UNIVERSITY OF PLYMOUTH

A feasibility multi-centre randomised controlled trial to test if a pre-operative two-week very low-calorie diet reduces intra-operative blood loss and improves post-operative outcomes following liver surgery, compared with a control group.

REducing **S**teat**O**sis prior to Li**V**er **RE**section (**RESOLVE**)

Statistical Analysis Plan

ISRCTN: 19701345
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	Name	Signature	Date
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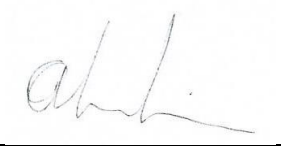
	Independent Statistician: Ashma Krishan		15th May 2024

ABBREVIATIONS

ASA	American Society of Anesthesiologists physical status classification
BMI	Body mass index
CCI	Comprehensive complications index
CI	Confidence interval
CONSORT	Consolidated standards of reporting trials
COPD	Chronic obstructive pulmonary disease
FLD	Fatty liver disease
HCC	Hepatocellular carcinoma
HDU	High dependency unit
HEAP	Health economics analysis plan
HPB	Hepato Biliary
HS	Hepatic steatosis
ITT	Intention to treat
ITU	Intensive therapy unit
LS	Liver surgery
MRI	Magnetic resonance imaging
NASH	Non-alcoholic steatohepatitis
NHS	National Health Service
PDFF	Proton density fat fraction
PT	Preferred term
RESOLVE	Reducing steatosis prior to liver resection
SAE	Serious adverse event
SAP	Statistical analysis plan
TAU	Treatment as usual
VLCD	Very low-calorie diet

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CONTENTS

1 INTRODUCTION

1.1 BACKGROUND AND RATIONALE FOR THE TRIAL

Hepatic steatosis (HS)/Fatty liver disease (FLD) is a pathological condition defined by the presence of large and small vesicles of fat accumulating within hepatocytes. FLD can occur in people who are overweight/obese, drink excessive alcohol, have type 2 diabetes or are on certain chemotherapy drugs [1]. Liver surgery (LS) to remove part of the affected liver from liver cancer, tumour deposits from bowel cancer and pre-cancerous tumours of the liver is standard treatment and offers a survival benefit [2]. In the year 2018/2019, almost 4000 liver resections were performed in England [3]. However, for those patients with FLD, liver surgery comes with an increased risk of bleeding and blood transfusion, complications, readmission and death [4]. Previous studies have shown that a pre-operative low-calorie diet may reduce surgical outcomes [5, 6], however, the studies are small and only include obese patients with no formal assessment of HS taking place before the dietary intervention.

The RESOLVE study aims to evaluate the feasibility of using a very low-calorie diet (VLCD) to reduce liver fat and improve surgical outcomes of patients with FLD. Participants will be randomised to receive either the VLCD or treatment as usual (TAU).

The VLCD consists of liquid meal replacements, providing 800 kcals and 80 g of protein (with additional protein provided if required) for two weeks before surgery, along with motivational support at day two or three of the diet from a dietitian. Adherence to the diet will be assessed through food diaries, changes in weight and number of empty sachets. The TAU consists of the individual site's usual procedures pre-surgery for LS patients, which may vary between sites.

This feasibility study aims to clarify whether patients are interested and willing to participate in the randomised trial, they are able to tolerate and adhere to the diet, dieticians and healthcare professionals are able to deliver the intervention consistently and to gather information to inform a sample size calculation, before a definitive trial.

1.2 PURPOSE OF THE STATISTICAL ANALYSIS PLAN

The study protocol includes an outline of the statistical methods to be adopted in the analysis of the data from the feasibility trial. The purpose of the Statistical Analysis Plan (SAP) is to provide the full details of the planned statistical methods to be used in the primary report of the RESOLVE feasibility trial results. The SAP has been drafted following the SAP guidelines [7]. Due to the nature of the feasibility trial, there will be no formal or inferential statistical analysis or hypothesis testing of the outcome measures in this trial. The Health Economics Analysis Plan (HEAP) will be provided separately.

1.3 TRIAL OBJECTIVES

1.3.1 Primary objectives

To conduct a randomised feasibility study of VLCD versus generic healthy eating instructions alone. The study will provide high quality data:

1. To estimate the rates of screening, recruitment, randomisation and retention.

2. To ascertain adherence to a VLCD and usual care prior to liver surgery and any possible contamination.
3. Ascertain completeness of data collection at baseline, day of surgery, day of discharge, 30 and 90 days post-operatively.
4. To allow a preliminary assessment of the VLCD intervention in the VLCD group.

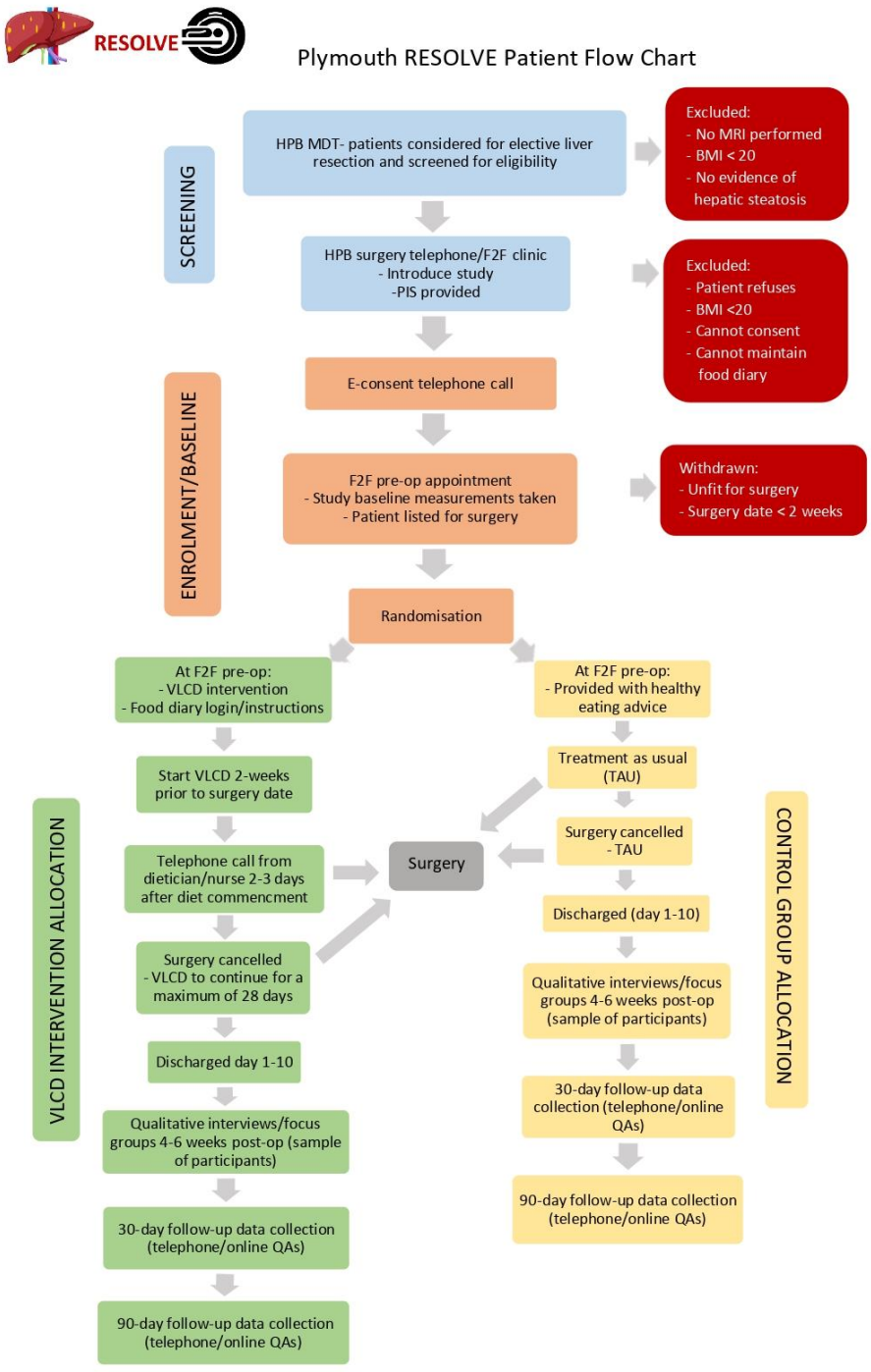
1.3.2 Secondary objectives

1. To estimate the resource use and costs associated with delivery of intervention, and to pilot methods for the cost-effectiveness framework in a full trial.
2. To identify if there is a need to modify the VLCD and its delivery within the NHS and if so, methods for improvement.
3. To identify the most clinically relevant primary outcome for the definitive trial: operating time, ease of liver surgery, blood loss, blood transfusion requirements up to discharge, time to functional recovery, Comprehensive Complications Index (CCI) at day 90 [8], length of stay, mortality, readmission within 90-days.

2 STUDY METHODS

2.1 TRIAL DESIGN

RESOLVE is a multicentre randomised controlled feasibility trial of VLCD (intervention) versus TAU (control). Figure 1 shows the participant's timeline through the RESOLVE trial.



This flowchart depicts the typical flow of participants. There may be some variation depending on site specific care pathways.

Figure 1: Typical participant flowchart through the RESOLVE study.

The full inclusion and exclusion criteria for the RESOLVE study can be found in Section 4.1. The VLCD consists of liquid meal replacement sachets for two weeks immediately prior to their surgery. If surgery is delayed, the VLCD can be followed for up to 28 days safely. Participants will take four sachets per day (providing 800 kcal and 80 g of protein). Participants on the VLCD are also permitted up to 100kcal per day of low-starch vegetables. If participants have been identified by the dietitians as needing more than 80 g of protein a day, they will be advised to take an additional protein powder supplement. Participants in the VLCD group are asked to record a food diary, capturing their compliance with the diet and their mood, hunger and energy levels. Two to three days into the study, participants on the VLCD will be contacted by phone by the dietitian, to support adherence and provide support.

TAU participants will receive the usual care at their study site; this may differ between the sites.

All participants will be scheduled for follow-up at 30 (±7) and 90 (±7) days post-surgery.

2.2 RANDOMISATION

A minimisation procedure with a random element (weighted at 0.9 in favour of minimising choice) will be used to allocate participants to receive VLCD or TAU. The following factors will be used in the minimisation procedure:

- Centre
- Type of surgery using the modified G-K liver surgery classification (Grade I, Grade II and Grade III) [9].

2.3 SAMPLE SIZE

As the trial is a feasibility study, a formal sample size calculation has not been performed. To assess the adherence rate with a confidence interval of ± 10 % and an estimated expected adherence rate of 75%, the required minimum sample size for this feasibility study is 72 participants (36 in each group), providing sufficient data to answer our feasibility and desirability questions. This feasibility study will include data from multiple UK-based centres that regularly perform liver resections. Most large Hepato Biliary (HPB) units would expect to perform 75-100 liver resections per year, so this will provide a large enough sample for this feasibility study.

In the UK-based centres that will take part in this study, we would expect a total of 800-900 liver resections to be performed per year. The prevalence of fatty livers is between 30-50%, which means we would expect 270-450 patients to have an underlying fatty liver that will be potentially eligible for the study during 12 months of recruitment. If at least 30% meet the criteria and agree to participate, there is an indication that enough patients could be approached to participate in this study.

2.4 BLINDING

The trial is non-blinded to participants and outcome assessors, as it is not possible to conceal the treatment allocation to them. Surgeons will be blinded to the treatment allocation. The trial statisticians undertaking the analysis will not be blinded to the treatment allocations, due to the assessed risk being low [10]. This SAP will be finalised prior to the end of the recruitment period, limiting any potential risk arising from the statisticians not being blinded. Any chosen definitions (for example adherence) will be documented in the SAP prior to the statisticians accessing any food diary

or outcome data. Updates to the SAP once signed off as a first draft will be reported alongside when they occurred with respect to blinding status.

2.5 Timing of Final Analysis

All analysis will be undertaken once the final participant has completed the final assessment at 90 days (+7 day window) post-randomisation and once the database is locked. There are no planned interim analyses. No hypothesis testing or inferential analysis will be undertaken.

2.6 Timing of Data Collection

Pre-baseline and baseline data collection is detailed in Section 4.4. This includes relevant surgical information, medical history, demographics, health related quality of life, physical measurements, and weight loss treatments.

The food diary for participants randomised to receive the intervention of the VLCD will be collected in the two weeks (maximum four weeks) prior to surgery. The food diary will collect the number of sachets taken each day along with protein supplements if required, and whether the participant has eaten over 100 kcal of vegetables or any other food or drink excluded from the diet. Mood, energy and hunger levels each day are reported.

On the day of surgery (pre-operative) physical measurements (weight and hand grip strength) and clinical measurements and assessments (including full blood count, liver and renal function, ASA – fitness for surgery, G-K classification of surgery, type of surgery and intended surgical approach) will be reported.

Post-operative day of surgery clinical assessments (including type of surgery, surgical approach, G-K classification, ease of liver surgery, duration of surgery, surgical complications, blood loss, blood transfusion requirements, haemostatic agents, intra-operative complications, full blood count, liver and renal function and blinding status of surgeon and guess of allocation) will be reported.

On the day of discharge clinical assessments (including blood transfusion requirements, post-operative complications, length of high dependency unit (HDU)/ Intensive Therapy Unit (ITU) stay, length of hospital stay, time to functional recovery, full blood count, and liver and renal function tests) will be reported.

At 30 (±7) days post-surgery clinical outcomes (including readmission, mortality, histology data, follow-up diagnoses, complications and blood transfusion requirements) will be reported.

At 90 (±7) days post-surgery clinical outcomes (including readmission, mortality, histology data, follow-up diagnoses and complications) will be reported.

3 STATISTICAL PRINCIPLES

3.1 CONFIDENCE INTERVALS AND P-VALUES

RESOLVE is a feasibility trial, and as such, no hypothesis testing or inferential analysis will be undertaken. Feasibility outcomes (including randomisation, retention rates and adherence) will be summarised and presented with two-sided 95% confidence intervals (CI).

Between-group differences of proposed main trial outcomes will be summarised and presented with two-sided 75%, 85% and 95% confidence intervals, as recommended by Lee et al. (2014) [11].

Estimates such as the standard deviation of proposed primary outcome, that may be used to aid future sample-size calculations, will be presented with two-sided 80% and 90% CIs [12, 13].

3.2 ADHERENCE AND PROTOCOL DEVIATIONS

Adherence to the VLCD will be monitored using the food diaries and the returned empty sachets.

Daily adherence to the VLCD is defined for participants as:

- Not eaten more than one portion of vegetables (100kcal) AND
- Not eaten any other food or non-zero calorie drinks AND
- At least 50% of protein requirements (if applicable) AND
- Maximum (number of sachets returned, the sum of sachets reported in the food diary rounded per day to the next largest integer) ≥ 3, where the number of sachets reported in the food diary will be assumed to be 1 if the whole sachet is reported, 0.75 if between half and whole sachet is reported, 0.5 if less than half is reported or 0 if none is reported.

Overall adherence to the VLCD is defined for participants as:

- Daily adherence (above) met on ≥ 10 days
  OR
- At least 75% of required sachets (i.e. sachets from days where the participant has not eaten more vegetables or other foods/drinks divided by (4 (total sachets per day)*days diet prescribed)) AND if applicable, at least 50% of protein requirement (i.e. protein from days where the participant has not eaten more vegetables or other foods/drinks divided by (protein requirement per day*days diet prescribed)).

Protocol deviations include but are not limited to: delays to surgery that mean participants cannot continue with the VLCD (i.e. delays of more than 2 weeks, as participants can safely remain on the VLCD for up to 28 days). The protocol deviations that are deemed to potentially significantly impact completeness, accuracy and/or reliability of the study data or that may significantly affect a subject's rights, safety or wellbeing, will be summarised.

3.3 ANALYSIS POPULATIONS

Primary analysis will be undertaken using the intention to treat (ITT) principle, where each participant is analysed according to their original allocated group as chosen by the minimisation procedure. A per-protocol sensitivity analysis will also be done to account for adherence to the VLCD.

The safety population will include all participants who have consented to participate in the trial, with safety data collected from consent to the 90-day follow-up or withdrawal.

4 TRIAL POPULATION

4.1 ELIGIBILITY

4.1.1 Inclusion criteria

Patients must satisfy all the following criteria to be enrolled in the study:

- Adult patients ≥18 years,
- Able to provide informed consent,
- Patients with Fatty liver with or without Non-alcoholic Steatohepatitis (NASH) requiring liver resection,
- Patients selected for LS for treatment of metastases, hepatocellular carcinoma, gallbladder cancer, peripheral cholangiocarcinoma, or pre-malignant hepatic tumours.

4.1.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from study participation:

- Patients with normal background liver on pre-op Magnetic Resonance Imaging (MRI),
- Patients with cirrhosis with or without signs of portal hypertension,
- Pregnant women,
- Patients that cannot tolerate low fat diet or are allergic or intolerant to components of VLCD meal replacement sachets,
- Patients that are lactose intolerant,
- Patients that follow a vegan diet,
- Patients who are unable to complete a food diary,
- Patients who are underweight (body mass index (BMI) <20kg/m^2),
- Patients who report unintentional weight loss of >5% in 0-3 months or >10% in up to 6 months.

4.2 RECRUITMENT

Details of participants from the screening process to the completion of the trial will be recorded and presented in the CONSORT-style flow chart (Figure 1 in Appendix).

In particular, the following data will be collected and provided, both overall and by intervention group where applicable:

- Number of people identified to participate in the trial.
- Number of people screened for eligibility.
- Number of people (percentage of screened) ineligible (with reasons where available).

- Number of people (percentage of screened) declined to participate (with reasons where available).
- Number of people (percentage of screened) consented to participate.
- Number of participants (percentage of consented) did not proceed to randomisation (with reasons where available).
- Number of participants (percentage of randomised) did not receive their allocated treatment.
- Number of participants (percentage of intervention) contacted at two/three days into VLCD.
- Number of participants (percentage of randomised) who completed post-surgery assessment.
- Number of participants (percentage of randomised) who completed discharge assessment.
- Number of participants (percentage of randomised) who completed the 30-day (±7 days) follow-up.
- Number of participants (percentage of randomised) who completed the 90-day (±7 days) follow-up.
- Number of participants (percentage of randomised) lost to follow-up.
- Number of participants (percentage of randomised) that withdraw from the trial.
- Number of participants (percentage of intervention) that discontinue VLCD.
- Number of participants (percentage of randomised) included in final analysis.

4.3 Withdrawal/Follow-up

There is potential for participant withdrawal from the trial intervention group due to a lack of tolerance of the VLCD, general feelings of unwellness or hunger. Participants in both arms may request to withdraw at any time during the study. These participants may continue to consent for follow-up and data collection (discontinuation of treatment only) or withdraw from future follow-up and data collection, allowing study use of only pre-collected data.

Reasons for withdrawal, where provided, will be summarised during each stage of the trial. Data will be summarised if there are any withdrawals from surgery (although this is not expected). The level of discontinuation, withdrawal and loss to follow-up will be used to inform the future sample size calculation of the main trial to allow for a sufficiently powered analysis.

4.4 Pre-Baseline data and Baseline Characteristics

Pre-baseline data and baseline characteristics will be summarised descriptively by allocation group (TAU or VLCD) to informally check for balance between groups and provide an overview of the trial population. Any considerable imbalance between allocated groups will be used to inform the design of the main trial. Continuous data will be summarised by mean and standard deviation, unless data are at least moderately skewed, in which case median and interquartile range will be used. Categorical variables will be summarised by frequencies and percentages.

Pre-baseline data collected include:

- Relevant surgical information: diagnosis (colon cancer/rectal cancer/Hepatocellular carcinoma (HCC)/adenoma/peripheral cholangiocarcinoma), number and size of colorectal metastases, number and size of HCCs, location and size of tumours, type of previous surgery

or ablation, methods of previous surgery (open/laparoscopic/hand-assisted/robotic), G-K classification of surgery.

- Pre-surgical chemotherapy information: type of chemotherapy, number of chemotherapy cycles and significant side effects encountered during chemotherapy.
- Comorbidities: diabetes, ischaemic heart disease/heart failure, cerebra vascular accident, atrial fibrillation, chronic kidney disease, pacemaker, chronic liver disease, chronic obstructive pulmonary disease (COPD), other.

Baseline characteristics collected include:

- Demographics: age (derived from date of birth), sex at birth, gender identity equal to sex at birth, ethnicity, religion, employment status, education status, marital/partner status, smoking status, performance status (if measured at pre-op).
- Physical measurements: height (cm), weight (kg), BMI (kg/m^2), hand grip strength in each hand (kg).
- Weight loss treatments: if the participant is currently taking part in any weight loss programs, if the participant has used any weight loss medications in the last 3 months.

5 STATISTICAL ANALYSES

5.1 OUTCOME DEFINITIONS

This SAP pertains only to the analysis of quantitative outcomes. Therefore, some feasibility outcomes are not described in the SAP, including the acceptability of outcome measurements, barriers and facilitators to delivering the intervention, fidelity of intervention (over time and site) and processes to ascertain Proton Density Fat Fraction (PDFF) quantification. Analysis of the health economic outcomes including the EQ-5D-5L and the health resource use questionnaire are detailed in a separate HEAP.

5.1.1 Feasibility trial outcome measures

To facilitate the design and planning of a future definitive trial, we will gather the following feasibility outcome measures:

- Number of patients screened, by site and overall,
- Number of patients recruited (consented) (and as a percentage of screened), by site and overall,
- Number of patients randomised (and as a percentage of screened), by site and overall,
- Retention rate at 30 and 90 days post-surgery (number and percentage of randomised), by site and overall,
- Success of blinding surgeons: percentage of correct surgeon guesses, by allocated group,
- The number of participants that adhere to the VLCD (and as a percentage of those randomised to the intervention group), as defined in Section 3.2.
- Completeness of outcome measures: number (percentage of randomised or applicable to) each of the proposed primary outcome measures and VLCD outcomes (listed in section 1.3.2 and 5.1.3 respectively) complete at day of surgery (pre- and post-operatively), day of discharge, 90-days post-operatively, as appropriate.
- The number and percentage of participants with a PDFF measure before randomisation and overall, by site and overall.

5.1.2 Patient-reported and other clinical outcomes

- Change in weight in kg.
- Change in handgrip strength (maximum of each hand) in kg.
- Duration of surgery (minutes).
- Ease of surgery using a surgeon-reported scale of 1-5 (1 = easiest, 5 = most difficult).
- Surgeon estimated intra-operative blood loss (ml).
- Blood transfusion requirement up to discharge (number of transfusions).
- Intra-operative surgical complications other than blood loss (including conversion to an open operation, injury to surrounding structures, cardiovascular events, cerebrovascular events and anaesthetic-related complications), including number of participants with complications and number of complications per participant.

- Clavien-Dindo classification post-operative complications [14], at discharge, 30 days and 90 days, including number of participants with complications and number of complications per participant.
- The CCI® [8] at discharge, 30 days and 90 days.
- Time to return to function in days.
- Length of hospital stay in days.
- Post-hepatectomy liver failure.
- Post-hepatectomy haemorrhage.
- Readmission within 30 and 90 days.
- Mortality within 30 and 90 days.

5.1.3 Very Low Calorie Diet

For the intervention group, measures captured within the food diary relating to the VLCD will be:

- Participant reported importance of success at adhering to the VLCD using a 1-10 scale (1 = not at all, and 10 = very important).
- Participant reported confidence in their ability to adhere to the VLCD using a 1-10 scale (1 = not confident at all, and 10 = very confident).
- The number of days that participants were required to be on the VLCD.
- The number of participants with surgery delayed, and the length of the delay.
- The number of empty sachets returned for each participant.
- The number of days the diary has been marked as completed for each participant (persistence).
- The number of days of minimal adherence to the diet for each participant in the intervention group.
- Participant reported daily dietary adherence scores using a 0–10 scale (0 = not at all, 5 = somewhat, and 10 = following the plan very well).
- The number of participants that initiate (completing minimal adherence to the diet for at least one day), discontinue (stop completing minimal adherence to the diet for at least 4 days in a row (excluding participants who return to the diet) before the end of the 14 day diet period), implement (completing at least 10 days of minimal adherence to the VLCD diet) with the dietary intervention for the two weeks [15].
- Daily mood scores reported in the food diary using a 0-3 scale (0=poor, 1=fair, 2=good, 3=very good).
- Daily energy scores reported in the food diary using a 0-3 scale (0=very low, 1=moderately low, 2=good, 3=very good).
- Daily hunger scores reported in the food diary using a 0-3 scale (0=extremely hungry, 1=quite hungry, 2=generally satisfied, 3=very satisfied).

5.1.4 Derived Outcome Measures and other derived variables

- Age at baseline calculated by date of baseline minus date of birth.
- The number of days intervention participants were required on the VLCD will be 14 unless the surgery is delayed or within 14 days (date of surgery – first day of VLCD).
- Operating time is defined as the sum of "knife to skin" time and "wound closure" time in minutes.
- Change in weight is calculated by weight (kg) at day of surgery minus weight (kg) at baseline.
- Change in handgrip strength is calculated by strength (kg) of the maximum recorded reading (left or right) at day of surgery minus strength (kg) of the maximum recorded reading (left or right) at baseline.
- Length of hospital stay as the number of days between surgery and discharge (date of discharge minus date of admission plus one).
- Time to return to function as the number of days between surgery and the date of proposed discharge.
- The CCI® [8]. To calculate the CCI, the highest grade (Clavien-Dindo grading) of each complication per participant is found. The weight of a grade I complication is wC1=300, a grade II complication is wC2=750, grade IIIa wC3=2750, grade IIIb wC4=4450, grade IVa wC5=7200, IVb wC6=8550. The overall CCI score is then calculated by:

$$CCI = \frac{\sqrt{wCI+wC2+\cdots+wCx}}{2},$$

for all x number of unique complications per participant, up to a maximum of 99 (i.e. if the CCI is calculated at 99 or above, the CCI will be 99). If a participant experiences a grade V complication, the CCI score is 100.

5.2 Missing Data

An outcome of the RESOLVE feasibility trial is to assess the completeness of the data collection of the potential outcome measures for the main trial. The summary of missing data may help inform the decision of the choice of primary outcome measure and may highlight areas to improve data collection in the main trial. There will be no imputation of outcome measures.

5.3 Analysis Methods

Due to the feasibility nature of the trial, it is not powered to support or justify any conclusions regarding treatment efficacy/effectiveness deduced from any hypothesis testing. As such, the analysis of this trial will not include inferential statistical comparisons or hypothesis testing between groups. All analysis undertaken will be descriptive with the aim to inform the design of the main, fully powered, RESOLVE randomised controlled trial in future.

Continuous measures will be summarised as means, standard deviations and ranges where the distribution appears approximately normally distributed, and as medians, inter-quartile ranges and ranges otherwise. Categorical data will be summarised by frequencies and percentages. Parameter estimates (e.g. between-group differences) will be presented with CIs.

Analysis of the quantitative data will be conducted to summarise the feasibility outcomes, evaluate the acceptability and concordance with the VLCD and assess the completion of the planned primary and secondary objectives.

5.3.1 Analysis of Feasibility Outcome Measures

Summary statistics of the outcomes described in Section 5.1.1 will be provided, where possible by allocated group and overall.

5.3.2 Preliminary Assessment of the Very Low-Calorie Diet

The feasibility trial aims to provide a preliminary assessment of whether the VLCD is effective for patients undergoing LS with HS. We will calculate summary statistics for each of the proposed primary outcomes listed in Sections 1.3.2 by allocated group and the VLCD outcomes in Section 5.1.3 for the intervention group.

For continuous outcomes, we will produce box or violin plots and calculate the mean and corresponding confidence interval by allocated group. The change in weight between baseline and pre-operation will also be presented.

The unadjusted between-group difference for each continuous outcome measure will be presented with the corresponding CIs. The adjusted between-group differences will also be presented, with corresponding CIs, adjusted for variables included in the minimisation procedure (site and type of surgery) along with baseline score. The adjusted analysis will be performed using multivariable linear regression.

For binary outcomes, we will produce frequency and percentages (with exact CIs) by allocated group and overall. The unadjusted between-group difference will be reported, derived from logistic regression models. The adjusted between-group difference will be reported, after adjustment of site and type of surgery.

5.3.3 Blinding of Surgeons

The frequency and percentage of the unblinding of surgeons to the participant's allocated group will be summarised within allocated group and overall. The surgeon's guess of the participant's allocated group will also be summarised by allocated group, for those that have not been unblinded.

5.3.4 Sensitivity analysis

A per-protocol sensitivity analysis will also be done for all proposed primary outcomes to account for adherence to the VLCD.

6 PROGRESSION TO THE DEFINITIVE TRIAL

The progression criteria, below, are proposed for consideration as part of the decision on whether or not to progress to planning a definitive trial. Progression to full trial will be considered if minimum success criteria for key feasibility aims/objectives are achieved:

- target population recruited within the recruitment window (<60% stop, 60-80% discuss and modify, >80% go).
- in participants randomised to the intervention group, adherence with diet (<50% stop, 50-70% discuss and modify, >70% go).
- completion of key outcome measures (potential primary outcomes, listed Section 1.3.2) separately and overall (including 3-month follow-up) (<60% stop, 60-80% discuss and modify, >80% go).
- evidence to suggest efficacy, i.e., that the very low-calorie diet holds promise as an effective intervention (demonstrated by an 80% confidence interval that indicates plausibility of the between-group difference).
- collection of data required to conduct cost-effectiveness analysis alongside a future full trial.

6.1 SAMPLE SIZE FOR DEFINITIVE TRIAL

We aim to present data resulting from the RESOLVE feasibility trial to aid in the formal sample size calculation for the main trial.

Potential primary outcomes for the definitive trial include operating time; ease of liver surgery; blood loss; number of blood transfusions at day of discharge; time to functional recovery; CCI at 90 days; length of stay; mortality; readmission.

To assist with the potential sample size calculations, we will calculate the standard deviation at baseline and point estimates of the mean of each potential primary outcome alongside 80% and 90% CIs by allocated group and overall.

6.2 SAFETY DATA

As participants are unlikely to experience any harm as a direct result of taking part in this trial, therefore the collection of safety data is restricted to Serious Adverse Events (SAEs). An SAE either:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a significant or important medical event.

SAEs will be captured from the time that consent is obtained until the 90-day follow-up for each participant. SAEs will be summarised by MedDRA preferred term (PT), allocated group and the relatedness to treatment, with the number of SAEs and the number of participants presented.

If more than 10 SAEs are reported, graphical representations of the safety data will be produced. These visualisations will include a bar chart presenting the number of adverse events per participant

by treatment allocation, a dot plot to display the absolute and relative risks within each MedDRA organ system class and treatment allocation, and a stacked bar chart displaying the percentage of participants with each SAEs within each organ system class and severity by treatment allocation, using the maximum severity for each participant within each category of event (see Figures A1-A3 in Phillips et al. [16])

6.3 Statistical Software

Statistical analysis will be undertaken using StataSE [17] version 17 or later and R [18] version 4.1.3 or later.

7 APPENDIX A: TABLES

Table 1: Reasons for non-participation

		n (%)
Eligibility (1)		
Declined	Unwilling to complete trial assessments	
	General health reasons	
	Unwilling to complete VLCD	
	Other	
	Total	
Excluded	Ineligible	
Eligibility (2)		
Declined	Too busy	
	Unwilling to complete trial assessments	
	General health reasons	
	Not interested	
	Unwilling to complete VLCD	
	Total	
Excluded	Ineligible	
	PIS not given in error	
	Total	
Pre-consent		
Declined	Too busy	
	Unwilling to complete trial assessments	
	General health reasons	
	Not interested	
	Unwilling to complete VLCD	
	Total	
Excluded	Ineligible	
	PIS not given in error	
	Participant does not consent	
	Total	

Table 2: Discontinuation and withdrawal

Post randomisation		**n (%)**
Withdrawal from trial	Personal choice (consent withdrawal)	
	In consultation with health professional	
	Total	
30 day follow up		
Withdrawal from trial	Personal choice (consent withdrawal)	
	In consultation with health professional	
	Total	
90 day follow up		
Withdrawal from trial	Personal choice (consent withdrawal)	
	In consultation with health professional	
	Total	

Table 3: Recruitment by site, sites to be added or removed as necessary *[n (%) unless otherwise stated]*

Plymouth	Screened	
	Recruited	
	Randomised	
	Proportion randomised [95% CI]	
	Retained at 30-day follow-up	
	Retained at 90-day follow-up	
Southampton	Screened	
	Recruited	
	Randomised	
	Proportion randomised [95% CI]	
	Retained at 30-day follow-up	
	Retained at 90-day follow-up	
Surrey	Screened	
	Recruited	
	Randomised	
	Proportion randomised [95% CI]	
	Retained at 30-day follow-up	
	Retained at 90-day follow-up	
Liverpool	Screened	
	Recruited	
	Randomised	
	Proportion randomised [95% CI]	
	Retained at 30-day follow-up	
	Retained at 90-day follow-up	
Leeds	Screened	
	Recruited	
	Randomised	
	Proportion randomised [95% CI]	
	Retained at 30-day follow-up	
	Retained at 90-day follow-up	
Nottingham	Screened	
	Recruited	
	Randomised	
	Proportion randomised [95% CI]	
	Retained at 30-day follow-up	
	Retained at 90-day follow-up	
Overall	Screened	
	Recruited	
	Randomised	
	Proportion randomised [95% CI]	

	Retained at 30-day follow-up	
	Retained at 90-day follow-up	

Table 4: Completeness of data at pre-baseline, baseline, day of surgery (pre and post-operative), discharge, 30-day follow-up, 90-day follow-up *[n (%) unless otherwise stated]*

Time point	CRF	Both	Intervention	Control
Pre-baseline	Intended surgery details			
	Medical history			
Baseline	Demographics			
	Physical assessment			
Pre-operative	Physical assessment			
	Pre-op clinical measures			
	Biochemical tests			
Post-operative	Biochemical tests			
	Intra-op clinical measures			
Discharge	Clinical measures			
	Blood transfusion requirements			
	Complications			
	Biochemical tests			
30-day follow-up	Follow-up assessment			
	Complications			
	Blood transfusion requirements			
90-day follow-up	Follow-up assessment			
	Complications			
	Blood transfusion requirements			

Table 5: Completeness of PDFF measure

Site	**n (%)**
Plymouth	
Southampton	
Surrey	
Liverpool	
Leeds	
Nottingham	
Overall	

Table 6: Adherence of VLCD

VLCD	Adherence	At least 75% of all sachets over the intervention period	Participants who adhered to the VLCD on at least 10 days	Days participants adhered to the VLCD	Number of sachets per day	At least 50% of protein requirement (if applicable)
n (%)						
n, Mean (SD) 95% CI						
Median (IQR)						
[Min, Max]						

Table 7: Participant characteristics at baseline [n (%) unless otherwise stated]

Characteristic	Both	Intervention	Control
Age (years)			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Assigned sex at birth			
Female			
Male			
Prefer not to say			
Missing			
Self-identified gender equal to sex at birth - yes			
Ethnic group			
White			
Mixed/multiple			
Asian/Asian British			
Black/African/Caribbean/Black British			
Other			
Prefer not to say			
Missing			
Religion			
No religion			
Christian			
Buddhist			
Hindu			
Jewish			
Muslim			
Sikh			
Other			
Prefer not to say			
Missing			
Highest education level			
Apprenticeship			
Degree-level or higher			
NVQ or equivalent			
A and AS level or equivalent			
GCSE or equivalent			
Left school at 15			
Other			
Prefer not to say			
Missing			
Employment status			
Working as an employee			
Self-employed or freelance			
Away from work ill			

Characteristic	Both	Intervention	Control
In full time education			
Other paid work			
Retired			
Semi-retired			
Other			
Prefer not to say			
Missing			
Marital status			
Single			
Co-habiting			
Long-term relationship			
Married			
Civil partnership			
Separated			
Divorced			
Widowed			
Prefer not to say			
Missing			
Smoking status			
Smoker (regular)			
Non-smoker			
Smoker (non-regular)			
Ex-smoker			
Missing			
Performance status			
0			
1			
2			
3			
4			

Table 8: Health characteristics at baseline [n (%) unless otherwise stated]

Characteristic	Both	Intervention	Control
Diagnosis			
Colon cancer			
Rectal cancer			
Hepatocellular carcinoma (HCC)			
Adenoma			
Peripheral cholangiocarcinoma			
Other			
Modified G-K classification of liver surgery (grade)			
I (low difficulty)			
II (intermediate difficulty)			
III (high difficulty)			
Previous cancer surgery			
Yes			
No			
Type of chemotherapy			
Capecitabine only			
FOLFIRINOX			
CAPE-OX			
FOLFOX			
GemCap			
Gemcitabine only			
Other			
None			
Missing			
Co-morbidities			
Diabetes			
Ischaemic heart disease/heart failure			
Cerebra vascular accident			
Atrial fibrillation			
Chronic kidney disease			
Pacemaker			
Chronic liver disease			
Chronic obstructive pulmonary disease (COPD)			

Table 9: Physical assessments at baseline [n (%) unless otherwise stated]

Characteristic	Both	Intervention	Control
BMI			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Weight loss medications in the last three months?			
Yes			
No			
Missing			
Left hand grip strength (kg)			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Right hand grip strength (kg)			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			

Table 10: Summary statistics for clinical and patient-reported outcomes *[n (%) unless otherwise stated]*

Outcome	**Both**	**Intervention**	**Control**
Change in weight			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Change in maximum handgrip strength (kg)			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Duration of surgery (minutes)			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Delay to surgery (days)			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Ease of surgery			
1			
2			
3			
4			
5			
Surgeon estimated intra-operative blood loss (ml)			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Blood transfusion requirements up to discharge (number of transfusions)			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Length of hospital stay (days)			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Time to return to function (days)			
n: mean (SD)			
Median (IQR)			

Outcome	Both	Intervention	Control
[Range]			
Missing			
Success of blinding surgeon - correct			
Surgeon guess of allocation - correct			
Intra-operative surgical complications other than blood loss			
0			
1			
2			
3 (to be extended as necessary)			
Clavien-Dindo classification post-op complications at discharge			
0			
1			
2			
3 (to be extended as necessary)			
Clavien-Dindo classification post-op complications at 30 days			
0			
1			
2			
3 (to be extended as necessary)			
Post-hepatectomy haemorrhage			
Grade A			
Grade B			
Grade C			
Post-hepatectomy liver failure			
Grade A			
Grade B			
Grade C			
Clavien-Dindo classification post-op complications at 90 days			
0			
1			
2			
3 (to be extended as necessary)			
CCI at 90 days			
n: mean (SD)			
Median (IQR)			
[Range]			
Missing			
Mortality at 90 days – yes			
Readmission at 90 days - yes			

Table 11: Summary statistics for VLCD outcomes *[mean (SD) IQR [min, max] unless otherwise stated]*

Outcome	**Intervention**
Important of success	
Confidence in ability	
Number of days on VLCD	
Surgery delayed – yes n (%)	
Number of empty sachets	
Number of days diary marked as complete (persist)	
Initiate – yes n (%)	
Discontinue – yes n (%)	
Implement – yes n (%)	

Table 12: Summary statistics for VLCD self-reported outcomes *[mean (SD) IQR [min, max] unless otherwise stated]*

		Hunger	***Mood***	***Energy***	***Adherence***
Days with a score of 0 (i.e. Poor mood, very low energy, extremely hungry, low adherence)	n: median (IQR) [Range] Missing				
Score per day n: median (IQR) [Range] Missing	*Day 1*				
	Day 2				
	Day 3				
	Day 4				
	Day 5				
	Day 6				
	Day 7				
	Day 8				
	Day 9				
	Day 10				
	Day 11				
	Day 12				
	Day 13				
	Day 14				

Table 13: Between group differences and confidence intervals of change between baseline and follow up

Outcome	Between group difference	75% confidence interval	85% confidence interval	95% confidence interval
Weight (kg)				
Maximum hand grip strength (kg)				

Table 14: Unadjusted between group differences and confidence intervals of continuous outcomes

Outcome	**Between group difference**	**75% confidence interval**	**85% confidence interval**	**95% confidence interval**
Duration of surgery (minutes)				
Ease of surgery				
Blood loss (ml)				
Time to functional recovery (days)				
CCI at 90 days				
Length of stay (days)				

Table 15: Adjusted between group differences and confidence intervals of continuous outcomes

Outcome	Between group difference	75% confidence interval	85% confidence interval	95% confidence interval
Duration of surgery (minutes)				
Ease of surgery				
Blood loss (ml)				
Time to functional recovery (days)				
CCI at 90 days				
Length of stay (days)				
Blood transfusion requirements (number at discharge)				

Table 15: Between group differences and confidence intervals of binary outcomes

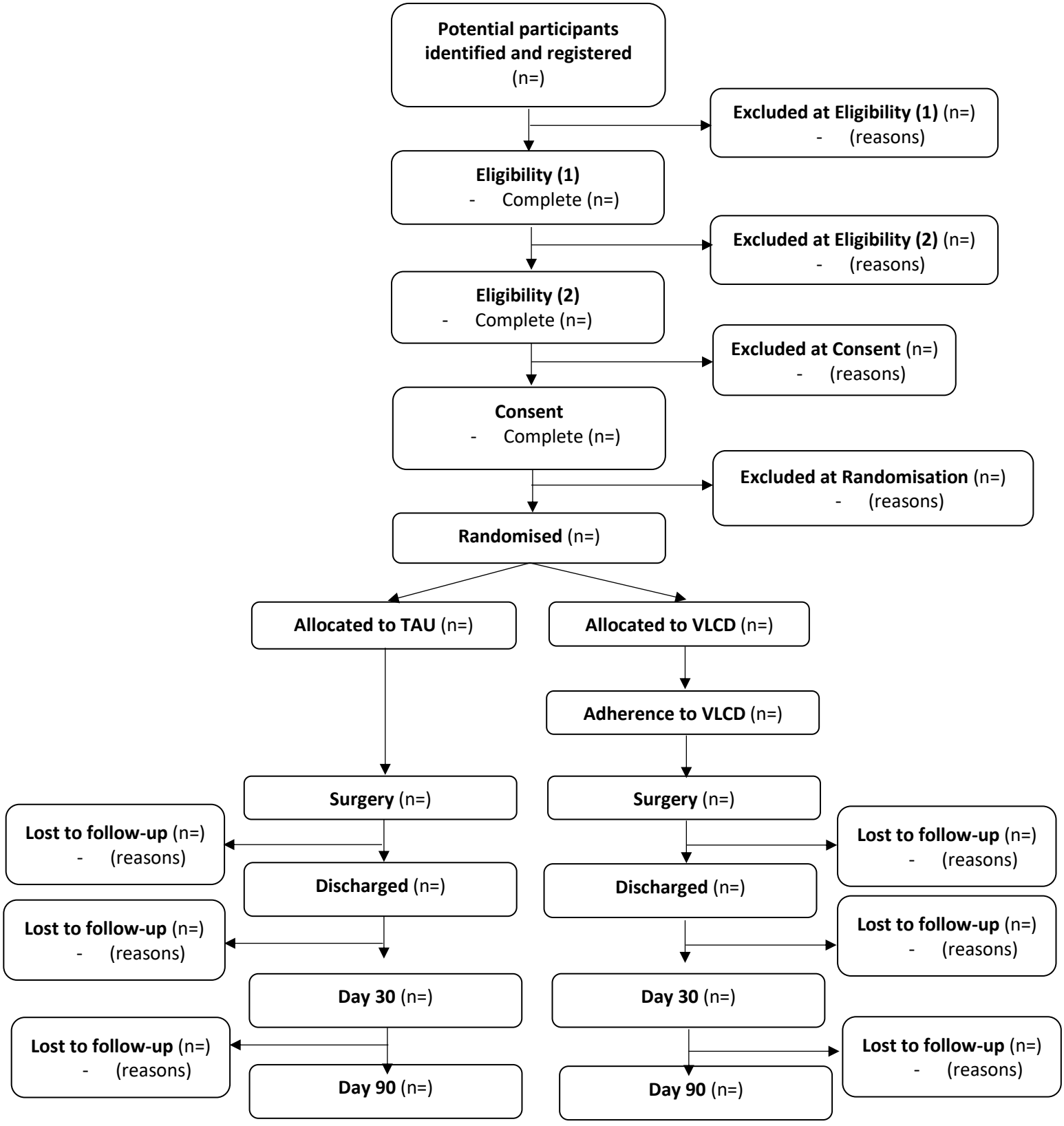
Outcome	**75% confidence interval**		**85% confidence interval**		**95% confidence interval**	
	Adjusted	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**
Mortality within 90 days – yes						
Readmission within 90 days - yes						

Table 15: Estimates of standard deviations for patient reported and clinical outcomes for the definitive trial

Outcome	Standard deviation	80% confidence interval	90% confidence interval
Duration of surgery (minutes)			
Ease of surgery			
Blood loss (ml)			
Time to functional recovery (days)			
CCI at 90 days			
Length of stay (days)			
Blood transfusion requirements (number at discharge)			

8 APPENDIX B: FIGURES

Figure 1: CONSORT style flow diagram through RESOLVE.



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