Ref:	17 NW 0517
EudraCT Number:	2017-002998-20
Universal Trial Number (UTN):	U1111-1189-5726
Date and Version No:	**Version 7.0; 29/01/2021**

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Funder: Novo Nordisk

Safety Monitor: University of Leicester

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential. No part of it may be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities and members of the Research Ethics Committee, by any Receiving Party to

any Third Party, at any time, or in any form without the express written permission from the Chief Investigator and/or Sponsor.

SIGNATURES

PROTOCOL: Effectiveness and cost of integrating a protocol with use of Liraglutide 3.0mg into an obesity service (STRIVE Study)
VERSION: Version 7.0;29/01/2021

By my signature below, I confirm that I have read this protocol and its attachments, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH Guidelines on good clinical practices and the applicable local laws and regulations. I will accept a monitor for the Sponsor overseeing the study. I will abide by the publication plan set forth in my agreement with Novo Nordisk, including all statements regarding confidentiality.

Chief Investigator:_____
[Title/Name]

Name of Facility: _____
[Study Site]

Signed: _____ **Date:** _____

Principal Investigator: _____
[Title/Name]

Name of Facility: _____
[Study Site]

Signed: _____ **Date:** _____

Sponsor Representative: _____
[Title/Name]

Name of Organisation: _____

Signed: _____ **Date:** _____

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date Issued	Author(s) of Changes	Details of Changes Made
Initial	V2.0	03/08/17	Siân Hill Emer Brady	REC Favourable Opinion granted for this version of protocol
SA1-UK (SA2-IRE)	V3 (v6)	27/03/18	Sarah Edwards Emer Brady (Siân Hill)	Changes made to management of sleep apnoea patients and tests. Removal of lipase blood test and exclusion criteria. Addition of lipase for confirming a suspected case of acute pancreatitis where amylase levels are normal, change to GLP-1 exclusion. Transfer responsibility for Trial Management and associated activities from the LCTU to the LDC. To add the use of Participant Identification Centre's (PIC) where applicable for recruitment purposes. Recruitment period error corrected to 'up to 24months' and '4-6 patients/month' to reflect the study contract with funder and the current REC approved LPLV timeframes which have not altered. Clarification to table visit windows (weeks vs no's) and visualisation of the titration profile for Appendix 3. Additional information given in the key. Administrative changes for clarity and to correct errors that do not alter the study procedures.
SA2-UK	V4	08/06/18	Emer Brady Siân Hill	(REC approved SA1-UK v3; HPRA non-acceptance (not approved) is addresses in this SA2-UK v4) Same as above clarifying concerns raised by HPRA in non-acceptance of SA1-UK.
SA3-IRE	N/A	20/02/2019	Sarah Clarke	Change to add a legal representative in Ireland due to Brexit coming into force on 29th March 2019. Clinical trials legislation required that the sponsor or legal representative of the sponsor is established in the EU/EEA. Change of the legal representative for the Strive study from University of Leicester to the University College Dublin. Sponsor responsibilities will continue to reside with University of Leicester but the University College Dublin will act as the legal representative for the study in the EU/EEA.
SA3-UK (SA4-IRE)	V5-UK V7-IRE	07/01/2019	Sarah Clarke	Change to the visit schedule to allow for some visits to be classified as optional. For participants in both arms of the study visits held at 2/52 (visit 3), 4/52 (visit 4), 12/52 (visit 6), 20/52 (visit 8), 40/52 (visit 10) and 78/52 (visit 12/13) will be defined as 'optional' to reduce study burden and maximise participant retention, as per the visit schedule (see

				Protocol, Appendix 3); Remove wording included in error following previous amendment sleep study capture in schedule, and Secondary Outcomes (see Protocol, Appendix 3; and Section 7.3; Clarification of reference ranges for TSH in terms of eligibility in the protocol to be amended to reflect the different normal ranges labs at each site used. This was highlighted at a recent monitoring visit where the 'normal' range stated in the protocol was different to that used in routine clinical assessment at site due the variable of local pathology laboratory reference ranges (see Protocol, Section 7.3); Update the exclusion criteria clarifying the time scale since weight loss procedures/surgery and the scope to allow for removal of gastric bands and gastric balloon whilst still be eligible for the study (see Protocol, Section 7.3). The consent form has been modified to include an extra question (question 3) surrounding lost to follow up and non attendance. This has been added as optional with yes or no boxes. Questions 8 and 10 have also been changed to optional yes or no boxes. Update to the current SmPC. Version 12/2016 will be replaced by version 06/2018.
NSA02 (UK only) IRE added as part of below SA5-IRE	UK 5.1	26/03/2020	Sarah Clarke	This was to update the recruitment target, which was increased from 384 to 392 and to update the recruitment end date which was amended from 31/12/2019 to 29/02/2020.
SA4-UK (SA5-IRE)	UK V6.0 IRE V8.0	19/05/2020	Sarah Clarke	As a result of the COVID19 global pandemic a risk assessment was conducted and an urgent safety measure was sent to the MHRA. The study team made several changes to the management and running of the trial due to the risks associated with face to face visits during the pandemic, in summary these include: provision of scales for participants to weigh themselves at home, adapted study drug deliveries/returns procedures, and virtual consultations via phone or video call. During this period the BP/HR measurements for those participants who do not have a home monitor and blood sampling for V11 and V13 visits will

				not be conducted. Addition of monetary incentive for all participants to aid retention, as suggested by the data monitoring safety committee (DMSC) and the trial steering committee (TSC). Extended the visit window for V11 primary end-point to support data collection; from+/- 14 days to +/- 3 months. QoL questionnaires to be issued to participants at an interim time point during the COVID19 pandemic. The study end date and recruitment target was amended in March 2020 as an NSA for all UK sites. Dublin site (IRE) requested that this be submitted as a substantial amendment so this has been added for IRE as part of this amendment (detailed in the IRE protocol).
SA5-UK (SA6-IRE)	V7.0 V9.0	29/01/2021	Sarah Clarke	Update to the current SmPC. Version 5.0 will be replaced by version 10.0. The study end date has been updated from 30/04/2022 to 30/06/2022. Update to the details around COVID-19 in section 8.10.

2. PROTOCOL SYNOPSIS

Study Title	**Effectiveness and cost of integrating a protocol with use of Liraglutide 3.0mg into an obesity service (STRIVE Study)**
Clinical Phase	Phase IV
Study Setting	The study will be co-ordinated by the appointed research team based at the Leicester Diabetes Centre (LDC). The Leicester Clinical Trials Unit (LCTU) will provide statistical input, and database management for this study. The study will include 5 sites in the UK and Ireland (Leicester, London, Liverpool, Glasgow, and Dublin (to include selected PIC's)).
Trial Design	A 26 month, parallel, two group, open-label, real-world randomised controlled trial (RCT) design for subjects with severe and complex obesity who are referred to a Tier 3 or equivalent specialist weight management/obesity service. Participants will be randomised to receive 1) standard care (obesity-specialist care), or 2) targeted prescribing pathway (obesity-specialist care plus targeted use of Liraglutide 3.0mg [LIRA 3mg] with pre-specified stopping rules for the medication). The aim of the study is to compare the effectiveness, budget impact, and cost-effectiveness between the two groups in a real-world setting among otherwise largely unselected patients.
Trial Participants	Eligibility criteria: • Body mass index ≥35 kg/m^2 • Referred to Tier 3 weight management or equivalent service • Stable body weight (less than 5 kg self-reported change during the previous 12 weeks) • Aged between 18-75 years old (inclusive) • Diagnosed with at least one or more obesity-related co-morbidity (i.e. at least one of prediabetes, diabetes, hypertension, or obstructive sleep apnoea) • Able to understand written and spoken English • Able to give informed consent
Planned Sample Size	392 participants in total (131 in standard care; 261 in targeted prescribing pathway). This sample size allows for a 25% drop-out rate and will have 80% power to detect an absolute difference of 11% between the two groups (based on 5% of the participants achieving ≥15% weight loss in the standard care group and 16% of the participants achieving ≥15% weight loss in the targeted prescribing pathway group).
Follow-up duration	Up to 24 months (104 weeks)
Primary Outcome	Binary outcome indicating whether weight loss of ≥15% was achieved at 52 weeks
Secondary Outcomes	Compare the targeted prescribing pathway and standard care groups in terms of: 1. Improving obesity-related co-morbidities (obstructive sleep apnoea, prediabetes, diabetes, hypertension, dyslipidaemia, depression) 2. Referral rates to other obesity interventions 3. Long-term maintenance (defined as the proportion of patients maintaining ≥15% weight loss at 104 weeks among those who achieved ≥15% weight loss at 52 weeks)

	4. Budget impact on a Tier 3 weight-management service 5. Long-term cost-effectiveness 6. Direct healthcare costs in terms of admissions, frequency, and cost of appointments 7. Safety-related outcomes 8. Adherence 9. Patient satisfaction
Investigational Medicinal Products	Liraglutide (Saxenda) 6 mg/mL solution for injection in pre-filled pen, which will be administered by subcutaneous injection. This product forms part of the targeted prescribing pathway in the treatment group.
Dose	Dose escalation from 0.6 to 3.0 mg daily

3. ABBREVIATIONS

ACR: Albumin Creatinine Ratio
AE: Adverse Events
AHI: Apnoea Hypopnoea Index
BMI: Body Mass Index
CRF: Case Report Form
CI: Chief Investigator
CPAP: Continuous Positive Airway Pressure machine
COVID-19: Coronavirus – SARS-CoV-2
DSMC: Data Safety Monitoring Committee
eGFR: Estimated Glomerular Filtration Rate
EMA: European Medicines Agency
EQ-5D: European Quality of Life -5 Dimensions
FBC: Full Blood Count
FDA: Food and Drug Administration
ICH GCP: International Conference on Harmonisation Good clinical practice
GP: General Practitioner
HbA1c: Glycated Haemoglobin
HSRUQ: Health Services and Resources Use Questionnaire
HCP: Health Care Professional
IPAQ-Long: International Physical Activity Questionnaire
ITT: Intention to treat
IWQOL –Lite: Impact of Weight on Quality of Life – Lite
LCTU: Leicester Clinical Trials Unit
LDC: Leicester Diabetes Centre
LFT: Liver Function Test
LIRA 3mg: Liraglutide 3.0 mg (Saxenda)
MDT: Multidisciplinary Team
PCOS: Polycystic Ovarian Syndrome
PHQ-9: Patient Health Questionnaire-9
PI: Principal Investigator
PP: Per Protocol
QoL: Quality of Life
REC: Research Ethics Committee
SAE: Serious Adverse Event
SAR: Serious Adverse Reaction
BP: Blood Pressure
RCT: Randomised Controlled Trial
SOP: Standard Operating Procedure
SUSAR: Serious Unexpected Suspected Adverse Reaction
TFT: Thyroid Function Test
TSC: Trial Steering Committee
TSQM: Treatment Satisfaction Questionnaire for Medication
T2DM: Type 2 Diabetes Mellitus
U+Es: Urea, creatinine and Electrolytes
UAR: Unexpected Adverse Reaction
WL: Weight Loss

4. BACKGROUND AND RATIONALE

'Severe and complicated obesity' (previously referred to as 'morbid obesity') is a substantial health problem that is defined as a body mass index (BMI) ≥35kg/m^2 with at least one major obesity-related comorbidity. In England, the proportion of adults with severe and complicated obesity has risen alarmingly over the last two decades [1]. Approximately 10% of the adult population in England now has a BMI ≥35kg/m^2 [2]. In this group, 8-16% have type 2 diabetes mellitus (T2DM), imposing colossal direct and indirect healthcare costs [2, 3].

In the United Kingdom, standard care for patients with severe and complicated obesity is currently variable, but generally includes referral to a 'Tier 3' or specialist weight management service, which comprises a multi-disciplinary team of experts, including psychological support. Depending on the centre, this team uses a combination strategy of optimal diet and lifestyle advice, meal replacements, and pharmacological therapies to facilitate weight loss. According to current guidelines, individuals with severe and complicated obesity qualify for bariatric surgery, which is one of the treatment options also available in a Tier 3 specialist weight management service [4]. However, the majority of patients prefer not to have surgical interventions for their obesity, but are unable to achieve adequate long term weight loss with currently available non-surgical options.

Liraglutide 3.0 mg (LIRA 3mg) has been recently approved for the treatment of obesity by the European Medicines Agency (EMA) and Food and Drug Administration (FDA), as evidence from large randomised controlled trials (RCTs) has demonstrated that it is a safe and effective treatment option for obesity in diverse patient groups [5-7].

The majority of the trials involving LIRA 3mg have been placebo controlled, have included patients with BMI as low as 27 kg/m^2, and have all continued LIRA 3mg treatment from the start of treatment for up to 3 years, irrespective of individual effectiveness, even for patients who fail to lose any weight [5-7]. Best clinical practice would suggest that patients who fail to lose weight should not be continued on treatment because they are exposed to increased risk of adverse effects without significant benefit in terms of weight loss. Moreover, being randomised, with the uncertainty as to whether an active agent is being given, is a disincentive to compliance with diet and exercise advice for some patients. Effect sizes may be affected by the strict protocols of an RCT and these data may not be optimal for health economic analyses as real-world applicability and generalisability of RCTs are limited. Nonetheless, within the populations studied, LIRA 3mg resulted in ≥15% weight loss in 14% of patients, compared with 3.5% of patients with placebo [5], a reduction which is likely to generate major health benefits and long-term cost-savings, especially if weight loss can be maintained [7]. Among obese patients with T2DM, weight loss is less, but the potential cost-savings are greater [6].

Post-hoc analysis of the SCALE Obesity trial comparing "early responders" (lost ≥5% of their starting weight after 16 weeks of LIRA 3mg treatment) with "early non-responders" (lost <5% of their starting weight after 16 weeks of LIRA 3mg treatment) found that 24.2% of early responders had lost ≥15% of their bodyweight at 56 weeks compared with 1.8% of early non-responders [8]. A different model for the use of LIRA 3mg has been suggested by the SCALE Maintenance study which required a substantial weight loss (≥5% of the baseline weight) with lifestyle changes (including meal replacement strategies) during a period of 12 weeks prior to commencing the drug. The study resulted in 26% of patients achieving ≥15% weight loss one year after treatment with LIRA 3mg compared with 6% of patients on placebo [7]. Overall, these results suggest that the patients who are more likely to achieve clinically significant long-term weight loss with LIRA 3mg are those who achieve ≥5% weight loss during the first 12-16 weeks either with lifestyle changes or with LIRA 3mg treatment.

As outlined above, it would be unethical to prescribe LIRA 3mg to all patients with severe and complicated obesity because the risk of adverse events would be increased without any likely benefit to the patient. Moreover, the cost of LIRA 3mg is likely to preclude routine use for the full range of patients included in clinical trials, or for all patients who currently present for treatment in 'Tier 3' obesity services in the UK. Conversely, there is strong evidence that LIRA 3mg can lead to substantial weight reduction in some patients with severe and complicated obesity, thus it is imperative that this treatment is available to those who would benefit from it. We therefore propose testing a targeted prescribing pathway that would provide a pragmatic means by which to optimise the use of LIRA 3mg in a specialist obesity service.

The targeted prescribing pathway directs the use of LIRA 3mg to patients likely to be "good" responders and aims to optimise health economic outcomes by initially starting all patients (in the targeted prescribing pathway group) on LIRA 3mg and then applying pre-specified rules for stopping LIRA 3mg at different time points for patients who do not achieve substantial weight loss. As part of the targeted prescribing pathway, patients who stop receiving LIRA 3mg would still receive standard care from the specialist-obesity service. The implementation of stopping rules for LIRA 3mg is expected to optimise the use of this medication and decrease the exposure and potential adverse side effects in non-responders. It is also expected that the cost-effectiveness and the budget impact would be improved by only treating patients with LIRA 3mg if they are "early and good" responders, whilst continuing to treat the remaining patients in the targeted pathway as per standard care.

The study will be an open label, randomised controlled trial of standard care (i.e. the care usually provided by the relevant Tier 3 or specialist weight management service) versus the targeted prescribing pathway (i.e. standard care plus LIRA 3mg with pre-specified stopping rules). The aims of this study are to:

a) compare effectiveness between the two groups, by comparing the proportion of participants achieving weight loss of ≥15% at 52 weeks after randomisation
b) compare long-term maintenance between the two groups, by comparing the proportion of participants maintaining weight loss of ≥15% at 104 weeks among those who achieved ≥15% weight loss at 52 weeks
c) evaluate the budget impact and cost-effectiveness of the targeted prescribing pathway over the 104 weeks of the study.

5. OBJECTIVES

5.1 Primary Objectives

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

5.2 Secondary Objectives

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

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

6. STUDY DESIGN

6.1 Summary of Trial Design

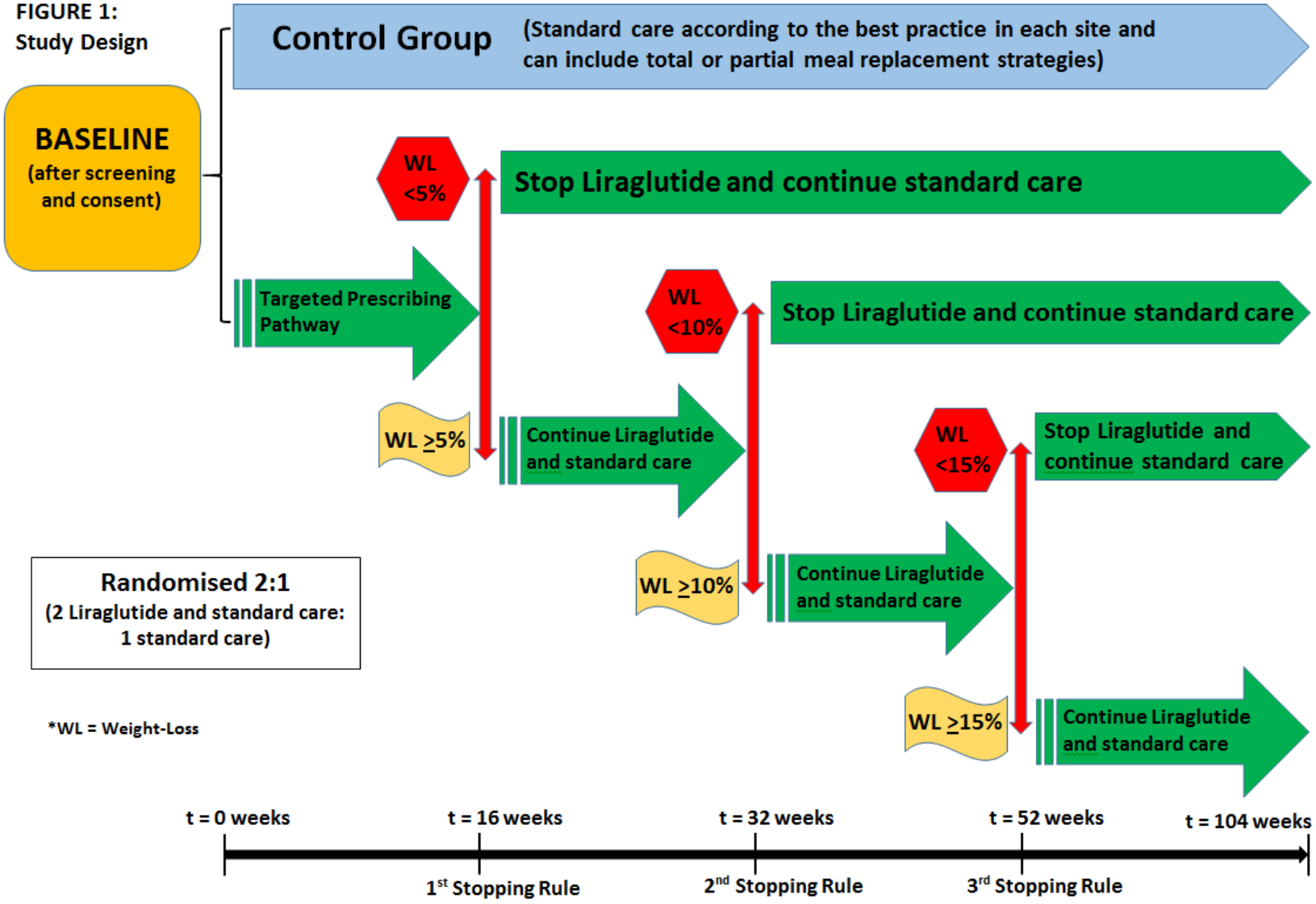
A 26 month, parallel, two group, open-label, real-world, RCT design for patients with severe and complex obesity who are referred to a Tier 3 obesity service (including patients who are referred to a Tier 3 service as part of the bariatric surgery pathway). The total duration of participation will be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

The first 52 weeks of the study (after randomisation) will determine whether using the targeted prescribing pathway in a Tier 3 setting will result in more participants attaining ≥15% weight loss compared with standard care. The 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 compared with standard care. Further, budget impact, cost-effectiveness, improvement in obesity-related co-morbidities, complementary aspects of safety, effectiveness, adherence, and treatment satisfaction of both treatment groups will be assessed and compared (see Section 6.4.2).

Participants will be randomised in a 2:1 fashion to either the intervention (targeted prescribing pathway + standard care) or control (standard care) group (2 intervention: 1 control). The control group will receive standard care in a specialist obesity service (Tier 3 or equivalent), according to the best practice in each site and can include total or partial meal replacement strategies. The intervention group will receive the same standard care as the control group (i.e. according to the best practice in each site) plus all participants will initially receive LIRA with pre-specified stopping rules. The targeted prescribing pathway is described in detail (including descriptions on stopping rules) below in Section 6.2 (see also Figure 1), but in brief, participants who do not meet the definition of a 'early and good responder' (defined as achieving ≥5% weight loss at 16 weeks, ≥10% weight loss at 32 weeks and ≥15% weight loss at 52 weeks) will have their LIRA 3mg treatment stopped. It is important to note that all participants will be analysed in the group to which they are randomised; in particular, participants in the intervention group who stop receiving LIRA 3mg will remain in the intervention group and will continue to receive standard care for the remainder of the study as per the targeted prescribing pathway (albeit, the part of the pathway where LIRA 3mg is not prescribed; see Figure 1).

The study is intentionally designed to reflect a pragmatic "real-world" scenario and each Tier 3 provider may require a different number of visits for their programme. However, study appointments for data collection, titration reviews, application of the stopping rules of LIRA 3mg, and dispensing will be standardised for all of the five sites (see Appendix 3 for outcome measures table).Should the study team be unable to contact a participant to invite them to attend study visits (lost to follow up) or for any reason a participant has had to miss a study visit (non attendance), the study team will ask that we are able to access data from existing hospital, GP or health records, where study visit data may exist in lieu of attendance at these study visits. Participants will be given the option to opt in or out of this on the consent form.

FIGURE 1:
Study Design



6.2 Intervention (Targeted Prescribing Pathway)

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

Tier 1: health promotion
Tier 2: lifestyle interventions
Tier 3: specialist multidisciplinary weight management services
Tier 4: bariatric surgery

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

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

1st stopping rule:
After 16 weeks (± 14 days) on the medication, only those participants who have lost ≥5% of their baseline weight will be offered further treatment with LIRA 3mg for another 16 weeks. Participants who have not met this weight loss target will have their LIRA 3mg treatment stopped but will still continue in the targeted prescribing pathway but will receive standard care only during the remainder of the study.

2nd stopping rule:
After 32 weeks (± 14 days) on the medication, only those participants who have lost ≥10% of their baseline weight and are still on treatment with LIRA 3mg will be offered another 20 weeks on LIRA 3mg. Participants who have not met this weight loss target will have their LIRA 3mg treatment stopped but will still continue in the targeted prescribing pathway but will receive standard care only during the remainder of the study.

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

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

Participants who fail to reach the pre-defined weight-loss targets to continue LIRA 3mg treatment, or who choose to stop receiving LIRA 3mg, will continue to be offered the standard care provided by the Tier 3 service. These participants will still attend the Clinical Review Visits but not the additional visits for participants who are still on LIRA 3mg (e.g. Weeks 65 & 91) because these visits will not be relevant to them; visits at Weeks 65 and 91 are intended to provide a new prescription of LIRA 3mg and to discuss adherence and any side effects; see Appendices 2 & 3).

Participants will remain routinely in the Tier 3 service in-line with NICE guidance throughout the duration of the research study. Participants may be offered treatment options within the duration of the study, including bariatric surgery, as per NICE guidance and according to the decision of the local Tier 3 Multidisciplinary Team. Participants who have undergone bariatric surgery after randomisation will only be included in the intention to treat (ITT) analysis. This decision was made because the proportion of participants undergoing bariatric surgery is likely to be unbalanced between the treatment groups (i.e. more participants in the control group are expected to have bariatric surgery than in the targeted prescribing pathway treatment group), and thus weight loss in these individuals could unduly influence the study results. Participants who have been prescribed and start anti-obesity medication (such as Orlistat) will be ineligible for LIRA 3mg treatment.

6.3 Control (Standard Care)

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

6.4 Primary and Secondary Outcomes

6.4.1 Primary Outcome

The primary objective will be to compare the proportion of participants with severe and complicated obesity (defined as BMI ≥35 kg/m2 with at least one major obesity-related comorbidity) achieving weight loss ≥15% at 1 year (52 weeks) with a targeted prescribing pathway (i.e. use of LIRA 3mg according to a pre-specified protocol in combination with standard care provided in Tier 3 services) versus standard care provided in Tier 3 services alone.

6.4.2 Secondary Outcomes

Unless stated, 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 (Obstructive Sleep Apnoea)

- Epworth Sleepiness Scale 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 compliance (hrs/day)
- 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 (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 (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 Tier 3 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 Tier 3 programme
- Cost of visits to dietician during Tier 3 programme
- Cost of visits to psychologist during Tier 3 programme
- Cost of exercise physiologist/physiotherapist during Tier 3 programme (if applicable)
- Cost of Multidisciplinary Team (MDT) discussion in Tier 3 service
- Cost of blood tests in Tier 3 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

(See Section 10.4 for definitions of hypoglycaemia)

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 Tier 3 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 Tier 3 service programme despite stopping LIRA 3mg at 16 weeks
- The number of participants who completed the 52 weeks of Tier 3 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)

Table 1: Variables collected in this study and whether these measurements are routinely collected as part of the Tier 3 service or whether they will be additional as part of this study.

Measurement	Outcomes	Standard Care	Research
Body weight	-% Change (absolute change, relative change, proportion of participants reaching weight loss of ≥5%, ≥10% and ≥15% [primary outcome], proportion of participants maintaining weight loss)	X X	
Height		X	
Waist circumference		X	
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	X X	
Heart rate		X	
Blood sample	-HbA1c -Lipid profile (including LDL & HDL cholesterol & triglycerides) -Renal profile (including U&E's, creatinine, eGFR) -Liver function test (LFTs) (including ALT, ALP, Bilirubin, Albumin) -Thyroid function test (TFTs) (including Free Thyroxine, Thyroid Stimulating hormone) -Haematology profile (including full blood count) -Amylase	X X X X X X X	 X
Urine sample	-ACR -Pregnancy testing		X X
Sleep apnoea	-Epworth Sleepiness Scale - Stop Bang Questionnaire -CPAP pressures (proportion of participants on CPAP, AHI figures) -Sleep study (home based ambulatory sleep monitor)	 X	X X
Monitoring of adherence & compliance	-To Tier 3 programme -With the LIRA 3mg (returned used pens)	X	 X
Questionnaires (Health status and obesity related co-morbidities)	-King's College Obesity Staging System -Health Service and Resources Use Questionnaire (HSRUQ) -Treatment Satisfaction Questionnaire for Medication (TSQM) -EuroQol Five Dimensions Questionnaire (EQ5D) -Impact of Weight on Quality of Life-Lite (IWQOL-Lite) -International physical activity questionnaire (IPAQ-Long) -Patient Health Questionnaire-9 (PHQ9)		X X X X X X X

Resource use	-Frequency of contact with GP and HCP		X
	-Frequency of hospital admissions		X
	-Number of outpatient appointments		X
	-Medication use and costs		X
	-Estimation of direct healthcare costs and budget impact		X
	-Referrals to Tier 4		X
Safety/adverse events	-Gastrointestinal symptoms		X
	-Hypoglycaemic events		X
	-Hypertensive events		X

7. TRIAL PARTICIPANTS

7.1 Participant Identification and Recruitment

There will be a standard approach to identifying and recruiting eligible participants who have agreed to participate in the Tier 3 service. Patients will be identified and approached by their usual clinical care team. Five sites in different geographical areas, which are culturally and racially diverse, will be used to reflect Tier 3 service range across UK and Ireland. Each site will plan to recruit up to 77 subjects over the recruitment period (up to 24 months or ~~(~~equivalent to 4-6 patients per month. The study will also make use of Participant Identification Centres (PICs) within these five Tier 3 sites where applicable. For context, data from a local Tier 3 service (Leicester) showed that at least 90 individuals who have been referred to the service in 2014 would potentially be eligible for this study (BMI ≥35 kg/m^2 and diabetes or impaired glucose tolerance, hypertension or obstructive sleep apnoea). Further details on recruitment are given in Section 8.1.

7.2 Inclusion Criteria

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

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

7.3 Exclusion Criteria

Patients who have met any of the following criteria will be excluded from the study:

- Diagnosis of Type 1 diabetes
- T2DM on treatment with DPP-IV or insulin currently

- Treatment with 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 (as described in Section 8.3.1
- 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, as defined by local sites pathology laboratory reference ranges as outside the normal range; mIU/litre (see local site laboratory reference ranges)
- 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 <1 year before trial entry weight loss procedures/surgery including removal of a gastric band and/or gastric balloon
- 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.

8. STUDY PROCEDURES

8.1 Invitation of Eligible Patients

Eligible patients will be mailed a brief invitation leaflet before they attend an appointment at their Tier 3 service or will be given the information leaflet during their appointment in the Tier 3 service by a member of the research team at the study site. Patients who are interested in participating in the study will return a completed reply slip to the study team indicating their interest. The study team will then contact the patient to provide further information, a full Participant Information Leaflet, and to invite them to attend a screening appointment. The patient will receive a letter confirming the details of the appointment. They will have at least 24 hours to consider participation before this appointment.

Awareness and interest in the study will be generated through primary and secondary care services, as well as other local community services (such as but not limited to pharmacies and libraries) using leaflets, posters and marketing. We will also utilise electronic and digital marketing via websites including social media such as Facebook and Twitter, as well as promotional campaigns via local/national media (e.g. in print, radio) where applicable.

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

The Screening and Consent Visit (Visit 1) is performed at least one day and up to 42 days prior to the Baseline Visit, depending upon the case record information relating to eligibility criteria (e.g. blood pressure measurement, renal function, thyroid function and sleep study [home based ambulatory sleep monitor] if specified).

Patients will attend an appointment with a healthcare professional at the study site. The healthcare professional will check their eligibility to participate, explain in detail what the study involves and answer any questions they may have. Full written informed consent to participate will then be obtained. The person obtaining informed consent will be a suitably trained and competent healthcare professional who, in the opinion of the PI of each site, is able to give a full, unbiased explanation of the study (including benefits and risks) to the potential participant. The person obtaining consent will also have been named in the delegation log of staff as undertaking this duty and approved as study personnel by the relevant governance procedures.

Each participant will also have a copy of the consent form and patient information leaflet; a copy will be placed in their hospital medical records and the original copy held in the site master file. This will also include explicit notice of their in-study medication and a standard label will be used on the front of the medical notes to highlight to any reviewer that this individual is taking part in the study and any issue regarding contra-indication of a procedure or medication outside of the study should be discussed with a study clinician. The standard label template is provided by the local Trust and should contain the following information;

PATIENT TAKING PART IN A CLINICAL TRIAL
Study Name. . . . . .
Patient ID No. . . . . .
Investigator: . . . . . .
Telephone: . . . . . .
Date Consent Form Signed . . . . . .
TRIAL START _ _/_ _/_ _ _ _ **TRIAL FINISH** _ _/_ _/_ _ _ _
Don't destroy the records before (*date*) _ _/ _ _/ _ _ _ _

After consent has been obtained, a member of the research team will record participant demographics, medical/surgical history and perform measurement of anthropometrics (height, weight, waist circumference, blood pressure and pulse rate) for all the patients in line with study Standard Operating Procedures (SOPs) and arrange for standard laboratory testing (HbA1c, FBC, U+Es, lipids, LFTs, TFTs) and pregnancy test (for females of childbearing potential). A urine ACR will be performed for patients with prediabetes, diabetes and hypertension. The King's College Obesity Staging assessment will be recorded in the CRF if it is available in the patient's notes. A Stop Bang questionnaire will be undertaken (to capture any undetected OSA cases) and an Epworth Sleepiness Scale (to capture daytime sleepiness) will be undertaken by all participants. Participants with undetected (OSA) defined as a score between 5-8 on the Stop Bang, will be informed that they are at high risk of this sleep disorder and a referral to the sleep clinic from the local PI will be made so that the participant can be considered for investigation. All sleep related therapy will then be the responsibility of the local sleep clinic as per standard practice.
Those participants that are already patients of the sleep clinic will have their notes reviewed to determine whether or not they are CPAP compliant and thus 'successful' against the below criteria.

a. CPAP usage >= 4 hrs/night = successful
b. CPAP usage < 4 hrs/night = struggling
c. CPAP usage < = 1 hrs/night = failure

A repeat screening visit may take place if indicated for eligibility (for example, repeat blood pressure measurement for patients with undiagnosed hypertension). The study clinician will assess and decide when all the blood results and investigations are available whether a patient is eligible for randomisation or not.

8.3 Data Collection Visits (Baseline, Weeks 52 and 104)

Eligibility criteria for each participant will be re-checked at every visit.

8.3.1 Baseline Visit (Day 0) – All Participants

Only those patients who are eligible based on the data collected at the Screening and Consent Visit will proceed to the Baseline Visit (Day 0). Weight, waist circumference, blood pressure and pulse rate will be recorded for all the patients in line with study SOPs. The patient will also complete questionnaires to provide demographic and medical history details and additional data will be collected as indicated in Appendix 3 (e.g. self-reported physical activity using the International Physical Activity Questionnaire). Serious Adverse Event (SAE) and Adverse Event (AE) recording and documentation of changes in medication or diseases will be performed. Randomisation will be

performed and participants will be informed of their group allocation (see Randomisation Section 8.3.1.1 below). Participants in both groups (standard care [control group] vs. standard care + LIRA 3mg [targeted prescribing pathway]) will be counselled about the study visits and what they can realistically expect with each treatment option. Participants allocated to the targeted prescribing pathway will receive injection training, storage and dispensing. All participants will be informed that they may contact their GP or the study team at any time.

Urine pregnancy tests will be performed for females of childbearing potential. Additional testing will also occur at any time during the trial if a menstrual period is missed or as required by local law. The test will be performed at the study site. Pregnancy testing will not be required for women who have undergone a hysterectomy or bilateral tubal ligation, or for women above the age of 50 years old, who have been without menses for at least 1 year. Participants will be given clear instructions regarding contraception throughout the study. Adequate contraceptive measures have been defined as sterilisation, intra-uterine device, oral contraceptives, consistent use of barrier methods, male sterilisation or true abstinence (when this is in line with the preferred and usual lifestyle of the participant) (www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf – accessed 21/07/2017.

8.3.1.1 Randomisation

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

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

or

2) Control Group - No additional treatment.

A 2:1 ratio will be used so that a sufficient number of responders will be available for responder analyses (see Section 11). Randomisation will be stratified by centre and BMI ($\geq$45kg/m^2; <45kg/m^2). Participants will be informed of their randomisation assignment during the Baseline Visit. A letter will be sent to the participant's GP notifying them of their patient's participation in the study. Both the participant and their GP will have the randomisation assignment confirmed by letter.

8.3.1.2 Titration Protocol

During the baseline visit, participants randomised to the targeted prescribing pathway group will be offered LIRA 3mg for the next 16 weeks and will be re-informed of the potential side effects of the medication. The research team will explain to participants in this group the titration protocol and the weight loss targets in order to continue receiving treatment with LIRA 3mg. All participants who will start on LIRA 3mg will be trained to self-administer the treatment injection once daily. Dose escalation of Liraglutide will occur according to a pre-specified titration protocol, from 0.6mg to a maximum of 3.0mg. Participants in the targeted prescribing pathway will continue to 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 Section 6.2 for stopping rules). Participants will be withdrawn from receiving LIRA 3mg if the doses are not tolerated during or following the titration period. Liraglutide dose will be initiated at 0.6mg and then steadily increased by the doses below. The up titration to maximum dose must be achieved by week 8.

- 0.6mg
- 1.2mg
- 1.8mg
- 2.4mg
- 3.0mg.

Participants in the Targeted Prescribing Pathway will undergo titration reviews fortnightly during weeks 0-8. During these visits, there will be the option for telephone calls between weeks 1-3 and weeks 3-5 available to research team and for participants to counsel them on titration requirements. The titration protocol will be explained to the participants during the baseline visit and reviewed by the clinician at weeks 3, 5 and 8.

8.3.2 Weeks 52 and 104 – All Participants

The Data Collection Visits at Weeks 52 (± 3 months*) and 104 (± 14 days) will take place at the study site for all participants in both study groups. Weight, waist circumference, blood pressure and pulse rate will be recorded in line with study SOPs, any AEs/SAEs will be noted, and documentation of inclusion/exclusion criteria and changes in medication and/or diseases will be performed. Blood samples for standard laboratory testing of biochemical outcomes (HbA1c, FBC, U+Es, lipids, LFTs, TFTs, amylase) will be taken and participants will be requested to complete research questionnaires (see Appendix 3). A pregnancy test will take place for all female participants of child-bearing potential (in both standard care and LIRA 3mg targeted prescribing pathway groups).

A urine ACR will be performed for participants with diabetes, prediabetes and hypertension.
All participants will complete the Epworth Sleepiness Scale to capture any improvement/decline in daytime sleepiness during the course of the study and the Stop Bang questionnaire to capture any undetected OSA cases, at 3 data collection visits (Baseline, Weeks 52 and 104). OSA patients will be managed through their local sleep clinic as per standard care. Those participants that are patients of the sleep clinic will have their notes reviewed to determine whether or not they are CPAP compliant and thus 'successful' against the below criteria.

a. CPAP usage >= 4 hrs/night = successful
b. CPAP usage < 4 hrs/night = struggling
c. CPAP usage < = 1 hrs/night = failure

Additional procedures at ***Weeks 52 and 104*** for the participants in the standard care group who have been prescribed and started anti-obesity medications (for example Orlistat) will be to ascertain whether they are still on the medication, their adherence, and any side effects.

Additional procedures at the ***Week 52*** visit for all participants who are on **LIRA 3mg** will include:

- Identification of participants on LIRA 3mg who have lost ≥15% weight loss and meet the pre-specified criteria to continue on LIRA 3mg. These participants will meet the study clinician in order to be offered LIRA 3mg for another 52 weeks, to receive a new prescription of LIRA 3mg and to discuss adherence with the treatment and any side effects. Pregnancy testing will be undertaken as standard for this visit and clear instructions regarding contraception until the end of the study will be provided
- Participants on LIRA 3mg who did not reach the target of ≥15% weight loss will meet the study clinician who will explain to them that they cannot continue on the medication any longer and that they will instead continue in the study on the Tier 3 programme with standard care. These participants will remain in the intervention group (targeted prescribing pathway), but will not receive LIRA 3mg as per the pre-specified stopping rules.

The purpose of the long-term (52-104 weeks) follow-up is to examine whether LIRA 3mg will help the "early and good" responders to maintain weight loss ≥15% in comparison with the control group over a longer period of time. Additional procedures at the ***Week 104*** visit for all participants will include:

- The study clinician at each site will assess all the patients who participated in the study that have not been referred for bariatric surgery
- Participants who had significant weight regain during the second year in either treatment group will be discussed in Tier 3 MDT and may include a recommendation to their GP to refer them to Tier 4 service for bariatric surgery
- For participants who are on LIRA 3mg: the clinician will make a recommendation to the participant's GP as to whether or not they should continue on the medication long-term, pending the local prescribing guidelines. Please note: participants on LIRA 3mg targeted prescribing pathway will only receive study medication for a maximum of 106 weeks (4 weeks titration, 100 weeks at 3mg, +/-2 weeks visit window). For those participants that achieve more than 15% weight loss or a BMI <35kg/m^2 prior to the 104 weeks, treatment with LIRA 3mg will be continued unless the patient begins to experience side-effects.

In an attempt to aid retention for the primary end point (week 52 – V11) all participants will be offered an incentive payment of £25 that will be paid on completion of the week 52 (visit 11) and dependant on us having weight data for that visit.

In response to the COVID19 global pandemic an interim time point for the quality of life questionnaires has been added (HSRUQ, TSQM, EQ-5D, IWQOL-Lite, IPAQ-Long and PHQ-9). These will be sent out to all participants during the COVID19 pandemic.

*Where possible the week 52 visit should continue to be scheduled within the (± 14 days) study visit window, however to aid retention and to help maximise data collection for the study primary end point, the week 52 visit window can be extended to ± 3 months.

8.4 Clinical Review (safety and retention) Visits (Weeks 2, 4, 8, 12, 16, 20, 32, 40 and 78) – All Participants

The Clinical Review visits will take place with a member of the research team at the study site. Where appropriate, the Clinical Review visits will be arranged in conjunction with the standard Tier 3 service appointments that participants will be scheduled to attend (e.g. appointments with the dietician). Additional study visits will be arranged in the event where this might not be possible. The participant appointment schedule will depend on the Tier 3 service schedule, the date of the required Clinical Review Visit, and the availability of participants. The participant's adherence to the Tier 3 programme will also be reviewed. The research team will endeavour to maintain a low level of burden for these multiple visits. For participants in both arms of the study visits held at 2/52 (visit 3), 4/52 (visit 4), 12/52 (visit 6), 20/52 (visit 8), 40/52 (visit 10) and 78/52 (visit 12 for LIRA arm/13 for control arm) will be defined as 'optional' to reduce study burden and maximise participant retention, as per the visit schedule. Our experience in undertaking successful longitudinal research with multiple follow-ups will support these follow-up visits. The frequency of appointments for the Tier 3 service offered to the participants in both groups will continue as per the standard practice for each Tier 3 service.

During these Clinical Review Visits, participant eligibility will be re-checked and consent for continuation in the study will be re-confirmed. Weight, waist circumference, blood pressure and pulse rate will be recorded in line with study SOPs, any AEs/SAEs will be noted, and documentation of inclusion/exclusion criteria and changes in medication and/or diseases will be performed.

For patients on LIRA 3mg, monitoring of any problems and side effects, adherence with the injection, and advice on dose titration (at Weeks 2 and 4) as per the pre-specified protocol will take place during these visits. A pregnancy test will take place for all female participants of child-bearing potential who are in the targeted prescribing pathway and continue to be eligible to receive supply of LIRA 3mg. Clear instructions regarding contraception until the end of the study will be given at each visit.

Additional procedures at the ***Week 16*** visit for all participants who are on **LIRA 3mg** will include:

- Identification of participants on LIRA 3mg who have lost ≥5% weight loss and meet the pre-specified criteria to continue on LIRA 3mg. These participants will meet the study clinician in order to be offered LIRA 3mg for another 16 weeks, to receive a new prescription of LIRA 3mg and to discuss adherence with the treatment and any side effects. Pregnancy testing will be undertaken as standard for this visit and clear instructions regarding contraception until the end of the study will be provided.
- Participants on LIRA 3mg who did not reach the target of ≥5% weight loss will meet the study clinician who will explain to them that they cannot continue on the medication any longer and that they will instead continue in the study on the Tier 3 programme with standard care. These participants will remain in the intervention group (targeted prescribing pathway), but will not receive LIRA 3mg as per the pre-specified stopping rules.

Additional procedures at the ***Week 32*** visit for all participants will include:

- Blood samples for standard laboratory testing of biochemical outcomes (HbA1c, FBC, U+Es, lipids, LFTs, TFTs, amylase) will be taken for all participants
- A urine ACR will be performed for participants with diabetes, prediabetes and hypertension for all participants
- Participants in the standard care group who have been prescribed and started on anti-obesity medications (for example Orlistat) will be monitored to ascertain whether they are still on the medication, their adherence, and any side effects
- Participants on LIRA 3mg who have lost ≥10% weight loss and meet the pre-specified criteria to continue on LIRA 3mg. These participants will meet the study clinician in order to be offered LIRA 3mg for another 24 weeks, to receive a new prescription of LIRA 3mg and to discuss adherence with the treatment and any side effects. Pregnancy testing will be undertaken as standard for this visit and clear instructions regarding contraception until the end of the study will be provided
- Participants on LIRA 3mg who did not reach the target of ≥10% weight loss will meet the study clinician who will explain to them that they cannot continue on the medication any longer and that they will instead continue in the study on the Tier 3 programme with standard care. These participants will remain in the intervention group (targeted prescribing pathway) for the purpose of analysis, but will not receive LIRA 3mg as per the pre-specified stopping rules.

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

These two additional Clinical Review visits will take place with a member of the research team at the study site for only those participants in the intervention group who are still on treatment with LIRA 3mg. The agenda for these visits will be identical to the other nine Clinical Review Visits as described above in Section 8.4. The purpose of these visits is to provide participants with a new prescription of LIRA 3mg and to discuss adherence with the treatment and any side effects.

8.5 Co-morbidity related investigations

For participants taking anti-hypertensive medication, it will be at the local Principal Investigator's (PIs) discretion to make recommendations on anti-hypertensive drugs and diuretic in response to participants' blood pressure and weight loss outcomes. Similarly, for participants taking anti-depressant medication, it will be at the local PIs discretion to make recommendations to alter the participants' anti-depressant medication if appropriate.

8.6 Source Data

The CRF and study questionnaires are the primary data collection instruments. All data requested on the CRF will be recorded. All missing data will be explained. If the item is not applicable to the individual case then N/A will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct the error, a single line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialled and dated. For clarification of illegible or uncertain entries, the clarification will be printed above the item and this will be initialled and dated.

A copy of the signed patient consent form and patient information leaflet will be placed in the hospital notes of all participants and in the Investigator Site File. A sticker will be placed on the cover of the notes (or inside cover) detailing the study title, contact details of the PI, participant ID and the fact that the notes should not be destroyed. All study visits and adverse events will be recorded in the hospital notes.

The PI and his/her staff must ensure that these documents are pseudonymised. Past medical history within the CRF required for inclusion in the study will be verified by participant hospital notes and/or GP medical history.

8.7 Definition of End of Trial

The end of the study is defined as the last participant's last visit.

8.8 Withdrawal of participants from the study and discontinuation of treatment

Certain circumstances will necessitate the stopping of any or all the study medication for a particular participant. Adverse event review and other safety/acceptability assessments will provide the information for the study clinician to withdraw the participant and/or discontinue the treatment drug at any time during the trial.

8.8.1 Withdrawal 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. If a participant decides to withdraw from the study, this will be recorded in the study records. They will be sent a letter thanking them for their participation, and informing them that the data collected up to the time point they withdrew will be included in the study analysis and that they will not be contacted again with regards to this study. They will not be asked to attend further visits. Furthermore, we will emphasise that their standard care will not be affected by their withdrawal from this study and that they will return to standard care.

Participants will be withdrawn from this study by the research team as agreed by the PI if:

- They are diagnosed with a terminal illness
- The PI, Sponsor and or study clinician deem it unsafe for continuation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations or Good Clinical Practice (GCP)
- They are considered to be lost to follow up as deemed by the clinician
- Loss of capacity during participation in research

- Treatment with medications which the PI determines to require permanent withdrawal from the study (e.g. systemic corticosteroids).

Again it will be emphasised that their standard care will not be affected by this withdrawal from the study and that they will return to standard care.

For participants who fail to return to the site, the research team should make reasonable effort to re-contact the participants (e.g., contacting participant's family or GP, reviewing available registries or health care databases) and to determine his/her health status, including at least his/her vital status. Attempts to contact such participants must be documented in the participant's records (e.g. times and dates of attempted telephone contact, receipt for sending a registered letter).

8.8.2 Treatment discontinuation (outside of the pre-specified stopping rules)

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).

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

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

Participants may withdraw from treatment with the investigational drug if they decide to do so, at any time and for any reason. The PI may also decide to withdraw a participant from the study based on an inability of the subject to adhere to the obligations of the study or for the safety of the participant. Items that will lead to permanent discontinuation in the study include:

- Pregnancy
- Episode of acute pancreatitis (only for participants in LIRA 3mg group)
- Breast malignancy (only for participants in LIRA 3mg group)
- They repeatedly violate or are non-compliant with the protocol
- Where LIRA 3mg doses are not tolerated by the participant
- Any other contraindication to the study medication which the PI determines to require permanent treatment discontinuation.

*Please note if a participant's amylase result is within the normal range but the study clinician suspects acute pancreatitis a lipase test will be conducted.

All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the CRF and medical records.

Any abnormal laboratory value that in the opinion of the clinician may be an indication for discontinuing the treatment of a participant will be rechecked by the PI or second clinician if the first clinician is the PI for confirmation before making a decision of permanent discontinuation of the investigational drug for the concerned participant. Threshold values for the discontinuation of investigational drug use shall be defined in collaboration with the Sponsor representative. The values will be adapted to the population studied, as appropriate.

8.8.4 Handling of participants after permanent treatment discontinuation

This study observes the effect of a targeted prescribing pathway (i.e. the use of LIRA 3mg when stopping rules are applied in combination with standard care in a Tier 3 service for patients with severe and complex obesity) compared with standard care alone. In case the GP or PI stops treatment or a participant withdraws from treatment with LIRA 3mg, e.g. for safety reasons, the participant will be offered standard care and the observation will continue.

If LIRA 3mg is stopped for other reasons not related to the applied stopping rules, it should be determined whether the stop can be made temporarily; permanent discontinuation of LIRA 3mg should be a last resort. Any discontinuation of the drug for reasons not related to the stopping rules should be fully documented in the CRF and medical records.

Participants must be instructed to notify the Investigator immediately if they become pregnant during the trial. Pregnancy will result in permanent treatment discontinuation (this will apply to both the LIRA 3mg and the standard care groups). The Investigator must report any pregnancy during the study to Novo Nordisk except for pregnancies occurring in the screening period prior to study treatment. Participants will give consent on enrolment that the Investigator will report any pregnancy during the study to Novo Nordisk and they will be asked to provide information about the pregnancy, delivery and the health of her infant until one month of age. Any AE in the child will be reported.

Participants will be followed according to the study procedures as specified in this protocol up to the scheduled date of study completion. If possible, and after the permanent discontinuation of investigational drug, the participants will be assessed using the procedure normally planned for the last onsite visit, if appropriate. All cases of permanent treatment discontinuation should be recorded by a member of the research team in the appropriate pages of the CRF and medical records when considered as confirmed. Study Sponsor is to be informed.

8.8.5 Handling of participants after temporary treatment discontinuation

Temporary discontinuation of LIRA 3mg may be considered by the PI because of suspected Adverse Events (AEs). A rationale (e.g. severe nausea and vomiting, other gastrointestinal symptoms) must be given in writing by the PI.

Re-initiation of treatment with LIRA 3mg may be done at a lower dose, under close and appropriate clinical/and or laboratory monitoring once the PI has considered, according to their best medical judgment, that the possible responsibility of the LIRA 3mg in the occurrence of the concerned event was unlikely and if the inclusion and exclusion criteria for the study are still met.

For all temporary treatment discontinuations, the duration of treatment discontinuation should be recorded by the research team when considered as confirmed.

8.9 Continued provision of the intervention for participants (if appropriate)

After the study, participants will be returned to the care of the weight management services where the local PI can make recommendations as to the continuation of the study treatment dependent on tolerance or side-effects (where applicable with regards to drug availability and local prescribing guidelines). Participants will be informed about the recommendation. For example, that they have been recommended to continue LIRA 3mg, but it will also be stressed that this will be down to the discretion of the GP and local prescribing guidelines.

8.10 Response to the COVID19 global pandemic (Urgent Safety Measure)

During the COVID19 global pandemic, a thorough risk assessment was conducted, and as a result the following appropriate adaptations have been made to the delivery of the study:

- Face to face study visits may be replaced with virtual consultations via telephone call or video call via the MyClinic application. Verbal consent will be sought from participants in advance of the video consultation (via MyClinic) and will be documented in the medical records. Face to face visits may continue at sites if this is in accordance with the local trust policy and appropriate risk mitigations are implemented at site to reduce the risk to participants. Risk and mitigations will be detailed in the risk assessment. During this period both face to face visits and virtual ones may be conducted in line with the USM adaptations detailed below.
- Participants due a V11 (study primary endpoint) are asked to weigh themselves at home on scales provided by the study team. A working instruction has been provided to participants to support them to record their weight in a standardised manner. During virtual consultations, the study nurse or doctor may witness the weight measurement process (following receipt of verbal consent from the participant). In the absence of consent from the participant, the participant will report the weight measurement verbally and follow this up with a photo of the weight value (source data). .
- A courier service has been arranged for study drug deliveries to participants; some sites are using a drop off/collection service either on site or to participant's homes. Participants on the Liraglutide arm will attend a virtual consultation and weigh themselves prior to additional study drug being dispensed.
- Participants in the Liraglutide arm who are of child bearing potential will receive a pregnancy test prior to their visit (to be used on the day of the visit) and the result reported either verbally to the study team during the video call or via a photo (source data) following a telephone call.
- The study quality of life questionnaire packs (HSRUQ, TSQM, EQ-5D, IWQOL-Lite, IPAQ-Long and PHQ-9) will be mailed to participants, where applicable, to be completed at home and returned to the study team via the postal system.

As a result of conducting virtual consultations and telephone calls, the following procedures will not be performed during the COVID19 pandemic, therefore have been halted as an urgent safety measure:

- BP and Pulse measurements – Participants who are known to have hypertension have home BP monitoring machines and their BP measurements are being collected and assessed by the study team during remote visits. There is no undue risk for those who do not have hypertension, as Liraglutide is not related to BP, and participants are all established on the drug.
- Bloods (lipids, renal, LFTs, thyroid, FBC & HbA1c, amylase) at V9, 11 & 13/15 only - The amylase test usually taken at visits 9, 11 & 15 is a safety blood in relation to pancreatitis. During the remote visits, all participants will be monitored for any new symptoms which will be appropriately managed by the study clinical team. The small number of participants who have diabetes will regularly check their blood glucose at home as usual. All other bloods are taken to assess efficacy, therefore not conducting them will have no impact on participant safety. All participants will be asked to report AE/SAE during remote visits.
- ACR urine test – Not conducting this poses no additional risk to participants.

Once restrictions due to the COVID19 pandemic have been lifted, a further risk assessment will be completed and in agreement with the Sponsor, Study team and NHS Host Organisations, face to face visits will be re-implemented. For the avoidance of doubt, virtual consultations will still be an option for study visits, as preferred by the participant or recommended by the study clinician, to aid the retention of participants and study visit attendance and collection of primary outcome data (via self-reported weight measurement data).

9. TREATMENT OF TRIAL PARTICIPANTS

9.1 Description of Study Treatment & Pharmacy Process

Novo Nordisk will be supplying the LIRA 3mg which will be handled according to their in-house protocols and standard operating procedures. Study drug will be managed in accordance with the requirements of all applicable regulatory guidelines.

LIRA 3mg will be provided to subjects as Saxenda® (manufacturer: Novo Nordisk).
Delivery is to be via a subcutaneous injection. LIRA 3mg has been licensed across the European Union via the EMA, for treatment of obesity for patients with and without diabetes (February 2015, Procedure No EMEA/H/C/003780/0000, Marketing ID: EU/1/15/992/001-003) and was launched within the UK in January 2017. Patients in the LIRA 3mg group (i.e., the targeted prescribing pathway/intervention group) will titrate the drug dose and will stop the medication according to the pre-specified protocol.

All study medication dosage will not exceed the stated recommendations of local guidelines and the British National Formulary. All contra-indications will be checked as part the eligibility criteria.

Study medication may be suspended or stopped by the study team if they become aware of the participant undergoing any contra-indicated procedure for out-of-study clinical care. This will be documented in the participant's study and medical notes and a decision on any potential withdrawal from the study on this basis will reside with the PI of each site. Recommencing of the study drug will follow individual safety assessments in-line with the procedure in question.

9.2 Dosage Information

Liraglutide doses will be self-administered by the participant through daily subcutaneous injections. Liraglutide dose will be initiated at 0.6 mg and then increased to 1.2mg in week two, 1.8mg in week three, 2.4mg in week four and 3.0mg in week five. The dose will then be maintained at 3.0mg. A slow escalation of the LIRA 3mg dose should help reduce the dropout of participants due to side effects. Where LIRA 3mg doses are not tolerated by the participant they will be withdrawn from the treatment condition.

9.3 Storage of Study Treatment

Study medication will be stored in a refrigerator at 2 – 8 ^{o}c. It will not be frozen. Participants in the LIRA 3mg treatment group will be instructed to store the drug away from the freezer compartment and to store below 30°C or store in a refrigerator (2°C - 8°C) after first use. They will also be instructed to keep the cap on the pen in order to protect from light.

The employment, dosing, handling, storage and destruction of LIRA 3mg will be conducted in accordance with the specified conditions of its approved labelling and in-line with pharmacy protocols and guidelines.

The Co-PI or delegated individual/personnel in each site or other personnel allowed to store and dispense the investigational medication will be responsible for ensuring that the investigational drug is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements. It is the co-PIs (or other delegated personnel's) responsibility to ensure that an accurate record of investigational medications issued will be maintained.

Any quality issue noticed with the receipt or use of an investigational medication (deficiency in appearance, pertaining documentation, labelling, expiration date) should be promptly reported to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of the investigational medication may be subject to initiation of a recall procedure by the Sponsor. In this case, the co-PIs will be responsible for promptly addressing any request made by the Sponsor, in order to recall investigational medication and eliminate potential hazards.

Under no circumstances will the PIs supply investigational medication to a third party, allow the investigational drug to be used other than as directed by this clinical study protocol, or dispose of investigational device(s) in any other manner other than that directed by pharmacy.

9.4 Compliance with Study Treatment

All participants in the study who have been prescribed LIRA 3mg should administer the drug daily. The participants will be instructed to return all unused, used or part-used medication/vials and packaging from used medication at each visit. Adherence questions will also be asked in follow-up visits for participants on LIRA 3mg. Examining medication returns and evaluating adherence will allow for an assessment of compliance and drug accountability. All participants should report all events which they believe may have impact on dose adjustment (such as nausea, vomiting). The Investigator may withdraw the participants if they consider dose compliance is unsatisfactory. Participants will be defined as treatment compliant if they take 70% of planned doses.

9.5 Accountability of the Study Treatment

The study medication will be supplied by Novo Nordisk to the host pharmacy. The employment, dosing, handling, storage and destruction of study medication will be conducted in accordance with the specified conditions of its approved labelling and in-line with local pharmacy guidelines.

Drug accountability will be the responsibility of the host pharmacy and will be fully documented.

The participant will be asked to bring all used, part-used and unused medication and used vials/packaging back to the clinic at each visit where it will be returned to pharmacy.

9.6 Concomitant Medication

Participants are allowed to continue the use of concomitant medication, which will be recorded in the CRF. However, consideration will be given also to reducing polypharmacy especially where participants have achieved significant weight loss and improvements in obesity related co-morbidities. If concomitant treatment has to be changed during the study period, this must be reported on the CRF provided (trade name and/or generic name) and in the participant's medical records. If any changes in glucose, lipid and blood pressure lowering therapy is required (e.g. due to disease progression or improvement) during the study, this must also be documented on the CRF. Addition of any medication that will significantly influence weight, such as corticosteroids is reason for discontinuation of the participant in the treatment.

10. SAFETY REPORTING

10.1 Definitions

The reference safety information (RSI) for this study will be the Summary of Product Characteristics (SmPC).

10.1.1 Adverse Event (AE)

An AE or adverse experience is:
Any untoward medical occurrence in a patient or clinical investigation participants administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the study medication).

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

10.1.2 Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose administered. The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

10.1.3 Severe Adverse Events (SAE)

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.4 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Is an AE, AR, or other untoward serious medical occurrence or effect that:

- Results in death,
- Is life-threatening*,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation**,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Is otherwise considered medically significant by the investigator****

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

**Hospitalisation is defined as an unplanned, overnight, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment, elective procedures (unless brought forward due to worsening symptoms) or for social reasons are not regarded as a SAE.

***Medical judgement should be exercised in deciding whether AE is serious in other situations. AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the SAE definition above, should be considered serious. Suspicion of transmission of infections agents must always be considered an SAE.

If a participant dies as the result of an SAE, any post-mortem findings including histopathology must be provided.

10.1.5 Suspected Unexpected Serious Adverse Reactions (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information Summary of Product Characteristics for LIRA 3mg (Saxenda).

Event Grade:

- Mild: Participant is aware of the event or symptom, but the event or symptom is easily tolerated.
- Moderate: Participant experiences sufficient discomfort to interfere with or reduce their usual level of activity.
- Severe: Significant impairment of functioning, participant is unable to carry out usual activities and/or the participant's life is at risk from the event.

After this initial evaluation the relationship of the AE to the study therapy/investigation medical therapy (IMP) will be assessed using the following definitions:

Definitely:

- The AE starts a reasonable time after the study therapy/IMP administration.
- The AE stops/ improves when the study therapy/IMP has been stopped.
- The AE can reasonably be explained by known characteristics of the study therapy/IMP.

Probably:

- A causal relationship is clinically/biologically highly plausible.
- There is a plausible time sequence between onset of the AE and administration of the study therapy/IMP.
- There is a reasonable response on withdrawal of the study therapy/IMP.
- It cannot be reasonably explained by known characteristics of the participant's clinical state.

Possibly:

- A causal relationship is clinically/biologically plausible.
- There is a plausible time sequence between onset of the AE and administration of the study therapy/IMP, however
- The AE could have been produced by the participant's clinical state or other modes of therapy administered to the patient.

Unlikely to be related:

- The time association or the participant's clinical state is such that the study therapy/IMP is not likely to have had an association with the observed effect.
- Another documented cause of the AE is most plausible.

Unrelated:

- The AE is definitely not associated with the study therapy administered.
- Another documented cause of the AE is most plausible.

10.2 Assessment periods

All Adverse events (AEs) will be recorded throughout the study whether serious or not. Members of the research team will ask the participants about AEs at each study time point (see Appendix 3) and will complete the participant AE form, which will be a continuous log so as to capture end dates, and the study serious adverse event (SAE) log. This will be evaluated and classed according to the definitions in section 10.3 below (European Directive 2001/20/EC).

10.3 Expected Serious Adverse Events/Reactions

Rare side-effects (less than 1%) will be reported as SAEs. The expected adverse events of renal impairment, cholecystitis and cholelithiasis will be reported as SAEs due to being medically significant.

10.4 Definitions of hypoglycaemia

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

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

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

10.4.1 Classification of hypoglycaemia for participants with type 2 diabetes

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

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

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

10.4.2 Novo Nordisk definition

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

Minor hypoglycaemic episode is defined as:

- An episode with symptoms consistent with hypoglycaemia with confirmation by plasma glucose < 3.1 mmol/L (56 mg/dL), or full blood glucose < 2.8 mmol/L (50 mg/dL) and which is handled by the subject himself/herself
- Or any asymptomatic plasma glucose value < 3.1 mmol/L (56 mg/dL) or full blood glucose value < 2.8 mmol/L (50 mg/dL) Minor hypoglycaemic episodes will be summarised according to this definition, and can be subject to additional analysis.

10.4.3 ADA hypoglycaemia classification

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

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

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

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

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

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

10.4.4 Classification of hypoglycaemia for participants without diabetes

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

The hypoglycaemia events for participants without diabetes will be reported spontaneously i.e., symptoms of hypoglycaemia (not biochemically confirmed) occurring outside of visits to the clinic; severe hypoglycaemia will be defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. In the event of severe or

symptomatic hypoglycaemia patients will be given a glucose monitor and asked to record their blood glucose whenever they feel symptomatic.

10.5 Reporting Procedures for All Adverse Events

All pregnancies, AEs, ARs, UARs, SAEs or SARs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF and the medical notes. They will be reported in accordance with the Sponsor, host organisation, Novo Nordisk procedures, policies and requirements.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study medication as judged by a medically qualified investigator or the Sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment (see section 10.1 and 10.2). A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

The relationship of AEs to the study medication will be assessed by a medically qualified investigator.

10.6 Pregnancy

Participants must be instructed to notify the Investigator immediately if they become pregnant during the trial. The Investigator must report any pregnancy during the trial to Novo Nordisk except for pregnancies occurring in the screening period prior to study treatment. Participants will give consent on enrolment that the Investigator will report any pregnancy during the trial to Novo Nordisk and they will be asked to provide information about the pregnancy, delivery and the health of her infant until one month of age. The Investigator must report information on pregnancy and follow-up according to Sponsor and local guidelines. If the pregnancy results in an abnormal outcome, such as congenital abnormalities, foetal death, spontaneous abortion, or SAE in the neonate, this should be regarded as an SAE with the same reporting requirements and timelines as for SAEs. If an SAE occurs in relation to a pregnancy, either to the mother or the newborn, then follow the same reporting requirements and timelines as for SAEs.

10.7 Follow-up of Adverse Events

During and following a patient's participation in the study, the Investigator will ensure that adequate medical care is provided to the participant for any AEs, including clinically significant laboratory

values related to the trial. The Investigator will inform the participant when medical care is needed for AE(s) of which the Investigator becomes aware.

The follow-up information will only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

All serious AEs and all non-serious AEs classified as severe or possibly/probably related to the trial product will be followed-up until the participant has recovered, recovered with sequelae or fatal and until all queries have been resolved. For cases of chronic conditions or if the participant dies from another event, follow-up until the outcome category is "recovered" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered".

The Sponsor guidance and processes for reporting SAEs will be adhered to.

10.8 Reporting Procedures for Serious Adverse Events

All SAEs must be reported to the Sponsor within 24 hours of discovery or notification of the event. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&I Management meeting. All SAE information must be recorded on a current CTIMP SAE form and sent to the Sponsor. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form and sent to the Sponsor. All SAEs that are at least possibly related to the study treatment – Serious Adverse Reactions (SAR) – still present at the end of the study will be followed at least until the final outcome is determined. Even if it implies that the follow-up continues after the participants leave the trial and when appropriate until the end of the planned period of follow-up.

The Sponsor will report all SUSARs to both the Competent Authorities (MHRA in the UK, HPRA in Ireland) and the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

The CI will copy Novo Nordisk into communications about SAEs, SARs and SUSARs when expediting to the Sponsor, health and regulatory authorities.

In addition to the expedited reporting above, within 90 days following the anniversary of the authorisation date for the study a Development Safety Update Reports (DSURs) will be sent by the Chief Investigator to the MHRA, HPRA and the Main Research Ethics Committee. A copy of the report will also be sent to Novo Nordisk (as the study funder), the University of Leicester (as the study Sponsor), and all host organisations.

10.9 Reporting Serious Unexpected Suspected Adverse Reactions (SUSARs)

In-line with the Medicines for Human Use (Clinical Trials) Regulations 2004, all relevant information about adverse drug reactions to the investigational medicinal product (LIRA 3mg, Saxenda®) in the proposed study, that are both serious and unexpected, will be subject to expedited recording to the appropriate Regulatory Authority and Research Ethics Committee (REC).

The University of Leicester, as Sponsor, will report all the relevant safety information previously described to the concerned competent authorities and to the Research Ethics Committee concerned. The Sponsor will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

A SUSAR that is fatal or life threatening will be reported to the relevant regulatory authority (MHRA/HPRA) and main REC within 7 working days after University of Leicester, the study Sponsor or their delegate becomes aware of the event. In each case relevant follow-up information will be sought and a report completed as soon as possible. It will be communicated to the MHRA/HPRA and the Ethics Committee within an additional eight calendar days.

A SUSAR that is not fatal or life threatening will be reported to the relevant regulatory authority (MHRA/HPRA) and main REC within 15 working days after the University of Leicester, the study Sponsor or their delegate becomes aware of the event. Further relevant follow-up information will be given as soon as possible.

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports will be submitted within the time limits as soon as the minimum following criteria are met:

- a suspected investigational medicinal product,
- an identifiable subject (e.g. study subject code number),
- an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
- an identifiable reporting source and, when available and applicable a unique clinical trial identification (EudraCT number).

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality will be actively sought from the reporter or other available sources. The University of Leicester, the study Sponsor or their delegate will report further relevant information after receipt as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

Electronic reporting will be the expected method for expedited reporting of SUSARs to the MHRA/HPRA. In that case, the format and content as defined by the Guidance 1 will be adhered to.

10.10 Reporting of Adverse Events to Novo Nordisk

Adverse events related to the Novo Nordisk drug might potentially disclose important safety information. The investigator should copy Novo Nordisk into all communications when expediting SARs or SUSARs to the Sponsor, health and regulatory authorities and should report all SAR's related to Novo Nordisk's product (LIRA 3mg, Saxenda®) to the local Novo Nordisk affiliate safety department. The submission to Novo Nordisk must be within 15 days from the Investigator's first knowledge about a valid case.

Therefore all UK cases will be reported to the UK affiliate Novo Nordisk UK on: Phone no: 0845 600 5055 Fax no: 01293 611819 Email: NNGB-safety@novonordisk.com	All Ireland cases will be reported to: Donna Sexton, Clinical Medical & Regulatory Manager Phone no: (+353) 01 678 5989 Fax no: Tel: (+353) 01 676 3259 Email: complaintireland@novonordisk.com

The following events will be reported to Novo Nordisk:

A. Serious Adverse Reaction or Suspected Unexpected Serious Adverse Reactions: as described in section 10.1.

B. Serious Adverse Drug Reaction: An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the Novo Nordisk drug and the occurrence of the event is suspected. The ADR should be classified as serious if it fulfils one or more of the seriousness criteria (www.wikipedia; search: emea seriousness criteria)

C. Pregnancies: where a foetus or embryo has been potentially exposed to the Novo Nordisk product. The outcome of such pregnancies must be reported and the child followed up for a period of 1 month after birth with any Adverse Events regarding the child reported.

For any of these events the following parameters must be recorded as a minimum:

- Study name
- Patient identification (e.g. initials, sex, age)
- Event (preferably a diagnosis)
- Drug (e.g. Saxenda)
- Reported identification (e.g. Name, or initials)
- Causality
- Outcome

All events should be recorded by the Investigator on standardised forms as follows:

- Serious Adverse Event Form (for SAE/SADR Safety Information)
- Pregnancy Form Part A

Serious ADRs follow special reporting procedures as follows:

- Initial information must be forwarded to Novo Nordisk within 24 hours of obtaining knowledge about the serious ADR.
- Completed forms must be forwarded electronically/fax/courier within 5 calendar days of obtaining knowledge about the serious ADR.

In addition to the above the reporting of SAE/SADR should also be submitted to local authorities according to national requirements.

11 STATISTICS

11.1 Statistical methods and analysis

A CONSORT diagram showing the flow of participants through the study will be produced. Baseline characteristics of the participants will be summarised by group using mean (standard deviation), median (interquartile range) or count (percentage) as appropriate.

The primary analyses will compare the proportion of participants achieving ≥15% weight loss at 52 weeks (primary outcome) after randomisation between the two study groups using a logistic regression model with adjustment for the stratification factors (site and BMI). The adjusted proportion (95% confidence interval) of participants achieving ≥15% weight loss will be estimated by group. The primary analyses will be based on the complete cases population, with intention to treat (ITT) and per protocol analyses as secondary analyses (see Sections 11.3 and 11.5). In all analyses, participants will be analysed in the group to which they were randomised at baseline; importantly, the participants in the intervention group who stop LIRA 3mg, because they meet a pre-specified stopping rule, will still be analysed in the intervention group. Participants who have undergone bariatric surgery during the period of the study will be excluded from the analysis for the primary outcome, because these participants are likely to have substantial weight loss, but are unlikely to be balanced between the groups (as it is expected that fewer participants in the intervention group will require bariatric surgery due to their expected weight loss). Missing primary outcome data will need to be imputed for the ITT analyses; this will be done by assuming that these participants did not achieve ≥15% weight loss at 52 weeks, which is a conservative approach. The characteristics of those with missing outcome data will be compared with those who have completed follow-up. The complete cases, ITT, and per protocol analyses will compare the two groups to demonstrate the effectiveness of the targeted prescribing pathway compared with standard care.

Secondary outcomes measured at 52 weeks and 104 weeks will be analysed in a similar way, with binary outcomes compared using logistic regression models and summarised using proportion (95% confidence interval), and continuous outcomes compared using linear regression models and summarised using mean (95% confidence interval). If continuous outcomes are non-normally distributed then they will be transformed or a more suitable regression model will be selected. In all analyses, participants will be analysed in the group to which they were randomised at baseline. Only the complete cases population will be used for the secondary outcomes to reduce the number of models being fitted. Participants who have undergone bariatric surgery during the period of the study will be excluded from these analyses. Data on treatment adherence, safety (including adverse events), and treatment satisfaction will be summarised and tabulated.

As additional secondary analyses, 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 (i.e. had achieved ≥15% weight loss at 52 weeks after randomisation). The purpose of these analyses is to compare the outcomes of “early and good” responders to the targeted prescribing pathway with those who received standard care only. Therefore, all participants randomised to the standard care group will also be included in these responder analyses.

11.2 Sample Size

Based on previous studies, it is expected that at one year approximately 5% of the participants in the standard care group will have achieved ≥15% weight loss (likely range: 3%-5%) [5, 7]. An achievable target for ≥15% weight loss at one year in the intervention group is 16% (likely range: 14%-20%) [5,7]. Based on these proportions, 25% drop out, 5% alpha and a 2:1 randomisation ratio with the higher proportion of participants being randomised to the intervention group, we would need to recruit 392 participants (261 intervention group; 131 standard care) to have 80% power to detect a significant difference between the groups at one year. With 261 participants randomised to the intervention group, and based on 16% achieving ≥15% weight loss at 12 months, an estimated 40 participants in the intervention group will be eligible for the responder analyses. All 131 participants in the standard care group will be eligible for the responder analyses.

11.3 Missing/unused/spurious data procedure

Attempts will be made to assess the primary outcome on all participants including those who have withdrawn from treatment. The number of missing observations for each outcome will be reported. If missing outcome data are present then the initial analysis will be based on the complete cases. A sensitivity analysis will then be carried out repeating the analyses with the ITT population to assess the possible impact of the missing data on the results produced. Missing primary outcome data will need to be imputed for the ITT analyses; this will be done by assuming that these participants did not achieve ≥15% weight loss at 52 weeks, which is a conservative approach. We will also attempt to address bias by comparing the characteristics of those with missing outcome data to those who have completed follow-up. This strategy for dealing with missing outcome data has been recommended by White et al. [9].

11.4 Disposition of Patients

Screened patients

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

Treated patients

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

Data from all randomised participants will be used in the study final report and analysis, with data analysed in the group to which the participant was randomised. Participants who have undergone bariatric surgery during the period of the study will be excluded from the complete cases, per protocol and responder populations.

11.5 Analysis Populations

Complete cases population

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

ITT population

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

Per protocol population

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

Responder population

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

11.6 Health Economic Input

A state-transition Markov cohort model has been developed, 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 (MI), stroke, asthma cancer or mortality in the long term (up to lifetime horizon) based on short term effects of interventions in surrogate outcomes – body mass index (BMI), systolic blood pressure (SBP) , total cholesterol, high-density lipoprotein (HDL) cholesterol and (for patients with T2DM) 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 [note: the current version of the model does not include the functionality for a 32 week stopping rule, but that will be added] (based on the pre-specified stopping rule) or at 52 weeks. Discontinuation at 3 months causes the cohort to move to the control group, and subsequently follow the clinical pathway of this treatment group who will be

receiving the standard care providing via the Tier 3 service. 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 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) – catch-up time – as defined by the user. 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 T2DM 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.

12 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

All source data, study documents, and participant notes will be made available for the Sponsor monitoring, and indeed any external audits and inspections by the Ethics Committee, Regulatory Authorities, Sponsor, LCTU and host institution.

13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and the SOPs and quality management procedures of Sponsor, host organisations and for those services provided by LCTU, the Unit's SOPs.

As part of the quality management process a risk assessment will be carried out and a monitoring plan will be developed by the Sponsor. The Sponsor will carry out all study monitoring. The Leicester Diabetes Centre will be responsible for all elements of trial management and carry out quality checks as identified within a quality management plan. A documented monitoring log and audit trail will be maintained throughout the lifetime of the study.

All study documentation containing identifiable patient data will be managed in accordance with ICH-GCP, UK Policy Framework for Health and Social Care Research, General Data Protection Regulation and the Data Protection Act as amended from time to time.

13.1 Responsibilities of the Principal Investigator(s)

The Investigator and delegated Investigator staff undertake to perform the clinical study in accordance with this clinical study protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The PIs are required to ensure compliance with all procedures required by the clinical study protocol and with all study procedures provided by the Sponsor (including security rules). The PIs agree to provide reliable data and all information requested by the clinical study protocol (with the help of the CRF or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives. With any data transfer, particular attention should be paid to the confidentiality of the subject's data.

The PIs may appoint such other individuals as he/she may deem appropriate as co-investigators to assist in the conduct of the clinical study in accordance with the clinical study protocol. All co-investigators shall be appointed and will have been delegated by the PI and will have signed the delegation log prior to commencing work on the study. The co-investigators will be supervised by and work under the responsibility of the PI. The PI will provide them with a copy of the clinical study protocol and all necessary information.

13.2 Responsibilities of the Sponsor

The Sponsor of this clinical study is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical study protocol as regards ethics, clinical study protocol compliance, and integrity and validity of the data recorded on the CRFs.

Following a risk assessment, the Sponsor will prepare and put into place a risk adaptive monitoring plan, detailing the frequency and type of monitoring visits. This may be by one or more of the following methods – remote data monitoring, site visits and in-house day-to-day to review study progress, Investigator and subject adherence to clinical study protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, signature logs, version control, SAE documentation and reporting, AE documentation, subject compliance with the investigational drug, investigational drug accountability, concomitant therapy use and quality of data. The LCTU will undertake its own study audit as part of its trial management procedures.

13.3 Deviation Procedures

A deviation is a change or departure from the clinical trial protocol and/or Good Clinical Practice (GCP) that does not result in harm to the study participants or significantly affect the scientific value of the reported results of the study.

Deviations may be identified by routine quality control procedures, or may be reported directly from the PI or other site staff, as a spontaneous written notification or by submission of a protocol deviation form included as part of the CRF. All such deviations should be documented in-line with Sponsor SOP's and retained within the Trial Master File and notification sent to Sponsor when serious breaches occur (as detailed in Sponsor SOPs). An assessment will be made by the PI as to whether the deviation is deemed to be serious or substantial (see below).

The deviation report should include:

- The title (full or accepted abbreviation) of the clinical trial
- The name of the CI and the PI
- A brief explanation of how the deviation was identified
- Details of initial corrective actions

Actions that result from a deviation may include:

- Alerting the investigator and asking for further explanation or data verification
- Audit of the investigator site or the clinical trial database (as applicable)
- Examination of data from the site by a statistician as a central monitoring procedure
- Review of other study data
- Involvement of an DSMC or the TSC

13.4 Misconduct or Serious Breaches of GCP/Protocol

If research misconduct or a serious breach is confirmed by clear and unequivocal evidence, it is the responsibility of the Sponsor (or delegate) to notify the MHRA and the main REC in the UK or the HPRA and EUREC in Ireland in writing within 7 days of the Sponsor becoming aware of the breach using the Serious Breach Notification Form and to investigate or take action simultaneously or after initial notification.

Deviations from the protocol and/or GCP that are assessed as serious are to be reported to the MHRA/HPRA as a serious breach by the study Sponsor (or delegate).

A serious breach is a violation or deviation that is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the study

(b) the scientific value of the study

Research misconduct is the deliberate reporting of false or misleading data or the withholding of reportable data. Concluding that an individual is responsible for misconduct in research relies on a judgement that there was an intention to commit the misconduct and/or recklessness in the conduct of any aspect of a research project. Misconduct includes: fabrication; falsification; misrepresentation of data and/or interests and or involvement; and plagiarism. It also includes a failure to follow accepted procedures or to exercise due care in carrying out responsibilities to avoid unreasonable risk or harm to participants in research, and/or a failure in the proper handling of information on individuals collected during the research.

14. CODES OF PRACTICE AND REGULATIONS

14.1 Clinical Trials Authorisation (CTA)

Approval for the protocol (and any subsequent substantial amendments) will be sought from the MHRA (UK Competent Authority) and HPRA (Irish Competent Authority).

14.2 Ethics

This protocol and any amendments will be submitted to the Health Research Authority (HRA) and Research Ethics Committee (REC) for ethical approval (or to EUREC for sites in Ireland).

This clinical study will be 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. All staff working on this study will have an up to date ICH-GCP certificate. Ethical and research governance approval will be sought for this study through the HRA, appropriate regulatory bodies and NHS Trusts prior to any participant activity.

In compliance with Novo Nordisk public disclosure commitments, this clinical study will be recorded in the public registry website clinicaltrials.gov before the enrolment of the first participant. The registry will contain basic information about the study sufficient to inform interested patients (and their healthcare practitioners) how to enrol in the study.

14.3 HRA

HRA approval will be sought concurrently with MHRA and REC approval for those sites in NHS England, which will perform an assessment of governance and legal compliance prior to any local NHS checks and approvals being completed.

For those sites that are not part of NHS England alternative appropriate regulatory approvals will be sought (e.g. Ireland approvals will be sought from the Health Products Regulatory Authority (HPRA) concurrently with English sites).

14.4 Sponsorship and Indemnity

Sponsorship and insurance for the study will be provided by the University of Leicester.

If a patient is harmed due to negligence, this would be covered by the local NHS Trust(s) indemnity arrangements for all participants in clinical trials. If a study participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them.

14.5 Host Organisation (R&I) Approvals

In accordance with the Research Governance Framework, R&I approval for the study will be obtained from each participating Trust once all other approvals have been confirmed (REC, MHRA, HRA, HPRA). The University of Leicester will undertake the role and responsibility of the research Sponsor and Sponsor greenlight will be obtained prior to any study activities commencing.

For all amendments Sponsor will review this prior to submission by the Investigator to the required regulatory body/bodies, and all approvals will be confirmed prior to commencement at the site.

14.6 Sponsor Standard Operating Procedures

All relevant current Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines.

14.7 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

14.8 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) June 1996.

14.9 Laws and Regulations

This study will be conducted in compliance with all international guidelines, national laws and regulations of the country in which the study is performed, and any applicable guidelines.

14.10 Other Ethical Considerations

14.10.1 Known and potential risks

LIRA 3mg is administered as a one daily subcutaneous injection and is available in a prefilled, disposable pen device comprising a pen injector and cartridge. There may be some anxiety and concern to starting treatment using a needle-based device and this will be discussed at length with their clinician. It can be taken at any time of the day and is meal independent. The pros and cons of LIRA 3mg will be explained to each participant during the initial consultation for study consent.
LIRA 3mg has a good tolerability profile; however the most frequently reported adverse effects of LIRA 3mg are gastrointestinal, including nausea, diarrhoea, vomiting, constipation, abdominal pain, and dyspepsia. These gastrointestinal adverse effects may occur more frequently at the start of treatment with LIRA 3mg, and usually diminish within a few days or weeks on continued treatment.
Hypoglycaemia is considered low risk with this treatment because its action is glucose dependent. However, participants suffering with diabetes on treatment with sulphonylureas may be at higher risk for hypoglycaemic episodes compared to the other participants.

Rare serious adverse events may include hepatobiliary diseases such as associated with gallstone formation and pancreatitis. An increase incidence of breast malignancies previously reported may be due to reduced adipose tissue in the breast and earlier detection.

14.10.2 Known and potential benefits

Multiple randomised controlled trials in different populations have demonstrated that LIRA 3mg is an effective treatment for obesity and obesity-related co-morbidities. Moreover, intensive lifestyle programmes offered as part of the Tier 3 service have been shown to be effective in promoting weight loss in subjects with severe and complex obesity [10, 11].

SCALE Obesity trial demonstrated that the combination of lifestyle changes and administration of LIRA 3mg from the beginning of treatment can lead to ≥ 15% weight loss in 14% of participants compared to just 3% in the placebo group at one year after treatment [5]. Moreover, the SCALE-maintenance trial showed that LIRA 3mg in combination with advice for lifestyle change after an initial weight loss of 5% with low calorie diet and meal replacements, could result in an additional 6.1 kg weight loss compared to placebo over the next year [7]. Overall, the SCALE-maintenance study resulted in a maintained weight loss of 12.2 kg for patients on LIRA 3mg and 26% of them achieved ≥15% weight loss [7].

Additionally, the SCALE Obesity study showed that the prevalence of prediabetes was lower one year after treatment with LIRA 3mg compared with the placebo group [5]. The SCALE Diabetes study demonstrated that LIRA 3mg could result in greater weight loss and HbA1C control in patients with diabetes compared with placebo [6]. All the phase 3 studies with LIRA 3mg have shown improvements in systolic blood pressure, markers of inflammation and cardiovascular health [5-7].

15. DATA MANAGEMENT

15.1 CRF/Data collection sheet management

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. If the item is not applicable to the individual case, N/A will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct the error, a single line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialled and dated. For clarification of illegible or uncertain entries, the clarification will be printed above the item and this will be initialled and dated.

Data captured in the paper CRFs will then be entered into a validated database under the management of the LCTU. A copy of the patient consent form and information sheet will be placed in the hospital notes of all participants and in the Investigator Site File. A sticker will be placed on the cover of the notes (or inside cover) detailing the study title, contact details of the PI and the fact that the notes should not be destroyed. All study visits and AEs will be recorded in the hospital notes.

All CRFs will be stored in a secure area. Each enrolled participant will be allocated a unique study ID so that the CRFs and electronic database remains anonymous.

According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor or duly authorised personnel, the Ethics Committee, and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (e.g., subject's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

15.2 Documentation storage, access, security

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.

Information will only be obtained from the patient if necessary for the study.

All electronic data will be stored on secure network drives, to which only the relevant study staff have access, which is granted by the IT services or the research team. This drive is backed up daily by the University of Leicester IM&T.

All study documents and data will be kept for 15 years or the minimum determined by the regulatory authorities, whichever is the longer. Archived files will kept in a secure location.

15.3 Database management

Paper CRF data will be entered by trained member(s) of the research team at site into a commercially available web based CDMS provided by the 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, with queries managed using the data clarification functionality within the CDMS system.

The contacts database (which contains participant contact details) will be held separately from the study database. This will be password protected and managed at site by the research team.

15.4 Data Confidentiality

Each participant will be assigned a unique identification number upon recruitment. Participant's contact details will be held on a database separate to the study visit data and used to arrange data collection visits at their local site. The database will be password protected and only researchers collecting data will have access. All data collected during the study will be stored pseudonymously on a separate database. Again access will be password protected and restricted to relevant members of the research team.

Paper copies of the case report forms and questionnaires will be stored in a locked filing cabinet in the relevant research office. Neither hard copies nor electronic files containing personal information will be removed from the research office. Quality control checks will be conducted by the lead site (Leicester) these electronic documents will be pseudonymised and stored in a secure manner. The study research team will comply with the Data Protection Policy of the University of Leicester and local NHS Trusts.

16. STUDY GOVERNANCE

The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and Medicines for Human Use (Clinical Trials) Regulations, 2004 and its subsequent iterations. The Sponsor responsible for checking research governance arrangements will be the University of Leicester.

16.1 Trial Steering Committee (TSC)

The TSC will comprise of the Chief Investigator and Co-Principal Investigators, with an Independent Chair, with at least one other independent clinician with expertise in a relevant field and a nominated representative from Novo Nordisk. The statistical team, and the trial management team may attend as required. This committee will be responsible for the overall management and oversight of the study and will meet once prior to start up and then every 6 months, normally within 2 months of the Data Safety Monitoring Committees (DSMCs) (although additional meetings may be called by the CI, TSC or DSMC chair) to review and approve protocol amendments and any sub-study proposals, review recruitment rates, protocol adherence, retention, compliance, safety issues, planned analyses and reports and act on recommendations of the DSMC. Minutes from the TSC will be copied to the Sponsor.

16.2 Trial Management Group (TMG)

The TMG will report to the TSC and will include the PI and the day-to-day project management team onsite, representatives from other sites, statistician(s), IT/Data Management, and research nurses as required. TMG meetings will be held at each site on a monthly or bi-monthly basis depending on need, either face-to-face or by teleconference, to discuss set-up, recruitment and retention, follow-up data collection and any other day-to day practical issues.

16.3 Data Safety and Monitoring Committee (DSMC)

The DSMC will meet every six months and report to the TSC. The DSMC will be appointed by the CI and the LCTU Statistical Team and will comprise members who are independent of the study, to include at least one statistician and at least one clinician. The CI and/or trial statistician may be invited to attend to provide specific input by the DSMC Chair. The DSMC will review safety data regularly and make recommendations as to whether the study should continue, be modified or terminated. A log of all AEs will be provided to the DSMC for this purpose. The DSMC will also review any statistical analysis plans.

16.4 Premature discontinuation of the study

Decided by the Sponsor

Decided by the Sponsor in the following cases:

- If the information on the product leads to doubt as to the benefit/risk ratio
- If the CI has received from the Sponsor all (N)IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
- In the event of breach by the CI of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines on GCP
- If the total number of patients is included earlier than expected.
- In any case the Sponsor will notify the Investigator of its decision by written notice.

Decided by the CI

The CI must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the CI), the appropriate Research Ethics Committee(s) and NHD Trusts should be informed according to applicable regulatory requirements.

17. PUBLICATION POLICY

It is envisaged that the results of the study will be published in the relevant Obesity/General Medical peer-reviewed journals. Acknowledgement of any supporting organisations, including funders, University of Leicester and the LCTU, will be included.

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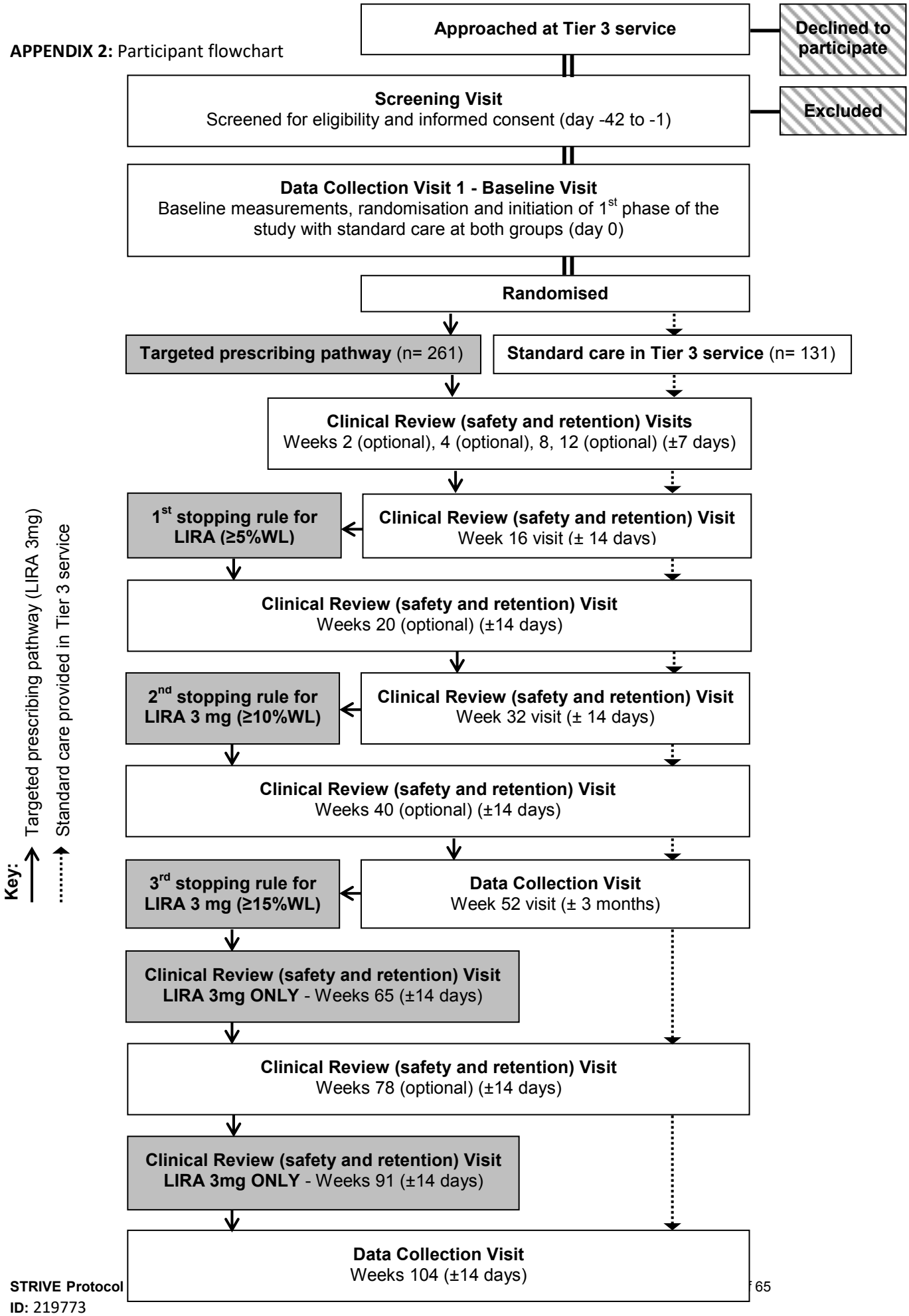
19. APPENDICES

APPENDIX 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 2: Participant flowchart



APPENDIX 3: Study schedule for measurements.

Table 2. 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	+/- 3 mths***	+/- 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)$$		X$$	X$$	X	X$$ 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	+/- 3mth -****	+/- 14dys	+/- 14dys	+/- 14dys	+/- 14dys
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12*	13* /13	14*	15* /13
King's Obesity Staging System		X									X				X
Epworth Sleepiness Scale		X									X				X
Stop Bang Questionnaire		X									X				X
CPAP compliance **		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				X
Adherence to Tier 3 (or equivalent) Service			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
[$]Target dose by week 8. [$$]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

****Where possible the week 52 visit should continue to be scheduled within the (± 14 days) study visit window, however to aid retention

and to help maximise data collection for the study primary end point, the week 52 visit window can be extended to ± 3 months.
[#] 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)

^^^In response to the COVID19 global pandemic, an interim time point for the quality of life questionnaires has been added (HSRUQ, TSQM, EQ-5D, IWQOL-Lite, IPAQ-Long and PHQ-9). These will be sent out to all participants during the COVID19 pandemic.

^^^^ These activities will not be completed during the COVID19 pandemic restriction period, however once restrictions are lifted participants that resume face to face visits will be completed as per the original protocol.