**Preoperative weight management to improve outcomes of cardiac surgery in adults with obesity (SLIMCARD): A multicentre feasibility RCT**

***Study references***

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Glossary / abbreviations

|  |  |
| --- | --- |
| AE | Adverse event |
| AKI | Acute kidney injury |
| CABG | Coronary artery bypass grafting |
| CPB | Cardiopulmonary bypass |
| CRFCTU | Case report formClinical trials unit |
| HDU | High Dependency Unit |
| HTA | Human tissue authority |
| ICU | Intensive care unit |
| IL | Interleukin |
| MI | Myocardial infarction |
| MOD | Multiple Organ Dysfunction |
| RCT | Randomised controlled trial |
| REC | Research ethics committee |
| SAESAP | Serious adverse event Statistical analysis plan  |
| SUSAR | Suspected unexpected serious adverse reaction  |

# Study Synopsis

|  |  |
| --- | --- |
| Title of Study | **Preoperative weight management to improve outcomes of cardiac surgery in adults with obesity (SLIMCARD): A multicentre feasibility randomised control trial** |
| Name of Sponsor | University of Leicester |
| Study Design | Pragmatic, parallel group, single blinded, multicentre, randomised controlled feasibility trial with embedded behavioural analysis. |
| Study Hypotheses | A weight loss intervention delivered by a commercial partner to adults who have obesity and are to undergo cardiac surgery will achieve satisfactory levels of adherence, and clinically important weight loss in the treatment group while the control group participants stay the same weight. |
| Study Objectives | To understand how best to manage patients who have obesity and who are referred for cardiac surgery (about 30% of the total) we propose to undertake a feasibility trial to see if the often elderly patients referred for cardiac surgery are able to attend weight management sessions regularly and lose weight, and are willing to enter the trial.The main outcomes for the trial are how often patients attend the weight management sessions and whether they lose any weight.We will also use behavioural analyses to understand how to explain the rationale for the trial to participants so that they feel confident that trusting this decision to chance is sensible. |
| Subject Selection Criteria | Patients may enter the trial if ALL the following apply:1. Adult patients (>17 years) referred for cardiovascular surgery.
2. Patients who have obesity; defined as a BMI ≥30 for patients of White-European ethnicity, and as a BMI ≥27.5 for all other ethnic groups.
3. Willingness and ability to commit to up to 12 weekly sessions of the intervention or to commit to weight stability.

Patients may not enter the trial if ANY of the following apply:1. Patients undergoing urgent or emergency surgery.
2. Patients who are participating in another interventional trial.
3. Patients who are currently/ recently (<3m) enrolled in a weight management programme.
 |
| Treatment Allocations | Eligible patients who consent to participate will be randomly allocated in a 1:1 ratio to: * Weight Management (Intervention): up to 12-weeks of a commercial weight management programme.
* Weight Stability (Control): advised to maintain current diet and a stable weight.

Allocation will be determined using the internet-based system Sealed Envelope with stratification by surgical site and BMI. |
| Follow-up | Participants will be followed-up:* At baseline for weight measurement, demography, medical history, concomitant medication, EQ-5D and Clinical Frailty Scale
* 2-4 weeks post-baseline with a telephone call to monitor and reinforce adherence to the randomised allocation (audio recorded),
* 1-day pre-surgery for weight measurement and EQ-5D,
* 120 hours post-operation for organ injury, infection, and adverse event (AE) monitoring,
* at 6 weeks post-surgery, when they will attend a routine outpatient clinic appointment where we will collect healthcare resource use data,
* at 3 months post-surgery, we will conduct a final telephone call to collect EQ-5D and healthcare resource use data.
 |
| Outcomes | Primary Feasibility Outcome:* Proportion of participants randomised to the intervention arm attending ≥75% sessions
* Proportion of participants randomised to the control arm whose weight at surgery remains within 1.5kg of their baseline weight.

Primary Efficacy Outcome:* Mean weight change at surgery relative to baseline.

Secondary Outcomes: 1. Recruitment rate, attrition rate, data completeness.
2. A composite endpoint of ischaemic organ injury: low cardiac output, acute kidney, brain or gut injury.
3. A composite endpoint of infection: surgical site infection, lower respiratory tract infection, urinary tract infection, sepsis.
4. Adverse events, including mortality, collected from randomisation to 3 months post-surgery.
5. Change in quality of life measured at baseline, 1-day pre-operation and 3 months using the EQ-5D-5L, a clinically validated and responsive instrument for measuring quality of life in cardiac surgery trials.
6. Resource use up to 3 months post-surgery estimated from a bespoke questionnaire.

For participants who are randomised to the intervention-arm, we will also collect weekly body weight data supplied to us by Slimming World, as a measure of process. |
| Behavioural Analysis | The behavioural work will investigate how to communicate the need for the trial to patients, optimise informed consent, and improve adherence to group allocation. |
| Planned Sample Size & Recruitment | We estimated that a total of 104 patients (52 in each arm) will be recruited to the trial. Additionally, 40 participants will be recruited into the interview-only aspects of the trial. Seven sites will participate.Behavioural Study #1 (all sites, months 1-4):Patients (n=15), HCPs (n=15)Behavioural Study #2 & Clinical Trial (Glenfield General Hospital only, months 5-6):Patients (n=40), HCPs (n=10)Behavioural Study #3 & Clinical Trial (all sites, months 9-21):Patients (n=64) |
| Statistical Methods | A detailed statistical analysis plan will be written prior to the analysis. The primary analyses will be performed on an intention-to-treat approach using all available data. Continuous outcomes data will be expressed as mean and standard deviation or median and interquartile range and binary outcomes be expressed as number and percentage.. The primary feasibility outcomes of (1) proportion of participants randomised to the intervention arm attending ≥75% of their scheduled sessions, and (2) proportion of participants randomised to the control arm with weight change at surgery within 1.5kg from their baseline will be calculated. The primary efficacy outcome is mean weight change at surgery relative to baseline. This will be analysed by linear mixed regression model, adjusting for baseline weight and stratification variables (surgical site, and BMI). Secondary outcomes will be analysed by linear regression for continuous outcomes or logistic regression model for binary outcomes.  |
| Governance | The trial funder is the British Heart Foundation.The trial sponsor is the University of Leicester.The trial will be conducted in accordance with all applicable regulatory guidelines and only after all applicable approvals have been obtained. |

# Background

## The clinical problem

Infection and organ injury affecting the heart, lungs, or kidneys, are common and severe complications of cardiac surgery. In the TiTRE2 trial1 severe sepsis, acute kidney injury (AKI), pulmonary dysfunction, and low cardiac output occurred in 11%, 34%, 16% and 12% of all cardiac surgery patients and preceded 28%, 42%, 36% and 17% of all deaths respectively. Patients who survived experienced sustained reductions in quality of life and utilised significant resources; in TITRE2 healthcare costs were 70% higher for patients with sepsis or organ injury (n=717, mean cost from surgery to 3 months £24,539) compared to those without (n=1291, £14,4501). If this were reflected in the UK cardiac surgical population, then the treatment of postcardiac surgery sepsis and organ failure would cost up to £125M per year. Despite improvements in clinical practice and decades of research effective prevention strategies for these complications remain elusive2-4.

## 2.2 Area of uncertainty

Obesity, defined as a body mass index (BMI) ≥30 or ≥27.5 for people of South Asian ethnicity is increasingly prevalent (>30%) in patients presenting for cardiac surgery in the UK5. Obesity presents specific challenges including increased complexity of surgery, poor wound healing, infection, impaired mobility, and slow recovery6,7. Patients who have obesity referred for surgery are often advised to lose weight prior to their procedure. In some areas of the UK, commissioning of routine surgery has been restricted for patients who have obesity unless they have lost weight8. This variation in care occurs in the absence of evidence-based guidance from the National Institute for Health and Care Excellence (NICE) or other national or international organisations. Patients who have obesity may also be refused lifesaving surgery, and this is more likely if they have chronic conditions affecting the heart, lungs and kidneys5. Improving the lives of patients who have obesity and/ or multiple chronic conditions are NHS research priorities9.

Obesity is harmful in the long-term but paradoxically is associated with reductions in organ injury in cardiac surgery patients. Modest weight loss (5-10%) in primary care populations reduces cardiovascular risk and long-term cardiovascular morbidity and mortality.10,11 However, whether acute weight loss immediately prior to surgery has clinical benefits is uncertain. Weight loss has positive effects on mobility,12 cardiac function,13 and glycaemic control,11 and should reduce recovery times and adverse events including infective complications.14-17 Observational data supports this indirectly; in a UK study cardiac surgery patients with WHO Class III obesity had a >5 fold risk for developing severe surgical site infection relative to healthy weight (18.5≥ BMI <25) patients. However, in the same analysis patients with BMI ≥30 had significantly lower rates (odds ratio 0.81 95% Confidence Intervals 0.76 to 0.86) of organ injury and death relative to patients with healthy weight5. These effects were consistent across multiple analyses that attempted to address known confounders including ‘healthy’ obesity, and highlight a knowledge gap with respect to weight management prior to cardiac surgery.18

Clinical uncertainty results in variability in care. Our PPI group undertook a patient survey in 6 UK surgery cardiac centres. Of these, 11/49 (22%) patients with BMI≥25 and 24/61 (39%) with BMI ≥30 were advised by a healthcare professional to lose weight pre- surgery. Of the 35 patients who were advised to lose weight, 26 received verbal advice, 4 received written advice (leaflet), 4 were referred to a dietitian, and 1 was referred to a commercial weight loss programme. This is evidence of variation in care in a patient cohort at high risk of post-surgery complications.

This research will provide high quality evidence to inform pre-operative weight management in cardiac surgery. Of the 36,000 patients undergoing cardiac surgery annually in the UK up to 11,000 will have obesity5. An unknown number of patients who have obesity are refused surgery. More than 1 million patients undergo cardiac surgery worldwide per year. In addition, in the UK, 26% of adult men and 27% of adult women have obesity19 and the findings of the trial may inform NHS policy on the clinical commissioning of surgery in patients who have obesity more generally, which is currently the subject of an ongoing public debate8.

## 2.3 Preliminary work

Our systematic review examined the evidence for pre-surgery weight management interventions in patients who have obesity referred for any type of surgery20. Three RCTs and 8 cohort studies enrolling a total of 2458 participants were included. All the studies had significant methodological limitations and no trials in cardiac surgery were identified. All but one study was undertaken in patients with morbid obesity undergoing bariatric surgery who differ markedly from the more elderly patients with multiple comorbidities that present for cardiac surgery21. In meta-analyses, there was insufficient evidence to assess whether pre-surgery weight loss interventions had an effect on mortality [risk ratio (RR) 1.20, 95% confidence interval (CI) 0.14 to 10.47; I2 = 0%, P=0.87], infection or thromboembolic complications relative to standard care.

To address this uncertainty we intend to evaluate the effectiveness, cost-effectiveness, and the acceptability to cardiac surgery patients of pre-surgery referral to a commercially provided weight management programme recommended for use in primary care by NICE22-24. In previous RCTs in primary care populations we have demonstrated that these programmes result in modest reductions in body mass (mean 4-5kg versus controls)25,26 that have demonstrable long-term health benefits27. However, it is unclear whether patients about to undergo major surgery, having outlined the evidence of uncertainty on the benefits of weight loss before surgery, will be prepared to enrol in the study and be randomised to try to lose weight with support or to refrain from losing weight if assigned not to do so. Before embarking on a large multicentre trial, we are proposing to evaluate the feasibility, acceptability and efficacy of administering the trial intervention across multiple sites in our target cardiac surgery population.

# Aims and Objectives

The trial will evaluate the pre-surgery referral to a commercial weight management programme (Slimming World) that adopts a multicomponent behavioural approach to promote and sustain weight loss delivered in up to 12 weekly sessions, each 1 hour long.

# Plan of Investigation

## Study design

Pragmatic, parallel group, single blinded, multicentre, randomised controlled feasibility trial with embedded behavioural analysis.

The trial will be in 3 phases:

1. Behavioural Study #1 will involve patients and HCPs at all sites and will consist of interviews only to develop a recruitment script.
2. The recruitment script will then be tested in the Clinical Trial at Glenfield General Hospital only, via interviews in Behavioural Study #2 with patients and HCPs.
3. The Clinical Trial will then be rolled out to all sites, with interviews continuing for patients only in Behavioural Study #3.

## Study population

The trial will be carried out in primary care and adult tertiary cardiac surgery centres in the United Kingdom. These units have been selected to reflect the range of social deprivation across the UK.

### Inclusion Criteria

Participants may enter the trial if ALL of the following apply

1. Adult patients (>17 years) referred for cardiovascular surgery.
2. Patients who have obesity; defined as BMI≥30 for patients of White-European ethnicity and as BMI≥27.5 for all other ethnic groups.
3. Willingness and ability to commit to up to 12 weekly sessions of the intervention or to commit to weight stability.
4. Behavioural Study 1: Willingness to be interviewed within 24-48 hours of the clinic appointment and have the interview audio recorded

### Exclusion criteria

Participants may not enter the trial if ANY of the following apply:

1. Patients undergoing urgent or emergency surgery.
2. Patients who are participating in another interventional trial.
3. Patients who are currently/ recently (<3m) enrolled in a weight management programme.

## Screening, Recruitment and Consent

The screening, recruitment, and consent process is outlined in **Figures 1a - 1c**.

Patients attending a pre-surgical, initial clinic will be posted the Participant Information Leaflet (PIL) at least 24 hours beforehand (the local research nurse will provide the clinical admin team with the PILS, and the clinical admin team will include a copy with the clinic appointment letter).

At the clinic, after their consultation with the surgeon, the patient will meet the local research nurse who will discuss the PIL, seek consent, and undertake the research procedures (or liaise with the behavioural researcher for the behavioural study). Upon reviewing the clinical notes, not all patients may be eligible to participate as determined by a delegated medic, and this disclaimer is made clear beforehand in the PIL.

For healthcare professionals undertaking the behavioural study, they will be provided with the PIL by the local research nurse in person.

Details of all participants approached for the trial and reasons for non-participation (e.g. reasons for being ineligible or refusal) will be documented by the research staff in the form of a screening log that will not contain identifiable information.

## Behavioural Study

Recruitment may prove challenging because potential participants will need to understand both the potential risks and benefits of weight management and must be prepared to abide by the randomisation. Participants randomised to the weight management arm will be asked to try to lose weight, an action lacking a strong evidence base. Participants randomised to the weight stable arm will have to refrain from ‘getting themselves in-shape’ for an operation.

We will follow the QuinteT recruitment process.28 This process will aim to maximise patients’ ability to make informed decisions while increasing recruitment.28 We will achieve this by conducting in-depth qualitative research to:

1. understand the recruitment process
2. identify ways to improve recruitment

The QuinteT Recruitment process has been used in a number of RCTs where randomisation presented potential participants with difficult choices that initially undermined recruitment, and all of these recruited to target.29 A strength of this approach is that it is iterative and cumulative.

The plan for the behavioural studies are summarised in **Figures 1a -1c.**

**4.4.1 Qualitative interviews (months 1-4) – “Behavioural Study 1”**

We will firstly conduct in-depth qualitative interviews with key stakeholders. The aim is to understand potential challenges with recruitment, including communicating equipoise and patient concerns.

**Inclusion/exclusion criteria**

Inclusion and exclusion criteria are the same as for the trial, but additionally incudes willingness to be interviewed within 24-48 hours of the clinic appointment and have the interview audio recorded.

**Sampling**

*Cardiac surgeons and Research nurses/recruiters (healthcare professionals):*

As this is rapid work to inform the main trial, we aim to sample using both convenience and snowball sampling approaches. We will initially interview any healthcare professional working at a trial site who is eligible and willing. We will then ask if they can recommend colleagues who would also be willing to be interviewed**.** We aim to interview 5 cardiac surgeons and 10 Research nurses/recruiters.

*People who are overweight and facing cardiac surgery:*

For the same reasons, we will take a convenience approach to sampling, interviewing any patient who agrees to take part in the behavioural study. We aim to interview 15 patients for qualitative interviews.

**Recruitment**

*Cardiac surgeons and Research nurses/recruiters (healthcare professionals):*

We will ask the local research nurse to contact cardiac surgeons and research nurses/recruiters from sites which will take part in the trial. They will include the patient information sheet and invite them to take part in a semi-structured interview by telephone. Interviews will focus on perceptions of equipoise, views about the RCT’s rationale, potential concerns, common misconceptions expressed by patients, and past experiences with recruitment.

*People who are overweight and facing cardiac surgery:*

Before the start of the trial, people who are overweight and facing cardiac surgery will be asked attheir pre-surgical initial clinic visit if they are willing to talk to a behavioural researcher about their thoughts and feelings about surgery, including their key concerns. This will be facilitated by the local research nurse who will arrange for a PIL to be posted out to the patient before their clinic appointment. Then on the day of the clinic, the research nurse will approach the patient to discuss the study and obtain consent along with their contact details. The research nurse will then pass these onto the behavioural researcher over the telephone, so that they can conduct the telephone interview at a time that suits the patient, but within 24-48 hours of their clinic appointment.

**Consent**

The local research nurse will discuss the details of the study with all participants and confirm that participants have read the PIS. The research nurse will then collect written informed consent, including consent to audio record the interview.

**Data collection**

Data will be collected from months 1-4. Data will be qualitative semi-structured interviews. These will focus on potential concerns, misconceptions, past experiences with recruitment, and understanding of cardiac surgery. The aim of interviews is to collect information which will be used to develop a ‘recruitment script’, addressing common problems and questions. An ‘interview topic guide’ will be developed by the behavioral team, with input from all trial investigators. In line with best practice in qualitative research, this ‘interview topic guide’ will be iterated after each interview, and new questions added where appropriate.

**Data handling and analysis**

Audio recorded interview data will be transcribed verbatim. It will be managed using NVivo 12 software and de-identified. Analysis will be thematic and inductive, following Glasner and Strauss’ constant comparison method.30

**Script design**

The behavioural team will use results from interview analyses, combined with previous research on trial recruitment, and results from our previous study of how to optimize recruitment to weight management services in participants with no thoughts of weight management,22,31 to review the PIS for the main trial, and develop a sample ‘recruitment script’. This will occur during month 4 and will aim to ensure that terminology identified as problematic or that hinders equipoise communication is adjusted, and common questions are clearly addressed.

**4.4.2 Initial script testing (months 5-6) – “Behavioural Study 2”**

We will test the ‘recruitment script’ and audio record recruitment discussions with the aim of identifying how the trial is described and how equipoise is communicated. This will be undertaken at the lead site only.

**Sampling, Recruitment, and Consent**

*Qualitative semi-structured interviews:*

We will follow the sampling, recruitment, and consent processes outlined above, aiming for a convenience sample.

*Audio recorded recruitment discussions:*

Patients will be asked to speak to a recruiter who will explain the study. Verbal consent to record these conversations will be requested prior to carrying them out. Having finished a conversation, the recruiter will ask for written consent to take part in the trial and retain the audio recording.

**Data collection**

Data will be collected during months 5 and 6. Data will be qualitative semi-structured interviews and audio recorded recruitment discussions.

*Qualitative semi-structured interviews:*

Two ‘interview topic guides’ will be developed by the behavioral team (one for recruiters and one for patients), with input from all trial investigators. In line with best practice in qualitative research, these ‘interview topic guides’ will be iterated after each interview, and new questions added where appropriate.

We will interview research nurses/recruiters about their experience of using the ‘recruitment script’. We will interview patients about their experience of being recruited. We will ask patients who declined or agreed to take part what they understood about the trial, and what contributed to their decision making.

*Audio recorded recruitment discussions:*

We will audio record recruitment because interviews give us people’s reported options about decision making but are subject to recall and social desirability biases. Recruiters will be provided with hand-held audio recorders which they will switch on prior to engaging in a recruitment discussion.

**Data handling**

Recruiters will share audio recorded interview data securely with the behavioural team using secure file sharing software. Interview data will be transcribed verbatim. Audio recorded recruitment discussions will be transcribed following Jeffersonian transcription conventions, which are necessary for conversation analysis.32 Data will be de-identified and managed using NVivo 12 software.

**Analysis**

*Interview analysis:*

Analysis will be thematic and inductive, following Glasner and Strauss’ constant comparison method.30

*Analysis of recruitment discussions:*

We will first map the interactions identifying what actions are being achieved in recruitment discussions. Following Roosenhas et al,30 we will use conversation analysis to analyse sections of the audio recorded data.33 This is an empirical method for generating an evidence base of conversational patterns. This will be focused on areas of the interaction which appear ‘troubled’(e.g., indicating confusing/conflicting ideas) or around decisions about RCT randomization. This will highlight communication issues potentially hindering recruitment, and identify the accuracy and clarity of the presentation of the RCT. This work will aim to show which words and phrases present the equipoise appropriately, and do not inadvertently subvert the likelihood of consent to trial entry or deter action on weight in the intervention group, or promote it in the control group.

**4.4.2 Conversation analysis of subsequent recruitment across study sites (months 9 -21) – “Behavioural Study 3”**

We will conduct further conversation analysis across study sites to provide us with evidence of recruitment strategies which (a) communicate equipoise appropriately (b) address common issues hindering recruitment. This will be used to inform the subsequent RCT after the completion of this feasibility study.

**Sampling, Recruitment, and consent**

We will ask 2 recruiters at each study site to audio record patient recruitment. We will follow the patient sampling, recruitment and consent processes outlined above.

**Data collection**

Data will be collected from months 9-21. Data will be audio recorded recruitment discussions.

**Data handling and analysis of recruitment discussions**

We will follow the data handling and analysis processes outlined above. Analysis will be iterative taking place alongside data collection.

**Figure 1a. Summary of Behavioural Study 1, All Sites, Months 1 - 4**

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**Figure 1b. Summary of Behavioural Study 2 & Clinical Trial, Glenfield General Hospital Only, Months 5 - 6**

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**Figure 1c. Summary of Behavioural Study 3 & Clinical Trial, Glenfield General Hospital Only, Months 9 – 21**

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## Intervention

Eligible patients will be randomised in a 1:1 ratio using the internet-based system Sealed Envelope with stratification by surgical site and BMI. The intervention will not be blinded to patients due to the nature of the trial intervention.

### Treatment Allocations

### Weight stability group (control)

Participants receiving standard care will discuss their allocation with the research team to reinforce the value of their allocation. Participants will be asked to continue their normal diet and exercise, and to maintain a stable weight.

As recommended by NICE, we will ask GPs to offer referral to weight management programmes to control group participants who have obesity at recovery from the operation and completing the trial. This will be done by sending out the ‘GP Letter – Control Arm (End of Trial)’ letter.

### Weight management intervention (treatment)

Participants receiving the weight management intervention will discuss their allocation with their caregiver to reinforce the value of their allocation. Participants will be given a ‘weight management referral form’ containing their Slimming World ID number by the research nurse. Participants will call Slimming World using the number provided on the form, and Slimming World will subsequently post them a voucher for a free 12-week programme that adopts a multicomponent behavioural approach to promote and sustain weight loss typically delivered over 12 weekly sessions. This replicates what is available in the NHS in many areas.

### Follow-Up

* Baseline: demography, medical history, concomitant medication, body weight, EQ-5D, Clinical Frailty Scale
* 2-4 weeks post-baseline: telephone call to monitor and reinforce adherence to randomised allocation (audio recorded), adverse event monitoring.
* 1-day pre-surgery: body weight, EQ-5D, adverse event monitoring.
* Operation day: operation details.
* 120 hours post-surgery: organ injury, infection, and adverse event monitoring.
* 6 weeks post-surgery: participants will attend a routine outpatient clinic appointment where we will collect healthcare resource use data (via telephone questionnaire) and monitor adverse events.
* 3 months post-surgery: a final telephone call will be made at 3 months post-surgery to collect EQ-5D, Clinical Frailty Scale, healthcare resource use data (via telephone questionnaire) and monitor adverse events.

### Non-adherence to Protocol

Participants will be asked about intentions with respect to weight management and stability in a neutral manner at each contact, and their intention and their actions recorded. In the event of intent not to follow their assigned allocation, this will be documented, and the patient will continue to be treated according to the randomised allocation.

Major non-adherence:

* In the weight stability group, this will be defined as intent to change weight with specific actions orientated towards this, such as energy restriction.
* In the weight management group, this will be defined by failure to adhere to weight management programme (<75% attendance).

### Preoperative Care

All patients will receive standard care pre-operatively as per local practice.

### Anaesthesia and Perioperative care

Local protocols for anaesthesia and perioperative care and cardiopulmonary bypass (CPB) will be used.

### Treatment of organ failure

Patients may receive medications and/or other therapies to treat adverse events as deemed necessary by the investigator or the patient’s physician. The use of inotropes or vasopressors, renal replacement therapy, or ventilatory support will be at the discretion of the attending physician.

## Primary and secondary endpoints

### Primary Feasibility Outcome

* Proportion of participants randomised to the intervention group attending ≥75% scheduled sessions
* Proportion of participants randomised to the control group whose weights at surgery remains within 1.5kg of their baseline weight.

### Primary Efficacy Outcome

* Mean weight change at surgery relative to baseline.

### Secondary outcomes

Secondary outcome measures are:

1. Recruitment rate, attrition rate, data completeness.
2. A composite endpoint of ischaemic organ injury: low cardiac output, acute kidney, brain, or gut injury.
3. A composite endpoint of infection: surgical site infection, lower respiratory tract infection, urinary tract infection, sepsis.
4. Adverse events, including mortality, collected from randomisation to 3 months post-surgery.
5. Change in quality of life measured at baseline, 1-day pre-operation and 3 months using the EQ-5D-5L, a clinically validated and responsive instrument for measuring quality of life in cardiac surgery trials.34
6. Resource use up to 3 months post-surgery estimated from a bespoke questionnaire.

## Sample size

A mean difference in weight loss between treatment and controls of 2-3kg at 90 days was considered clinically important in two previous trials of commercial weight loss interventions in primary care.25,26 In these trials, the observed mean differences between treatment and control for intention to treat comparisons were approximately 4-5kg (SD 4.35). On the basis that the primary efficacy analysis in the current trial will be intention to treat, 92 patients randomised in a 1:1 manner (46 per group) will have a 90% power to detect a minimal clinically important difference of 3kg or an 80% power to detect a difference of 2.6kg. In previous trials 35,36 we have observed that up to 5% of cardiac surgery patients who are randomised will receive nonsurgical treatment due to changes in clinical status and around 5% may not complete the study for other reasons. We will therefore randomise 104 participants (52 in each group) to the trial. This sample size will be sufficient to establish a confidence interval (CI) with the lower bound no less than the targeted 60% (i.e. 95% CI 60% - 78% where the expected adherence rate is 69%)37. An adherence of ≥60% is a Public Health England Key Performance Indicator for adherence to weight loss programmes This will be enabled by the elderly cohort; in the WRAP trial older patients demonstrated high levels of uptake, adherence and weight loss in primary care (personal communication, Dr Amy Ahern from27), and the selection of patients willing to attend a weight management programme.

# Study Methods

**Figure 2. Consort Diagram Showing Design of SLIM-CARD Trial.**

**Consented**

Declined to consent

**Eligible and approached for consent**

Screened as not eligible

Baseline data collection: Body weight, demography, medical history, concomitant medication, EQ-5D, Clinical Frailty Scale

**Surgery:** Operative characteristics

**Allocated to weight stability (n=52)**

**1-day pre-operation:** Body weight, EQ-5D

**Outcomes at post-discharge Follow-Up (n=104)**

**6 week:** Assessment of adverse events and questionnaire (conducted in person or by telephone/extracted from medical record)

**3 month:** Assessment of adverse events, EQ-5D, Clinical Frailty Scale, and questionnaire (conducted by telephone/extracted from medical record)

**Intervention period (up to 12 weeks):** adherence to randomized allocation monitored, reinforced (audio recorded) and adverse events monitored at 2-4 weeks

**Outcomes from surgery until discharge (n=104)**

clinical follow up for organ injury, infection, and adverse events at 120 hours (day 5).

**Allocated to weight management (n=52)**

## Trial specific tests and procedures

These are summarised in **Table 1.** Participants will undergo these tests and procedures as part of the research and they are therefore in addition to tests and procedures undertaken as part of routine care.

## Duration of participation in the trial

The pre-surgical intervention period is 2-3 months, and the final follow-up is 3 months post-surgery. The total duration of participation in the trial is therefore approximately 6 months.

## End of the trial

For an individual participant, the end of the trial is defined as completion of the 3-month follow-up assessment.

Participants will be considered lost to follow-up only if there is insufficient information to determine their status at 3 months and no contact has been re-established following 3 documented attempts by the research team. The definition of the end of the trial for the individual participant is the date when they have completed the 3-month follow-up or have been lost to follow-up. The definition of the end of the trial as a whole is final data capture.

## 5.4 Data collection

Before surgery, anonymised, non-personal data will be collected on pre-printed screening forms for trial eligibility. For patients who agree to participate and provide signed consent, all eligibility criteria (e.g. demographic data and willingness to participate), will be confirmed. In addition, the participant’s initials, date of birth, hospital number and gender will be entered into the internet-based randomisation service to allow the randomised allocation code to be generated for a trial participant. This will be conducted through Sealed Envelope Ltd, an MHRA recognised service. Explicit consent for this use of participant initials, date of birth, hospital number and gender will be sought.

Source data will be collected on designated CRF’s. The patient’s medical notes will be a source for additional clinical data.

Follow-up data (collected at the routine 6 week follow-up visit and at 3 months post-surgery via questionnaire) will include data on other surgical complications and other adverse events occurring after discharge. These will be verified with reference to the medical notes, results of investigations and, if necessary, general practitioners. If participants fail to attend either of their visits, the data will be ascertained by these latter methods.

**Table 1: Key data collection points**

|  | Baseline | 2-4 weeks post-baseline | 1-day pre-operation | Op’n Day | Day 5 (120 hrs post-op) ± 12 hours, or discharge if sooner | 6 wks ± 3 weeks | 3 months |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Eligibility (age, BMI, commitment to allocation) | ✓ |  |  |  |  |  |  |
| Written consent | ✓ |  |  |  |  |  |  |
| Demography, medical history, concomitant medication | ✓ |  |  |  |  |  |  |
| Clinical Frailty Scale | ✓ |  |  |  |  |  | ✓ |
| Randomisation | ✓ |  |  |  |  |  |  |
| Operative details |  |  |  | ✓ |  |  |  |
| Body weight | ✓ |  | ✓ |  |  |  |  |
| Adherence to randomised allocation (audio recorded) |  | ✓ |  |  |  |  |  |
| Clinical organ injury, infection, or death. |  |  |  |  | ✓ |  |  |
| Adverse event monitoring |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| EQ-5D-5L\* & healthcare resource use questionnaire^(telephone call or review of medical/GP notes if no attendance to clinic) | ✓\* |  | ✓\* |  |  | ✓^ | ✓\*^ |

##

## Planned recruitment rate

Over 75% of patients who have obesity surveyed by our PPI group stated that they would participate in this trial. Across the 7 centres approximately 260 patients present for elective coronary artery bypass grafting (CABG) +/- Valve surgery every month (http://bluebook.scts.org/) of whom 30% will be eligible to take part, or 78 patients per month. We expect to recruit an approximately 11 patients per month for 9 months, or 17% of eligible patients. This is less than the recruitment in a previous pragmatic trial (44% of eligible patients) we have conducted in these centres.38

## Discontinuation/ withdrawal of participants

A participant is free to withdraw from the trial at any time for any reason. If a patient wishes to withdraw for any reason we will include any data already collected in our analysis as per the consent form, unless the patient expresses a wish for their samples and any associated data to be destroyed. We anticipate up to 10% of patient may not complete the study and this has been factored into our sample size calculations.

The investigator may also withdraw the participant at any time in the interest of safety. The primary reason for withdrawal must be recorded in the participant’s medical record and on the withdrawal form in the CRF. The withdrawal of a participant from the trial should be discussed, where possible, with the Chief Investigator. All attempts should be made to complete all follow-up assessments and visits for participants withdrawn for any reason during or after the intervention. Any comments (spontaneous or elicited) or complaints made by the participant or clinical care team, together with the reason for termination, date and time of withdrawal must be recorded in the CRF and source documents.

## Likely rate of loss to follow-up

Until discharge from hospital, the likely losses to follow-up will be due to death or a participant withdrawing, or more commonly, incomplete collection of post-operative data. Based on our other trials measuring similar endpoints (the PASPORT Trial ISRCTN23557269, the REDWASH trial ISRCTN27076315) we predict that this may occur in approximately 10% of patients. We also expect all participants to come to their routine clinical follow-up appointment at 6 weeks, as per standard care; patients that fail to attend the routine follow-up will be sent up to 3 reminders inviting them to attend subsequent clinics (performed every two weeks).

## Expenses and benefits

Participants in Behavioural Study 1 will receive payment for taking part (£85.00 cash for cardiac surgeons, £20.00 cash for other HCPs (i.e. nurses), and £15.00 voucher for patients). All other participants will not receive payment for taking part in the trial. Participants randomised to the weight management programme will receive this free of charge, however travels costs to the sessions will not be reimbursed.

## Measures taken to avoid bias

The trial will be analysed on an intention-to-treat basis, i.e. outcomes will be analysed according to the treatment allocation, irrespective of future management and events, and every effort will be made to include all randomised patients. Selection bias will be minimised by concealed randomised allocation. The intervention will not be blinded to patients due to the nature of the trial intervention. Procedural bias will be assessed by careful documentation of session attendance and assessment of changes in weight by research staff and mitigated by our behavioural analysis. Performance bias will be minimised by blinding of clinical staff caring for participants. Decisions about discharge from ICU, HDU, and from hospital will be made by clinical staff based on existing institutional protocols. ICU/HDU transition will be defined as transition from level 3 (1:1 nursing ratio) to level 2 (1:2 nursing ratio). HDU/ward transition will be defined as time of arrival on the ward. Detection bias will be minimised as Slimming World will be collecting the primary outcome data as part of their programme, and this is analogous to data collected as part of routine care. To minimise attrition bias, every effort will be made to complete all follow-up assessments. There will be dedicated research staff in each participating site to manage patient follow-up and the corresponding data collection. Reporting bias will be mitigated by trial registration and protocol publication. Funding bias: the commercial weight management organisations providing services free of charge have had no input into the design of the study.

## Balance of risks and benefits

The justification for a clinical evaluation of any intervention must weigh up the possibility of benefit from the intervention in only half the recipients, the risk of harm from the intervention, versus the absence of benefit in the control arm.

In the case of SLIMCARD trial there is very little data to inform this choice. It is common for people to lose weight before major surgery, but our own research has shown that this practice is not based on any evidence of benefit from previous studies. We have demonstrated that being overweight or obese is associated with improved outcomes following surgery. However, we do not know whether this is cause and effect, and these observations may be due to other factors that were not measured in these analyses, like frailty.

The absence of clear evidence to guide practice leads to variations in care. In a previous study we found that 35% of people who were overweight were advised to lose weight prior to surgery, although in most cases they were not provided with any help to do this.

We believe that uncertainty about the correct approach to diet and weight management before surgery, coupled with the variation in advice given to people about to undergo surgery justifies a clinical trial.

People will be randomly allocated to either the weight loss arm or the stable weight arm. This is equivalent to the choice of treatment being decided by the toss of a coin. This ensures that the treatment received is not unduly influenced by factors like age or sex or other things that could bias the trial result.

For people allocated to the weight management group, we know that this results in lower cholesterol levels and blood pressure. These effects, if sustained are known to reduce the progression of cardiovascular disease over months and years. Whether these changes affect the risks from surgery in the shorter term are unknown.

For people allocated to the weight stability group, the risks and benefits are unlikely to be different to that of the over 70% of overweight people who undergo surgery currently but who have received no weight loss advice or help prior to surgery.

Over 70% of people referred for cardiac surgery are overweight. This trial will help establish whether advising people to lose weight before surgery might be beneficial or not.

# Statistical Analyses

## Plan of analysis

A detailed statistical analysis plan will be written prior to the analysis. Outcomes will be analysed with an intention-to-treat approach using all available data. Continuous variables are summarized as mean (SD) or median (interquartile range, IQR), and categorical variables are summarized as number of cases and percentage.

Primary feasibility outcomes

Attendance of the sessions in the intervention arm will be supplied by Slimming World. For each participant, the proportion defined by the number of sessions attended dividing by the number of scheduled sessions will be computed. Missing data on attendance are considered as non-attendance. Then the proportion of participants randomised to the intervention arm attending ≥75% of their scheduled session will be calculated.

Proportion of participants randomised to the control arm with weight change at surgery within 1.5kg from their baseline will be calculated.

As a measure of the process, weekly attendance and body weight data supplied to us by Slimming World in participants randomised to the intervention-arm will be summarised. Change in body weight data at 4 week, 8 week and 12 week will be analysed using repeat measure modelling adjusted for baseline weight.

Primary efficacy outcomes

The primary efficacy analysis is to assess the difference between the intervention groups in mean weight change at surgery from baseline. This outcome will be analysed based on a linear mixed regression model adjusting for the baseline weight and the stratification variables, surgical site and BMI.

Secondary outcomes

Secondary outcomes will be compared using linear regression for continuous outcomes or logistic regression for binary outcomes. All analyses for secondary outcomes are exploratory as the study is not powered to detect such effects.

## Sensitivity analyses

Per protocol analyses for the primary feasibility and efficacy outcomes will be performed.

## Frequency of analysis

No formal interim analysis will be performed.

## Criteria for stopping the trial early

As this is a feasibility trial, no interim analyses are planned, and no stopping criteria are specified.

# Trial Management

## Day-to-day management

The trial will be managed by an Executive Group appointed by the Trial investigators. This will include representatives from the Cardiac Surgery Clinical Trials Team at the University of Leicester, the Leicester Diabetes Centre and Lifestyle Theme of the Leicester NIHR Biomedical Research Centre, and the Leicester Clinical Trials Unit (CTU).

The trial will be managed by a Trial Coordinator with oversight from the Senior Research Manager, supported by a Clinical Research Nurse from the Cardiac Surgery Clinical Trials Team at the University of Leicester. The Clinical Trials Team will design the trial, develop and maintain the trial database, check data quality as the trial progresses, and carry out trial analyses in collaboration with the clinical investigators. They will be responsible for identifying potential trial participants, randomising patients, collecting trial data and ensuring the trial protocol is adhered to. The PI or other qualified person delegated by the PI (for example research nurses) will take fully informed consent. This will be fully documented in the medical notes including inclusion and exclusion criteria. The trial is funded in its entirety by the British Heart Foundation.

## Trial Steering Group

As this is a feasibility trial with low risk, the trial will be led by the trial management group (TMG).

# Safety Reporting

##  Definitions

Adverse Event (AE)

Is defined as any untoward medical occurrence in a patient or clinical trial participant administered a clinical intervention, procedure, treatment, or medicinal product and which does not necessarily have a causal relationship with this medical intervention.

Serious Adverse Events (SAEs)

Is defined as any untoward medical occurrence in a trial participant that

* Results in death
* Is life threatening (the participant was at risk of death at the time of the event)
* Requires hospitalisation other than for planned surgery or prolongation of an existing hospitalisation
* Results in persistent or significant disability or incapacity
* Consists of a congenital anomaly or birth defect
* Other serious important medical event: an event that may not be immediately life threatening or result in death or hospitalisation, but which may jeopardise the participant or may require intervention to prevent one of the other serious outcomes listed in the definition above.

## Adverse event reporting

Adverse events will be recorded and reported in accordance with the University of Leicester’s standard operating procedure for processing and reporting serious adverse events (SOP S-1009 UoL). This is summarised in **Figure 3**.

Data on adverse events will be collected at the designated data collection points from the time of randomisation until the participant has completed their involvement in the trial. These events will be recorded in the appropriate section of the CRF. Serious adverse events will also be recorded in a separate ‘serious adverse event report’ form.

The Principal Investigator (PI) at each site will assess the relationship between the intervention and the occurrence of each adverse event. The PI or an appropriately delegated member of staff will then submit this to the Sponsor (UoL) for review. This review may lead to queries being issued via email to complete the event documentation.

In cardiac surgery, post-operative transient complications are not unexpected and are not infrequent. The research team will only record and notify fatal events, and any events not listed in **Table 2** to the Sponsor (UoL).

All events recorded will be included in the trial TSC every 6 months for review, and all serious adverse events will be included in the annual progress report to the REC. Where an event could be related to the intervention and is unanticipated, the CI or an appropriately delegated individual will report the event to the Sponsor within 24 hours of becoming aware.

## Expected events

**Table 2. Expected Events**

|  |
| --- |
| Any element of the composite primary outcome, including:* Sepsis
* Low cardiac output
* Stroke/ transient ischaemic attack/ delirium
* Acute kidney injury
* Acute liver injury or pancreatitis
* Gut infarction
 |
| GI complications, including:* Peptic ulcer/GI bleed/perforation
* Pancreatic (amylase >1500 iu)
* Other (e.g. laparotomy, obstruction)
 |
| Severe post-operative haemorrhage:* Post-operative haemorrhage 12 mL/kg/4 hrs
* Cardiac tamponade
* Resternotomy for haemorrhage
 |
| Pulmonary complications, including:* Acute respiratory distress syndrome
* Re-intubation and ventilation
* Tracheostomy
* Initiation of mask continuous positive airway pressure ventilation after weaning from ventilation
* Pneumothorax requiring chest drainage
* Pleural effusion requiring drainage
 |
| Arrhythmias, including:* Supraventricular tachycardia or atrial fibrillation requiring treatment
* Ventricular fibrillation or tachycardia requiring intervention
* Permanent Pacing
 |
| Re-operation for any reason, including:* Bleeding
* Cardiac arrest
* Wound dehiscence requiring rewiring or treatment for reason other than infection
* Mediastinitis
 |
| Thromboembolic complications, including:* Deep vein thrombosis
* Pulmonary embolus
 |
| Myocardial complications or requirement for haemodynamic support related to low cardiac output including:* Any inotropes
* Pulmonary artery catheter
* Vasodilator
* Myocardial infarction; new Q’s in 2 contiguous leads, raised Troponin I >5000 ng/ml, new ST depression >2 mm in 2 leads
* Resuscitation involving ventricular defibrillation/DC shock
* Intra-aortic balloon pump
* External/internal cardiac massage
* ECMO or VAD Support
* Myocardial Infarction
 |
| Renal complications, including:* Urinary retention
* Haematuria
* Urinary tract infection
* Acute kidney injury
* New haemofiltration/dialysis
 |
| Infective complications including;* Sepsis (defined as infection plus an increase in SOFA score of >2 within 72 hours of commencement of antibiotic treatment)
* Bacteraemia
* Wound infection
* Respiratory infection
 |

**Figure 3: Serious adverse event reporting flow chart**

AE

Does it meet the criteria for “serious”?

YES

NO

SAE

expected

unexpected

Did the event result in death?

YES

NO

* Report to the Sponsor within 24 hours of becoming aware.
* Reporting to REC will be as described in the Protocol.
* Include in the TSC report
* No requirement to report to the Sponsor unless identified as critical to evaluations of the safety of the trial. Regardless of this, all adverse events must be documented in CRF and medical notes.
* Report to the Sponsor within 24 hours of becoming aware.
* Reporting to REC will be as described in the Protocol.
* Include in the TSC report
* No requirement to report to the Sponsor unless identified as critical to evaluations of the safety of the trial. Regardless of this, all adverse events must be documented in CRF and medical notes.

## Review by an NHS Research Ethics Committee

Ethics review of the protocol for the trial and other trial related essential documents will be carried out by a UK NHS Research Ethics Committee (REC). Any substantial amendments to these documents, after a favourable opinion from the REC has been given, will be submitted for approval prior to implementation. Non-substantial amendments will be submitted to the HRA for approval.

# Research Governance

This clinical trial will be sponsored by the University of Leicester and will be conducted in accordance with:

* The principles of the Declaration of Helsinki (2013)
* International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines (CPMP/ICH/135/95, July 1996)
* UK Policy Framework for Health and Social Care Research (2017)
* General Data Protection Regulation (GDPR) (EU) 2016/679.
* Human Tissue Act 2004

## Sponsor approval

Any amendments to the trial documents must be approved by the Sponsor prior to submission to the HRA and REC and/or implementation.

## HRA approval

HRA approval must be granted prior to the start of the trial. Any substantial amendments to approved documents will need to be submitted to the REC via the HRA current processes. Non-substantial amendments will be submitted to the HRA for approval.

## Investigator’s responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed-off by all parties prior to Sponsor Green Light being issued. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor, CTU, NHS Trust or any regulatory authorities.

Investigators will be required to read, acknowledge, and inform their trial team of any amendments to the trial documents that they receive and ensure that the changes are complied with.

## Monitoring by Sponsor

The University of Leicester operates a risk-based monitoring and audit programme to which the SLIMCARD trial will be subject to.

## Indemnity

For the design and management of the trial the University of Leicester will provide indemnity. NHS indemnity will be in place for the conduct of the trial at the NHS site.

# Data Protection and Patient Confidentiality

## Data protection

Data will be collected and retained in accordance with the General Data Protection Regulation (GDPR) (EU) 2016/679.

## Data handling, storage and sharing

### Data handling

We will be processing personally identifiable data that is newly and directly collected from the participants and also from existing records both within and outside of the NHS (such as Slimming World).

Data will initially be entered into a workbook (CRF); this, along with documents containing identifiable information (completed consent forms and enrolment log) will be kept in a locked cabinet within a locked room with limited access at each hospital site in line with organisation processes. The data will then be transcribed directly onto a purpose designed database and data validation and cleaning will be carried out throughout the trial. Standard operating procedures (SOPs) for database use, data validation and data cleaning will be available and regularly maintained through the REDCap database. Each recruiting site will have access to the REDCap database, with individual login details for each user.

Organisational safeguards include awareness and training, segmented access control and access control lists (users will only have access to what they need), network authentication (username and passwords), anonymization and pseudonymization, password protected hardware (i.e. the audio recorders), and data sharing via secure browser-based, institutional services (FileDrop (Leicester), OxFile (Oxford)).

### Data storage

All study documentation relating to the clinical trial will be retained in a secure location during the conduct of the study and for 5 years after the end of the study. Study documentation for the behavioural study data will be retained for 3 years, except for the audio interviews (audio recordings, transcripts and consent forms) which will be retained for up to 40 years with consent. After this time, all patient identifiable paper records will be destroyed by confidential means. In compliance with the MRC Policy on Data Preservation, the pseudonymised dataset, a separate secure electronic ‘key’ with a unique patient identifier, and relevant ‘meta’-data about the trial will be retained in electronic form indefinitely (at the University of Oxford for the interview data, and the University of Leicester for all other data) because of the potential for the raw data to be used subsequently for secondary research.

The University of Oxford will store all interview data collected including audio files, transcripts, and consent forms in secure locations or servers. The Clinical Trial data will be entered onto the REDCap database. Original data collected at each recruiting site will be archived locally, with pseudonymised data only being transferred externally (except for where contact details need to be shared with the University of Oxford in order to undertake interview follow-ups or for the transport of consent forms for the behavioural study).

### Data sharing

The data will be shared outside of the University of Leicester with Sealed Envelope Ltd for the randomisation service, the University of Oxford as collaborators on the behavioural studies, and Prestige Network for the transcription service.

Data shared will be either anonymised or pseudonymised, using either password protected files via e-mail, or non-password protected files via secure browser-based software (e.g. FileDrop, OxFile). For the behavioural researchers to conduct telephone follow-ups, the research site will need to share the participant’s contact details and this will be done over the phone. The research site will also be required to transfer the consent forms for the behavioural study to the University of Oxford and this will be done securely.

After the publication of the main results of the study, fully anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods, and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be made available for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body.

# Dissemination of Findings

The trial protocol will be prospectively registered and published in a peer reviewed journal. The findings will be disseminated by usual academic channels (i.e. presentation at international meetings, as well as by peer-reviewed publications) and through patient organisations and newsletters to patients, where available. The anonymised trial data will be made available to other researchers in ethically approved studies after the publication of the main trial findings.

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# Amendments to protocol

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Amendment number****(i.e. REC and/or MHRA amendment number)** | **Previous version** | **Previous date** | **New version** | **New date** | **Brief summary of change** |
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# Protocol Signature Page

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| --- | --- |
| **Study Title:** | **Preoperative weight management to improve outcomes of cardiac surgery in adults with obesity (SLIMCARD): A multicentre feasibility RCT** |
| **Study Identifier:** | The SLIM-CARD Trial |
| **Protocol Version:** | 2.0 |
| **Sponsor Number:** | 0806 |
| **IRAS Number:** | 286239 |
| **Details of Sponsor:** | University of Leicester, Research Governance Office,Academic Departments, Leicester General Hospital,Gwendolen Road, Leicester, LE5 4PW, Tel: 0116 258 4099/258 4867, Email: rgosponsor@leicester.ac.uk |
| **Funding Reference:** | PG/20/10/34886 |
| **Chief Investigator:**(Specify Name, Institution, Address) | Professor Gavin Murphy (British Heart Foundation Chair of Cardiac Surgery, Director, Leicester Clinical Trials Unit), NIHR Leicester Biomedical Research Centre – Cardiovascular Theme, Department of Cardiovascular Sciences, College of Life Sciences,University of Leicester, Clinical Sciences Wing,Glenfield Hospital, Leicester, LE3 9QP |

**Chief/Principal Investigator Agreement:**

I, the undersigned, have reviewed this protocol and agree that it contains all necessary details for carrying out the clinical investigation described therein. Furthermore, I agree to conduct this clinical investigation in compliance with the ISO 14155:2011, as well as in accordance with Good Clinical Practice, the ethical principles set forth in the Declaration of Helsinki, The Medicines for Human Use Regulations and the applicable Local Research Governance Policies.

Signature: Date:

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Sponsor Representative: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_