FULL/LONG TITLE OF THE TRIAL

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 improve post-operative outcomes following liver surgery, compared with a control group.

SHORT TRIAL TITLE/ACRONYM

REducing SteatOsis prior to LiVer REsection (RESOLVE Feasibility Trial)

IRAS number:	**323252**
ISRCTN:	**19701345**
FUNDER'S reference:	NIHR203632
PROTOCOL VERSION:	**V1.5_17_06_2024**

This protocol has regard for the HRA guidance and order of content

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and in accordance with the UK Policy Framework for Health and Social Care Research, the Data Protection Act 2018, the principles of Good Clinical Practice (GCP) and the Sponsor's (and any other relevant) SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the trial will be given; any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: L. Garner	Date (dd/mm/yyyy): 18/06/2024

Name (please print): Laura Garner

Position: Quality Assurance Manager

Chief Investigator:

Signature: 	Date (dd/mm/yyyy): 18/06/2024

Name: (please print): Somaiah Aroori

Chief Investigator:

Signature: 	Date (dd/mm/yyyy): 18/06/2024

Name: (please print): Professor Victoria Allgar

Trial Statisticians:

Signature:	Date (dd/mm/yyyy):
	18/06/2024

Name: (please print):
Dr Lexy Sorrell

Signature:	Date (dd/mm/yyyy):
	18/06/2024

Name: (please print):
Jade Chynoweth

PROTOCOL AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
AM01_NSA01	V1.2	19/04/2023	Helen Neilens	• Dietitian training changed from 6 hour modules to 3 hours face to face online • Randomisation technique amended • Added ISTRCN registration number • Spelling errors corrected and inconsistencies addressed.
AM02_NSA02	V1.3	14/08/2023	Helen Neilens	• Sponsor representative changed to Laura Garner • Clarification of surgical complications versus post-operative ones • Defined ‘operating time’ • Updated sites • Updated Figure 1, flow chart • Updated measures and timepoint inconsistencies • Clarified timepoints
AM03_NSA03	V1.4	08/11/2023	Angela King	• Add three new sites • Clarification of use of screening data held by UoP for future study contact with patient/participant with verbal consent.

AM05	V1.5		Helen Neilens	• Extend recruitment until 30th September 2024 • Removal of two sites not opened • Couple of outcomes clarified.

KEY TRIAL CONTACTS

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Trial Steering Committee – Independent members	Mr Sanjay Pandanaboyana, Consultant Hepatopancreatobiliary and Transplant Surgeon, Newcastle Hospitals NHS Foundation Trust Dr Stuart McPherson, Consultant Hepatologist, Newcastle Hospitals NHS Foundation Trust David Bourne, Dietitian, Newcastle Hospitals NHS Foundation Trust Mrs Heather Boult, Patient representative Peter Latchford, Patient representative Dr Ashma Krishan, Trial Statistician, University of Manchester

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ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BMI	Body Mass Index
BT	Blood Transfusion
BTR	Blood Transfusion Rate
CEA	Cost-effective analysis
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trials Unit
eCRF	Electronic Case Report Form
F2F	Face-to-face
FLD	Fatty Liver Disease
GCP	Good Clinical Practice
HCC	Hepatocellular carcinoma
HRA	Health Research Authority
HS	Hepatic Steatosis
ICF	Informed Consent Form
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
LCD	Low Calorie Diet
LS	Liver Surgery
MRI	Magnetic Resonance Imaging
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
NHS R&D	National Health Service Research & Development
PenCTU	Peninsula Clinical Trials Unit
pCRF	Paper Case Report Form
PDFF	Proton Density Fat Fraction
PI	Principal Investigator
PPI	Patient and Public Involvement
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QUALY	Quality adjusted life-year analysis
RCT	Randomised Controlled Trial
REC	Research Ethics Committee

SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TAU	Treatment as usual
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
US	Ultrasound
VLCD	Very Low-Calorie Diet

iii. TRIAL SUMMARY

Trial Title	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.
Short title/acronym	REducing SteatOsis prior to LiVer rEsection (RESOLVE)
Clinical Phase	Phase 3
Trial Design	Feasibility multi-centre randomised controlled trial
Trial Aim	To test the feasibility of undertaking a randomised controlled trial of a very low-calorie diet (VLCD) versus usual care in people undergoing elective liver surgery (LS) who have magnetic resonance imaging (MRI) confirmed hepatic steatosis (HS)
Primary objectives	1. To estimate the rates of screening, recruitment, randomisation, and retention, 2. To ascertain adherence to a VLCD prior to LS and any possible contamination. 3. Ascertain completeness of data collection at baseline, day of surgery, 30 and 90 days follow up. 4. To allow a preliminary assessment of the VLCD intervention.
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.
Study Population	
Trial Participants	Adult patients undergoing elective liver surgery who have MRI confirmed hepatic steatosis
Inclusion criteria	• Adult patients ≥18 years • Able to provide informed consent • Patients with HS with or without non-alcohol steatohepatitis (NASH) requiring liver resection • Patients selected for LS for treatment of metastases, hepatocellular carcinoma, gallbladder cancer, peripheral cholangiocarcinoma, or pre-malignant hepatic tumours
Exclusion criteria	• Patients with normal background liver on pre-op 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 • Patients that are lactose intolerant • Patients that follow a vegan diet • Patients who are unable to complete a food diary • Patients who have a low BMI (<20kg/m2)

	• Patients who report unintentional weight loss of >5% in 0-3 months or >10% in up to 6 months
Qualitative Evaluation	Mixed method approach comprising: • 6 to 7 focus groups (one for usual care, one for those who withdrew and 4 to 5 for participants in the intervention group) • Telephone interviews will be an option for those who would rather not participate in a group • One 60-minute focus group for all dietitians involved in the intervention to explore the acceptability of the VLCD and the diary, to identify barriers and facilitators to intervention delivery, to identify methods to improve delivery and implementation within the NHS • Telephone interviews with radiologists to discuss the process of obtaining Proton Density Fat Fraction (PDFF) quantification • Audio recordings of intervention delivery at the start, the middle and towards the end of recruitment to assess fidelity of it and whether training effects reduce over time
Summary of outcome measures	
Feasibility	• Number of patients screened, consented (as a proportion of patients screened) and randomised (as a proportion of patients screened). • Number of recruited patients completing measures on day of surgery. • Number of patients completing food diary over period of VLCD. • Successfully blinded surgeons. • Adherence to VLCD-Self-report in food diary, discussions in qualitative interviews and focus groups, difference in weight between baseline and day of surgery (pre-op), empty sachet returns. • Completeness of data capture and outcome measures to include baseline and day of surgery, plus self-reported food diary. • Discussions and feedback from dietitians and radiologists
Clinical and patient-reported outcomes	• Pre-operative weight loss • Energy and protein intake – actual vs prescribed • Operating time • Ease of surgery • Blood loss • Blood transfusion requirement • Surgical complications • Functional recovery • Length of stay • Post-operative complications – Clavien Dindo grade I to V and Comprehensive Complication Index (CCI) • Readmission rate and mortality within 90 days • EQ-5D-5L • Health Resources Use Questionnaire
Treatment duration	2 weeks pre-operatively
Follow-up	30- and 90-day post-operative follow up
Planned Trial Period	Set-up 6 months, recruitment 12 months; follow up 3 months, data analysis and reporting 3 months (24 months total)

Study treatment	
Control arm	Treatment as Usual
Intervention arm	A pre-operative two-week very low-calorie diet.

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL SUPPORT GIVEN
NIHR RfPB	£268,392.00

v. ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor for this study, University Hospitals Plymouth NHS Trust, assumes overall responsibility for the initiation and management of the trial.

The Sponsor and funder will not have direct involvement in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The trial was designed by the Chief Investigator and co-applicants with support from the NIHR Research Design Service and the Peninsula Clinical Trials Unit.

vi. ROLE OF THE COORDINATING CLINICAL TRIALS UNIT (CTU)

The Sponsor of the study has allocated tasks associated with overall trial management and data management to the Peninsula Clinical Trials Unit (PenCTU). CTU's management of the trial includes the delivery of site initiation training and monitoring. A detailed breakdown of tasks undertaken by PenCTU on behalf of the CI and trial Sponsor is described in a formal written Sponsor agreement.

vii. ROLES OF TRIAL OVERSIGHT COMMITEES AND GROUPS

The Trial Steering Committee (TSC) is an executive oversight body operating on behalf of the Sponsor and will make decisions as to the future continuation (or otherwise) of the trial. The TSC has an independent chair (Mr Sanjay Pandanaboyana) and a second independent clinician (Dr Stuart McPherson), an independent Dietitian (David Bourne), two patient representatives (Mrs Heather Boult, Peter Latchford), and an independent statistician (Dr Ashma Krishan). The TSC will meet every 6-7 months in accordance with an agreed set of terms of reference to review the progress of the trial and any serious adverse events and will report to the Sponsor.

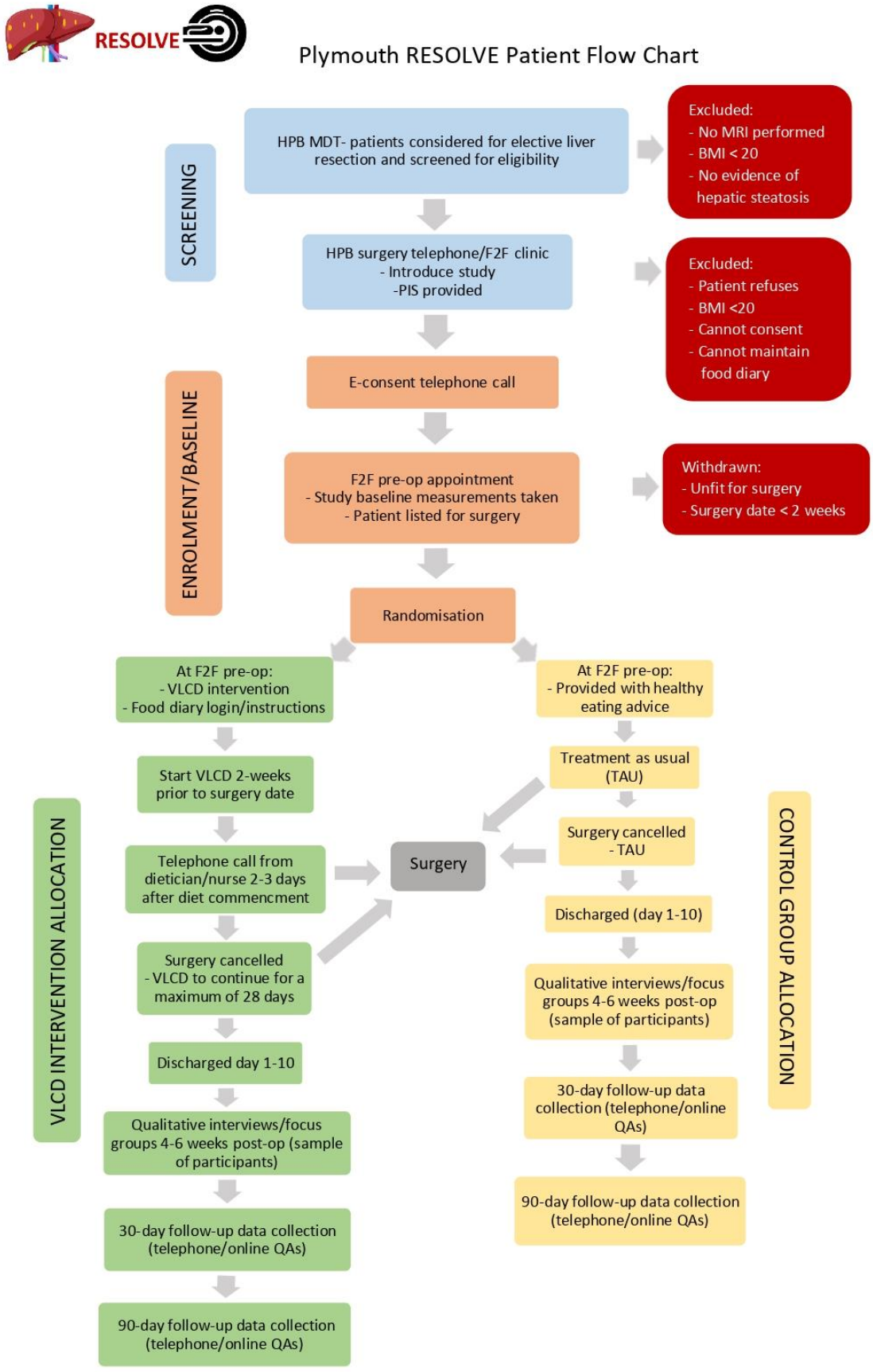
The Trial Management Group (TMG) is chaired by the Chief Investigators and includes representation from the Sponsor, statistics team, PenCTU and patient representatives. It also includes representation from co-investigators and leads for the qualitative and health economic components. The TMG will meet monthly to review trial progress and to ensure appropriate management of the trial, in accordance with the terms of reference for the Group.

A Data Monitoring and Ethics Committee will not be convened for this trial, which is considered to pose low risk of harm to participants.

viii. KEY WORDS:

Very low-calorie diet; hepatic steatosis; liver surgery

ix. PATIENT JOURNEY FLOW CHART



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

1. BACKGROUND

1.1 Background summary

Excessive accumulation of fat in the liver causes fatty liver disease (FLD). This can occur in people who are overweight/obese, drink excessive alcohol, have type 2 diabetes, or on certain chemotherapy drugs as part of cancer treatment. In the UK, 1 in 3 adults are obese and 4 million have a diagnosis of type 2 diabetes mellitus (T2DM). Removal of part of the liver is performed for tumours, commonly for tumours that have spread from bowel cancer. Many of these patients will have chemotherapy before surgery, which is well-known to contribute to fatty liver. In 2018/2019, just over 4000 liver resections were performed in England. Almost 30-50% of patients undergoing liver resection have underlying fatty liver.

The mainstay of treatment for primary liver cancer, tumour deposits from bowel cancer, and for pre-cancerous tumours of the liver, is removal of the affected part of the liver. Liver surgery (LS) offers a clear survival benefit for patients who are fit enough to undergo surgery. Before liver surgery, it is standard practice for a patient to have a Magnetic Resonance Imaging (MRI) scan of the liver. MRI of the liver helps doctors with detailed evaluation of the liver abnormalities and allows the surgeons to plan the operation. Using this MRI scan, a radiologist can also evaluate the presence of and then grade the severity of liver fat.

Liver surgery in patients with underlying FLD can be challenging, associated with a two-to-three-fold increased risk of bleeding and blood transfusion (BT), two-to-three-fold increased risk of complications, 50% increased risk of dying, and two-fold increased risk of readmissions to the hospital following surgery. BT reduces cancer-free and overall survival following liver surgery for cancer. So, any intervention that reduces the amount of fat in the liver can potentially reduce the risk of bleeding during surgery, blood transfusion rate (BTR), and overall complications. In combination, these outcomes will benefit patients and save money for the NHS.

Low-calorie and very low-calorie diets (LCDs and VLCDs) are routinely used for 2-4 weeks before weight-loss and gallbladder surgery to reduce liver size and the fat inside the abdomen to make surgery safer. These diets typically provide 800-1200 kcal/day and involve either restricted regular food with a vitamin and mineral supplement or a commercially produced balanced liquid meal replacement. There is, however, a lack of scientific evidence on the usefulness of these diets in liver surgery. There is a lack of information for patients on dietary treatments and patients informed us during our Patient and Public Involvement (PPI) focus groups that they are not given any specific dietary advice pre-surgery.

This trial will evaluate the feasibility of conducting a study to determine if a very low-calorie diet (VLCD) is tolerated, acceptable, results in decreased blood loss and BTR, improves time to functional recovery and reduces overall complications compared to regular diet in patients with fatty liver prior to LS. We will use x4 sachets/day of commercially available liquid meal replacements (Tesco Slim shake, Tesco), providing 800kcals and 80g protein, for the purpose of the study. Zero calorie drinks and a limited quantity of low starch vegetables will also be allowed. We will ask patients scheduled for liver surgery with MRI confirmed fatty liver to join our study. Everyone that enters will have an equal chance of getting either the VLCD dietary intervention or standard written information on healthy eating determined at random by a computer.

The provision of a diet with adequate protein is essential for this patient group as a higher protein intake is associated with reduced loss of muscle mass, greater energy expenditure and satiety. High protein is also essential for the regeneration of the liver. For those patients with higher protein requirements, that cannot be met by the liquid meal replacement diet alone i.e., more than 80g/day, additional protein will be provided by means of a whey isolate.

A combination of diet, physical training and behaviour therapy is typically used in the treatment of obesity. The overweight person learns strategies and techniques to change behaviour and achieve long-term sustained weight loss. This process can take a long time and can only be accomplished with patient motivation and long treatment periods. Although sustained weight loss is not the goal of the current study, patients will be supported by the study dietitian, or by a health professional trained by the dietitian, to provide motivational support and ensure they are following the dietary regimen. The PPI group has informed us that patients are willing to participate in any diet for two weeks which will provide a better outcome after surgery.

Adherence to the diet will be assessed by means of food intake diaries, collection of empty sachets and assessment of changes in body weight. Weight and hand grip strength will be measured before starting the diet and before surgery. The study dietitian, or professionals trained by the dietitian, will telephone intervention patients on day 2 or 3 of the diet to provide motivation and support adherence.

1.2 Literature Review

Hepatic steatosis (HS) (FLD) is a pathological condition defined as the presence of large and small vesicles of fat, predominantly triglycerides, accumulating within hepatocytes. HS may occur due to overweight/obesity, alcoholism, chemotherapy, and metabolic conditions such as diabetes[1]. Chemotherapy increases the incidence of HS, and the frequency and severity of HS varies between different chemotherapeutic agents[2]. Liver surgery is the mainstay of treatment for liver metastases from colorectal cancer, primary liver tumours and adenomas and it offers a clear survival benefit[3]. In the year 2018/19, almost 4000 liver resections were performed in England alone[4]. The prevalence of fatty liver in patients undergoing liver resection is estimated to be between 30 to 50%.

The presence of HS or steatohepatitis and grading of HS increases both overall and hepatic-related morbidity after liver resection[5]. In a cohort of 485 patients, Kooby et al[6] observed higher complication rates in those patients with severe steatosis (62%), compared with mild steatosis (48%) and normal parenchyma (35%). The overall infective complication rate was also higher in severe steatosis group (43%) compared to mild steatosis (24%) and normal parenchyma groups (14%).

The gold standard for HS diagnosis remains a percutaneous liver biopsy[7]; however, this is an invasive procedure with risk of bleeding and death[8]. HS is now routinely diagnosed with non-invasive investigations such as ultrasound (US) and MRI scan[9]. Standard US has the added benefit of detecting HS through the alteration in reflectivity of the liver and assessing the vascular changes of chronic liver disease, however, is not quantitative. Most liver resection patients will undergo a pre-operative MRI scan to characterise the liver tumour and inform surgical planning. MRI can also diagnose and quantify the severity of HS. MRI uses a unique technique called the Proton Density Fat Fraction (PDFF) to quantify the HS[10]. MRI assessment of HS correlates highly with histology steatosis grade[11] and is more sensitive to changes in HS quantification, so it can be used to identify patients with HS before liver surgery. This study will test whether pre-operative quantification and strategies to reduce HS may reduce intra-operative blood loss, BTR, improve time to functional recovery, and overall intra-and post-operative complication rates.

There is a strong research base behind each individual component of this study:

1.2.1 Quantification of hepatic steatosis:

A meta-analysis performed by Yokoo et al[12] concluded that MRI PDFF measurements have excellent linearity, bias and precision across different field strengths, manufacturers, and reconstruction methods. Serai et al[13] have recently demonstrated that the estimation of PDFF using MRI is highly reproducible across different readers and again demonstrated that the results were very similar across different field strengths and imaging platforms. This is of paramount importance for the RESOLVE study as the preoperative MRI scans will be performed within different hospitals and by different scanners.

1.2.2 Hepatic Steatosis:

A review article from Doherty et al[14] outlined the mechanisms by which this occurs. Before the progression of HS towards fibrotic or even cirrhotic changes, it can be reversed through dietary and lifestyle modifications alone. Pre-operative ketogenic low-calorie diets have been demonstrated to reduce liver volume by between 5 to 43% in patients undergoing weight–loss surgery[15-18]. Using a Mediterranean diet, Gelli et al[19] demonstrated a reduction in the percentage of patients with steatosis grade two or higher (moderate severity) from 93% to 48%, and steatosis regressed entirely in 20% of cases. Belghiti et al[5], in a cohort of 478 elective liver resection patients, demonstrated that steatosis was an independent risk factor for postoperative complications, with complications occurring in 8% of patients with steatosis versus 2% in patients with normal parenchyma. Little et al[20] also reported a negative effect of steatosis on in-hospital mortality. In a cohort of 727 patients, 224 patients (31%) had some degree of steatosis with mortality significantly increased compared with normal background livers (4.9% vs 2.0%).

1.2.3 The effect of low-calorie diets on liver surgery outcomes:

Burnand et al[21] conducted a randomised controlled trial (RCT) assessing the effect of a two-week Very Low-Calorie diet (VLCD) on laparoscopic cholecystectomy and found a significant reduction in weight and operative time. A small RCT (60 patients) by Barth et al[22] demonstrated a reduction in mean blood loss during liver surgery in the pre-operative dietary intervention group (452 vs 863ml, p = 0.02). In the same study, blinded surgeons judged the liver to be easier to manipulate in the diet group, based upon a 1-5 Likert scale (1.86 vs 2.90, p = 0.004). A study by Reeves et al[23], compared a cohort of 111 patients who underwent liver resections. The most recent 51 patients were assigned to a one-week low-calorie diet. Pre-operative diet patients had less mean intra-operative blood loss than the control group (600 ml vs 906 ml, p = 0.002). The authors retrospectively analysed HS incidence and found that HS was lower in patients who received a pre-operative diet, (15.7% vs 25.5%, p = 0.05), than the non-diet controls. These studies have shown that a pre-operative low-calorie diet reduces intra-operative blood loss and results in a liver that is easier to mobilise. However, both studies are small, only included obese patients, and no formal prospective assessment of HS took place before dietary intervention. Furthermore, there was also lack of clarity on the types of diets they have used and how they measured adherence.

1.2.4 Adherence to low-calorie diets:

Short-term adherence to pre-operative low-calorie diets in bariatric and gastric cancer surgery is reported to be between 100% and 97%, respectively[15,24]. In the study by Barth et al[22], in patients undergoing liver resection, 94% of patients fully adhered to the diet. Our PPI group felt that following an intense diet for a short period with a final cut off would be worthwhile to improve their cancer outcomes. Opinions differed regarding the type of strict diet they would follow, food or liquid; however, they all agreed they would try anything at this point in their treatment.

2. RATIONALE

The presence of HS leads to more technically challenging liver resections, with up to 50% increase in blood loss and the need for blood transfusions. It is also associated with two to four-fold increase in overall intra and postoperative complications and a 50% increase in 90-day mortality[5,20]. The overall BTR in patients undergoing LS is between 30 to 60%[25] (1200 to 2400 patients in England). Blood product administration during the peri-operative period is associated with nine-fold increase in 90-day mortality, two-day longer median length of hospital stays, and up to 50% increase in readmission rate[26]. Transfusion is associated with decreased recurrence-free and overall survival (OS) by up to 50% following colorectal cancer surgery[27]. These complications come with increased economic costs to the NHS and detrimental effects on patients' wellbeing. Currently, routine care for patients

undergoing liver resection surgery does not require them to follow any dietary regime. Patients are not given any specific dietary advice. Patients in our PPI group have informed us that they would be keen to follow a diet as part of their treatment, if such treatment might improve their outcomes.

Before running a definitive study to assess the effectiveness of the VLCD in patients with HS undergoing liver resection we need to find out and clarify several outstanding issues: whether patients are interested and willing to take part in the randomised trial, whether they are able to tolerate and adhere to the diet, whether dietitians and healthcare professionals are able to deliver the intervention consistently and to gather information in order to calculate the sample size needed for a definitive trial.

Other uncertainties will also be addressed, such as the ability to collect outcome measures (e.g., intraoperative bleeding), randomisation, recruitment, and consent procedures.

3. ASSESSMENT AND MANAGEMENT OF RISK

Studies of VLCD have used wide-ranging periods e.g., two weeks to 5 months, with few safety concerns identified[28-31]. Two recent studies that assessed the role of VLCD on sustained weight loss and diabetic control have shown that VLCDs are safe[32,33]. In a study using four-week VLCD in patients awaiting gastric bypass, the compliance rate was excellent, and patients reported a high degree of satisfaction[34]. In a study that assessed the feasibility of 8-week VLCD on sustained weight loss, Scragg et al[35] observed minor adverse events. These were: constipation (37%), dizziness (19%), headaches (11%), and sensitivity to cold (7%)[25]. No significant change in skeletal muscle mass was found after VLCD, which is essential given the potential concern that VLCD intervention might induce or increase sarcopenia among patients. Lean et al[36] reported similar side effects in the DiRECT study, which assessed the impact of 3-month VLCD on weight loss and control of diabetes. During the 12 months follow-up period of the DIRECT trial, just two serious adverse events (biliary colic and abdominal pain), occurring in the same participant, were deemed potentially related to the intervention[36]. Another study that assessed the effect of one-week VLCD on blood loss associated with liver surgery, Barth et al. did not report any dietary intervention related side effects[22].

In contrast, there is evidence linking the presence of HS and severe surgical complications, including: increased blood loss, higher readmission rate, higher infective complications[6, 37] overall post-operative morbidity[6, 37-39] and mortality in patients undergoing liver surgery[38]. The risk of Blood Transfusion (BT) associated with LS in patients with HS is 2 to 3-fold higher compared to patients with normal liver[6, 39]. Blood transfusion during the perioperative period is associated with a nine-fold increase in 90-day mortality, higher infective complications[6,40,41], longer median length of hospital stays, and an up to 50% increase in readmission rate[27]. Blood transfusion is also associated with decreased recurrence-free and overall survival following liver surgery for colorectal cancer metastases[42-45]. In the RCT by Barth et al[22], there was a significant reduction in blood loss in the VLCD intervention group.

Given the excellent safety profile of VLCD and the significant risks associated with liver surgery in patients with underlying FLD, it is essential to study the impact of VLCD intervention on these patients' outcomes.

In this study, the dietary intervention will be used for two weeks, and patients will be advised to resume their regular diet as soon as they can eat and drink, which is the day following surgery for most patients. The chosen liquid meal replacements are formulated with a low carbohydrate and fat content to encourage fat loss through ketosis and high protein content to preserve lean body mass. A diet with adequate protein is essential for our patient group as a higher protein intake is associated with reduced loss of muscle mass, more significant energy expenditure and satiety. High protein is also critical for the regeneration of the liver. Patients will also be given options for zero calorie drinks and low starch vegetable portions.

If operation dates are postponed, based on evidence of prolonged VLCD, participants may remain on the diet for a further two weeks safely. A further contact phone call will be at two weeks of the diet to provide further support and monitor progress.

To capture any adverse events participants will also be encouraged to contact the study team if they are not feeling well or wish to report any adverse events.

Any potential harms caused because of participating in this research will be detected and addressed in accordance with safety reporting work instructions (see Section 14- Safety Reporting for more details).

4. OBJECTIVES AND OUTCOME MEASURES / ENDPOINTS

In the future definitive trial, the primary research question will be:

P: In patients with a diagnosis of hepatic steatosis who are having elective liver surgery, does

I: VLCD with dietitian education and support,

C: compared to Treatment as Usual at each site

O: lead to improvements in patient outcomes including decreased intra-operative blood loss, ease of liver surgery, faster time to functional recovery, decreased overall blood transfusion rate, length of surgical time, postoperative length of hospital stay, overall post-operative complication rates, readmission rate within 90-days, and 90-day mortality.

At this point, we are unable to design the definitive RCT with confidence due to uncertainties around trial processes and the dietary intervention. This study aims to conduct a feasibility randomised controlled trial to obtain the data and experience necessary to inform the conduct of the definitive study.

4.1. Primary objectives

To conduct a randomised feasibility study of VLCD versus Treatment as Usual (TAU). 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 study requirements prior to LS and any possible contamination.
3. Ascertain completeness of data collection at baseline, day of surgery plus 30- and 90-days post operatively.
4. To allow a preliminary assessment of the VLCD intervention.

4.2. 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 (calculated from knife to skin and wound closure time), ease of liver surgery, blood loss, blood transfusion requirements, time to functional recovery, Comprehensive Complications Index (CCI)[46] (overall Clavien-Dindo grade I-V postoperative complications[47]), and length of stay, 90-day mortality and 90-day readmission.

4.3. Outcome measures

4.3.1. Feasibility trial outcome measures

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

- Screening and recruitment rate (overall and by centre)
- Randomisation rate
- Retention rate (overall and by centre)
- Success of blinding surgeons
- Adherence to VLCD as measured by changes in body weight, food diaries, number of empty sachets, qualitative interviews and focus group data
- Completeness of data collection
- Acceptability of outcome measurements
- Barriers and facilitators to delivering the intervention
- Fidelity of intervention (over time and site)
- Processes to ascertain PDFF quantification

4.3.2. Participant reported and other clinical outcomes

The proposed primary outcome for a future definitive study will be related to liver surgery outcomes. Several outcomes will be measured to be able to decide which is the most appropriate to use. Other clinical and patient-reported measures will be collected at the same time points.

4.3.2.1 Pre-operative measurements

- Weight will be measured and used as a pragmatic surrogate marker of liver size reduction due to VLCD. Hand grip strength will be measured to identify any significant changes in muscle strength.
- All participants in the intervention group will complete a food diary detailing the supplements and any other food and drink consumed each day whilst on the VLCD. The diary will include daily dietary perceived adherence scores using a 0–10 scale (0 = not at all, 5 = somewhat, and 10 = following the plan very well[48]. See RESOLVE Patient booklet for following VLCD).
- To report adherence, the number of participants that initiate, discontinue, implement, and persist with the dietary intervention for the 2 weeks will be collected. Empty food sachets will also be collected on the day of surgery.
- Daily mood scores will also be collected using a 0-3 scale (0=poor, 1=fair, 2=good, 3=very good[49]. See RESOLVE Patient booklet for following VLCD).
- Daily hunger scores (0=extremely hungry, 1=quite hungry, 2=generally satisfied, 3=very satisfied) and overall energy levels (0=very low energy levels, 1=moderately low energy levels, 2=good energy levels, 3=very good energy levels) will also be collected.
- Total energy and protein intakes over the 2-week preoperative period will be calculated using the food diary records.
- EQ-5D-5L to measure health-related quality of life.

4.3.2.2 Day of surgery

- Intra-operative blood loss
- BTR (Units)
- Haemostatic agents required
- Duration of surgery (calculated from knife to skin and wound closure time)

- Type of surgery
- Surgical approach
- Ease of liver surgery (Subjective measure of 1 to 5)
- Surgical complications (conversion to an open operation, bleeding, injury to surrounding structures, cardiovascular events, cerebrovascular events, anaesthetic related complications etc.,)

4.3.2.3 Post-operative measurements

- Postoperative length of hospital stay
- Overall, in-hospital BTR (number of transfusions)
- Post-hepatectomy liver failure as measured by the liver function tests (See Post-hepatectomy Liver Failure Grading document).
- Post-hepatectomy haemorrhage (see Post-hepatectomy Haemorrhage document)
- Overall postoperative complication rates (CCI). **CCI** is calculated as the sum of all complications and is more sensitive than any existing morbidity endpoints. Each complication is weighted according to severity based on Clavien-Dindo classification of complications[49]. The final CCI formula yields a continuous scale to rank the severity of any combination of complications from 0 to 100 in a single patient
- Time to functional recovery (Date of proposed discharge as opposed to actual date of discharge)
- Readmission rate and mortality within 30 and 90-days
- EQ-5D-5L to measure health-related quality of life (See EQ-5D-5L).
- Participant-level data on the use of health, social care, and wider societal resources, measured using a self-report, Resource Use Questionnaire (see Resource Use Questionnaire).

5. TABULATED SUMMARY OF OBJECTIVES AND OUTCOMES

Feasibility Objectives	**Outcome Measures**
Rates of recruitment and randomisation rate	Number of patients screened, consented (as a proportion of patients screened) and randomised (as a proportion of patients screened)
Rates of retention	Number of recruited patients completing measures on day of surgery Number of patients completing food diary over period of VLCD
Success of Blinding	Successfully blinded surgeons
Adherence to VLCD	Self-report in food diary Discussions in qualitative interviews and focus groups Difference in weight between baseline and day of surgery (pre-op)

	Food record diary analysis (participants that initiate, discontinue, implement, and persist with the dietary intervention) Collection of empty sachets
Data completeness	Completeness of data capture and outcome measures to include baseline and day of surgery, plus self-reported food diary
Barriers and facilitators to delivering the intervention	Discussions and feedback from dietitians
Acceptability of intervention and outcome measures	Discussions in qualitative interviews and focus groups with participants
Fidelity of intervention	Audio recordings of interventions
Surgical outcomes	
Day of surgery (Post-op)	Intra-operative blood loss (estimate by eye) Blood transfusion requirements Haemostatic agent requirements Duration of surgery (in minutes. Calculated from knife to skin and wound closure time) Ease of liver surgery Surgical complications (bleeding, injury to surrounding structures, cardiovascular events, cerebrovascular events, anaesthetic related complications) Surgical approach used (laparoscopic vs open) Type of Surgery G-K classification
Post-operative measurements	Length of stay (in days)Clavien-Dindo classification of complications (Post-operative complications (CCI Score)) Readmission rate and mortality within 30 and 90 days Overall, in hospital BTR (Units, 30 days) Time to Functional Recovery (Date of proposed Discharge) Bloods (FBC, LFTs, Creatinine, Urea, GFR, CRP)
Participant reported and other clinical outcomes	

Total energy and protein intakes over the 2-week preoperative period	Self-report in diary (Number sachets per day+ any additional food/fluids consumed)
Weight and Hand Grip Strength	Pre and post diet
Mood, hunger and energy levels	Self-report 4-point scale in diary
Side-effects of VLCD	Self-report to research team
Health-related quality of life	EQ-5D-5L
Use of health, social care, and wider societal resources	Resource Use Questionnaire

Table 1. Objectives and outcome measures. Refer to tabulated schedule of events (Section 10) for timings of outcome measures.

6. TRIAL / STUDY TREATMENTS

All patients will be undergoing liver resection as per the clinical pathway at their hospital. All clinical problems will be managed by their usual clinical care team.

6.1 Intervention arm

Patients who attend the hospital for their Pre-op appointment will be provided with the instructions and liquid meal replacement sachets needed for the two-week period by the dietitian/healthcare professional (see RESOLVE Patient booklet for following VLCD). If their usual care involves a virtual pre-op appointment, a study visit will be arranged.

The intervention group will undertake a VLCD in the two weeks immediately before surgery. The VLCD will be in the form of liquid meal replacement (4 sachets (Tesco slim shake) per day), providing 800kcals 80g protein). Participants will be given a list of permitted low starch vegetables (up to 100kcal per day), as well as zero calorie drinks, that can be consumed freely during the study. Participants whose protein requirements, calculated by the study dietitian, are more than 80g/d will be advised to take an additional protein powder supplement.

They will be given a study information booklet and food record diary with instructions to complete for the two weeks. The diary may be digital or paper-based (see Food and Mood Diary). Participants will be required to record all food and fluids consumed daily for two weeks, in addition to recording mood, hunger, and energy level. These factors may change with VLCD and may influence motivation. Dietitians / healthcare professionals will deliver the instructions for the diet after receiving training by an experienced dietitian (see Section 6.2). Participants will be educated on the dietary requirements of the study and the need to sustain the diet for two weeks before surgery only.

Potential complications/side effects will be listed in the diet information booklet and explained, and guidance will be provided on coping strategies to support maintenance. Participants will also receive daily SMS reminders to complete the food diary. To support adherence and provide motivational support, participants will be contacted by phone by the dietitian 2-3 days into the study. Dietitians will explore participant's experience of the diet, their thoughts, and emotions around managing the diet, working with them to acknowledge areas of success, elicit concerns and support further problem solving of areas that may be challenging. Food diaries will be used to facilitate these focused discussions to help motivate participants for the remaining study period.

If the surgery is postponed, it is safe for participants to remain on the VLCD for up to 28 days. Further supplements will be supplied plus they will be contacted by their dietitian /healthcare professional to provide further phone support at two weeks.

6.2 Training of Dietitians and Healthcare Professionals delivering the Intervention

Dietitians/ healthcare professionals will deliver the VLCD intervention at site at the baseline visit after randomisation. To ensure consistency, all will be provided with the same training and instructions as described in the following.

Prior to recruitment of any patients, all site dietitians and healthcare professionals identified to deliver the VLCD intervention to participants will have an online 3 hour training session with the Senior Lead Dietitian on the RESOLVE research team. This has been developed and tested with on site NHS dietitians and will be recorded for repeated access if required.

They will also be provided with a training manual with detailed instructions on how to deliver the intervention, including a script that can be used as a prompt to support consistency in approach (See Dietitians' Handbook for supporting patients undertaking a VLCD).

6.3 Control arm

Participants will receive 'Treatment as Usual' at their site. Those participants who consent but do not have a F2F pre-op will attend the hospital for a research visit to collect baseline information. Any clinicians and research staff collecting the baseline and pre-operative measures will be trained to use the same methodology e.g., weight, hand grip strength.

6.4 Design considerations for minimising bias

6.4.1 Randomisation:

A minimisation procedure with a random element will be used to allocate participants to receive VLCD or TAU. The following factors will be used in the minimisation procedure:

- Centre (Plymouth, Liverpool, Surrey and Southampton, Leeds, Royal Marsden, QMC Nottingham)
- Type of surgery using the modified G-K liver surgery classification[50] (Grade I, Grade II and Grade III).

6.4.2 Blinding:

This 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 treatment allocation. The trial statisticians undertaking the analyses will not be blinded[51].

7 PARTICIPANT ELIGIBILITY CRITERIA

7.1 Inclusion criteria

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

Inclusion criteria	• Adult patients ≥18 years • Able to provide informed consent • Patients with HS with or without NASH requiring liver resection • Patients selected for LS for treatment of metastases, hepatocellular carcinoma, gallbladder cancer, peripheral cholangiocarcinoma, or pre-malignant hepatic tumours

7.2 Exclusion criteria

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

Exclusion criteria	• Patients with normal background liver on pre-op 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 with a low BMI (BMI <20kg/m2) • Patients who report unintentional weight loss of >5% in 0-3 months or >10% in up to 6 months

8. TRIAL / STUDY SETTING

This is a multi-centre feasibility randomised controlled trial conducted in seven secondary care trusts: University Hospital Plymouth NHS Trust, Aintree Hospital, Liverpool, Royal Surrey NHS Foundation Trust, and University Hospital Southampton NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust, Queen's Medical Centre, Nottingham University Hospitals NHS Trust. Participating units are supported by a principal investigator, a research nurse, and a dietitian. All participating units are tertiary referral centres for liver surgery. There are no site-specific requirements, but this protocol will consider any differing clinical pathways at each trust.

9. TRIAL / STUDY CONDUCT

Site Principal Investigators (PI's) will be responsible for promoting the study amongst relevant staff at their hospitals to optimise participant recruitment. Recruitment performance at each site will be closely monitored by the Trial Management Group (TMG).

9.1 Participant identification and eligibility screening

The local hepato-biliary multi-disciplinary teams, supported by the local clinical research network nurses, will identify, and recruit potential participants following routine MRI with experienced Consultant Gastro-intestinal (GI) surgeons.

All adult patients requiring elective LS at participating centres will be screened for their eligibility into the study by the local hepato-biliary multi-disciplinary teams, supported by the local clinical research network nurses.

The clinical teams will screen for potential patients at the HPB MDT. Patient identifiable information provided by the referring clinical team or general practitioners will be used to identify likely patients. Patient identifiable information will be entered on to the research database held by the Peninsula Clinical Trials Unit (University of Plymouth) to facilitate future contact with patients in regard to the study with their verbal consent. Members of the research team will not require access to identifiable patient data for the purpose of identifying potential participants.

Patients identified at the HPB MDT that fulfil all inclusion criteria and MRI confirmed HS would be eligible for the study.

9.2 Participant recruitment and consent

The site Principal Investigator (PI) or an authorised delegate must obtain informed consent prior to the collection of any baseline data. Authorised delegates must be suitably trained in the relevant principles of Good Clinical Practice and the requirements of the trial protocol. Training materials will be provided

by the coordinating clinical trials unit (PenCTU). Doctors and registered nurses or Allied Health Professionals (band 5 or higher) may be authorised to obtain consent in this study, only after patients have had enough time to discuss the study with their clinicians.

Patients for consideration of LS are first seen in a face-to-face or telephone clinic appointment. After discussing the surgery, the surgical team will inform the patients about the RESOLVE trial. Time will be given for discussion of the study and what it involves.

Patients will be advised that they have the right to refuse participation without giving reasons and that they are free to withdraw at any time without giving reasons and without prejudicing his/her further treatment.

They will also be advised on how their data will be used and signposted to further information about data used for research purposes.

The PI or authorised delegate will discuss with the potential participant about the nature and objectives of the study and possible risks associated with their participation.

If the patient is interested, they will be provided with a Patient Information Sheet (See RESOLVE Participant Information Sheet) either in person, or by post or email if it is a telephone appointment. They will be asked for consent for a follow-up call to discuss the study further in a couple of days from a member of the research team (PI or delegate, see Work Instruction Confirming eligibility & taking informed consent). Patients who agree will receive a follow-up phone call at least 24 hours after receiving the PIS from a member of the RESOLVE research team to discuss the study requirements in more detail.

The researcher will review the eligibility criteria with the patient prior to obtaining consent. The only eligibility criteria that cannot be verified until the Baseline measure appointment is BMI. The patient will be informed that if their BMI is found to be low at that appointment, they will not be able to continue with the study.

After ascertaining a patient's willingness to take part in the study on the phone, further explanation of the study will be given and any questions the patient may have after reading the PIS responded to. If the patient is happy to proceed, consent may then be taken (See RESOLVE Participant ICF). If there is any doubt that the patient is willing or is eligible, a further phone call may be offered within the time limits available.

- When telephone consent is planned for the research it is the responsibility of the PI or delegate to ensure an information sheet has been given or sent to a potential participant.
- It is the responsibility of the CI or sponsor to create a script for the consent process. A consent script should include the same elements as would be in a consent form, but in a more conversational manner.
- The PI or delegate will ensure the potential participant is granted sufficient time to consider whether or not to participate in the research. After allowing the potential participant sufficient time, the PI or delegate should d answer any additional questions the participant may have. The PI or delegate may then obtain telephone consent to participate in the research.
- When documenting the consent process the PI or delegate should record the reading of a consent statement, and the answers of the participants indicating willingness to participate.

The documented record of events verifies the telephone consent process.

Researchers will follow a study-specific work instruction (see Work Instruction Confirming eligibility & taking informed consent) and take responsibility for ensuring that all participants consent voluntarily with full understanding of what is involved in the study.

Individual clauses from the ICF will be read out by the researcher to the patient, including the optional clauses pertaining to the patient's willingness to be invited to take part in the qualitative components of the study.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence. Where a participant can consent for the trial but later becomes incapacitated, the participant will be withdrawn from the trial because following the VLCD instructions will not be possible.

Original versions of completed ICFs should be stored in the Investigator Site File (ISF). One copy should be provided to the participant for them to retain when they attend their next appointment, a copy should be filed in the hospital notes/electronic health record and a de-identified copy should be provided to the CTU for central monitoring purposes (see section 17)

Once patients have consented, they will be informed that they will be randomised to one of the groups at their next F2F meeting. For patients who have an in-person Pre-op appointment that will be then. For patients who do not attend hospital until their surgery, a research visit will be scheduled as soon as possible by the research team. Baseline measures will also be recorded at the next meeting prior to randomisation. Participants will be informed that if they are in the intervention group their study meeting will take up to 30 minutes longer as they will receive the VLCD instructions also.

The researcher will update the screening log, the details of all screened patients collected on a secure password protected database created by the CTU. Confirmation of patient eligibility and consent provided will be added.

9.3 Payment

Participants who do not have any additional appointments for the study will not be paid for being involved in the study. Those who are at sites where they require an additional appointment for the research will be reimbursed for their reasonable travel expenses for attendance at hospital.

9.4 Recording screening and recruitment information

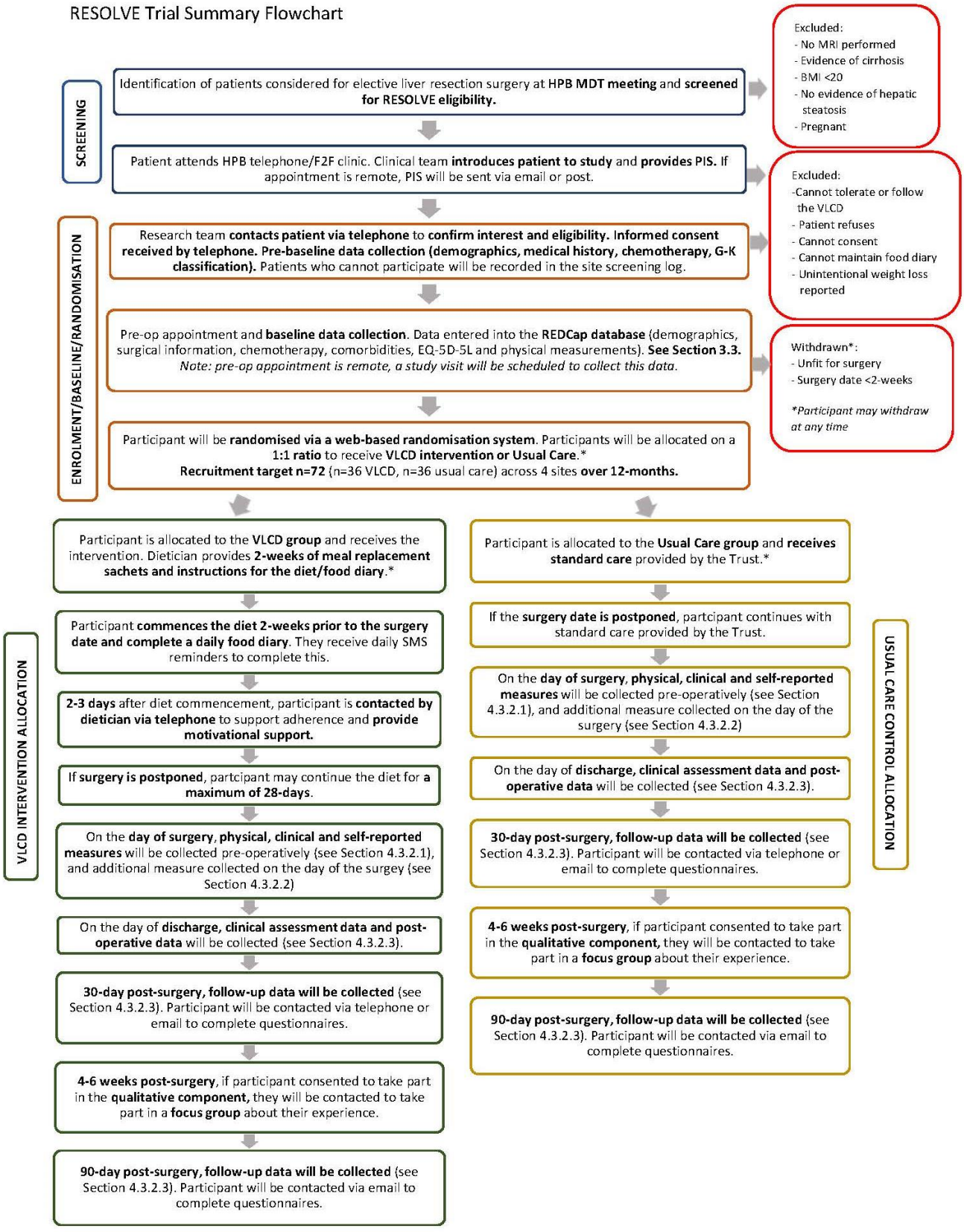
Given the Feasibility nature of this trial, investigator sites will be required to keep accurate records in the provided Screening Log of:

- the number of potential participants identified by the clinical team at the MDT
- the number of patients screened for eligibility by the Clinical/research team
- the number of patients deemed ineligible (with reasons where available)
- the number of patients provided with a PIS
- the number of patients declining to give consent (with reasons where available)

10. TRIAL SCHEDULE

This section describes the conduct of the trial in chronological order, following participant recruitment, detailing procedures for data collection at each of the time points. A patient journey flow chart is illustrated in **Figure 1: Patient Journey.**

Figure 1: Patient Journey



** Randomisation and provision of VLCD intervention or Usual Care occurs at the pre-op appointment, after collection of baseline data.*

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

A tabulated summary of the trial schedule is given in **Table 2: Tabulated Summary of Trial.**

Table 2. Tabulated summary of trial

	Pre-baseline	Baseline	Two weeks Pre-op *	Post-allocation			
TIMEPOINT		*T0*		***Day of Surgery*** ***Pre-op***	***Day of surgery*** ***Post-op***	***Day of Discharge***	***+30 and 90 days post surgery***
ENROLMENT:							
Eligibility screen	X	X					
Informed consent	X						
Demographics		X					
Medical History & Concomitant medications	X						
Relevant past surgical and chemo history	X						
G-K Classification	X				X		
Randomisation		X					
INTERVENTION / TREATMENT PERIOD:							
Intervention Group: ***VLCD***							
Control Group: ***TAU***							
ASSESSMENTS:							
weight		X		X			
height		X					
Hand Grip strength		X		X			
Adherence to Diet (VLCD)			X	X			
Mood, Hunger and Energy levels on Diet (VLCD)			X				
Type of Surgery				X	X		
Surgical approach				X	X		

ASA – Fitness for surgery				X			
Surgical complications)					X		
Clavien-Dindo classification Post-op complications						X	X
Ease and duration of Surgery					X		
Blood loss					X		
Blood transfusions					X	X	X (30 days)
Haemostatic Agents					X		
Blood tests			X**	X***	X	X	
Quality of Life EQ-5D-5L		X		X			X
Health Resource use Questionnaire							X
Time to Functional Recovery						X	
Length of stay						X	
PDFF rating	X						
Readmission rates							X
Mortality						X	X
SAFETY MONITORING:							
Serious Adverse Event reporting			←				→

**at time of diet commencing*
***routine bloods taken*
****bloods reported on eCRF*

10.1 Pre-baseline data collection

Relevant surgical and chemotherapy information

- Diagnosis (colon cancer/rectal cancer/HCC/adenoma)
- Number and size of colorectal metastases
- Number and size of HCCs
- Location and size of tumours
- Type of previous surgery
- Methods of previous surgery (open/laparoscopic/hand-assisted/Robotic)
- G-K classification of surgery

Pre-surgical chemotherapy information

- Type of chemotherapy
- Number of cycles of chemotherapy
- Date of chemotherapy commenced and completed
- 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 Airways Disease
- Other

10.2 Baseline visit / baseline data collection

After consent (telephone or face to face) patients will either be scheduled for a routine pre-operative visit or will be provided with an appointment to attend the clinic for baseline measurements and randomisation. At the baseline visit the following details will be collected on a REDCap database, created explicitly for the RESOLVE study. The database will be password protected and will be accessed by the research team and authorised clinical team members.

Demographics

- Age
- Gender identity
- Postcode
- Ethnicity
- Religion
- Employment status
- Education status
- Marital/partner status
- Smoking status
- Performance status 0 to 5 (0 = Fully active to 5 = dead (If measured at pre-op)

Health related quality of life

- EQ-5D-5L questionnaire

Physical measurements

- Height
- Weight
- Hand Grip Strength

Patients will be asked whether they are currently on a weight loss program and whether they have used any weight loss medications in the previous 3 months. This is not part of the exclusion criteria

but to monitor. To check participants are not malnourished they will also be asked whether they have any unexpected weight loss in the past 3 to 6 months. Participants will be randomly allocated to either the intervention (VLCD) or the control group (TAU) after the baseline measures are taken, using a web-based randomisation system provided by the PenCTU in conjunction with a statistician independent of the trial team.

10.3 Randomisation procedure

A minimisation procedure with a random element will be used to allocate participants to receive VLCD or TAU. The following factors will be used in the minimisation procedure:

- NHS recruitment site
- Type of surgery using the modified G-K liver surgery classification[50] (Grade I, Grade II and Grade III).

Treatment allocation will be achieved using a web-based randomisation service provided by the UKCRC-registered PenCTU in conjunction with a statistician independent of the trial team.

Allocations will be assigned in order of participants baseline appointment (earliest to latest). Communication will be achieved via emails automatically generated by the randomisation system.

Participants allocated to the TAU group will be informed and receive usual care at their healthcare setting.

Participants allocated to the intervention group will receive a VLCD as described in Section 6.

Surgeons will be blinded to treatment allocation. Randomised patients in the intervention group will be provided with meal replacement sachets that they need to take for two weeks after the date of surgery has been confirmed by the clinical team. In case surgery is either postponed or cancelled, patients will be asked to continue the VLCD for up to a maximum of 28 days. After this time patients will resume normal eating patterns.

- The participant's GP is informed (using approved GP letter) and a record of this is made in the patient's hospital record, along with a copy of the letter.
- Participation in the study is recorded in the patient's hospital record by documenting a record of the baseline visit and contact with dietitian/healthcare professional for dietary advice.
- A copy of the completed consent form is filed in the ISF, the patient's hospital record and record that a copy was given or sent to the patient.
- Flag the hospital record that they belong to a participant in accordance with local site policy
- Data are entered into the eCRF according to instructions provided by PenCTU.

All participants will be provided with information on what happens next and what to expect. They will automatically receive emails thanking them for continued participation in the study and emphasize the value of the data they will provide.

Patients in the VLCD arm will be asked to commence their diet if they have been informed that the surgery date is in two weeks,

OR

Patients will be asked to wait for a phone call from the dietitian/healthcare professional or surgeon telling them their operation date and when to start (the Surgeon will provide operation date only as they are blinded to randomisation).

10.4 VLCD Period

Participants on the VLCD arm will complete a food diary for the two weeks that they are participating in it (up to 28 days if surgery delayed).

- Daily quantification of VLCD sachets, low starch vegetables and zero calorie fluid intake
- Mood, energy and hunger levels
- Any other foods

Further details of the food diary can be found in RESOLVE Patient booklet for following VLCD).

10.5 Day of Surgery (pre-op)

On the day of surgery, prior to their operation the following physical, clinical, and self-report measures will be taken.

Physical measurements

- Weight
- Hand Grip Strength

Clinical measurements and assessments

- Blood tests reported
  Full blood count
  Liver function tests (LFTs): ALT/ALP/AST/GGT/Albumin/INR/Bilirubin
  Renal function: Creatinine/Urea/GFR/CRP
- ASA/Cardio-pulmonary exercise test (CPET) – Fitness for surgery
- Type of surgery intended
  Non-anatomical resection/s
  Anatomical resection
  Right hepatectomy/left hepatectomy/extended right/extended left/posterior sectionectomy/left lateral sectionectomy/segmentectomy etc.,
- Surgical approach intended

Patient self-reported measures

- EQ-5D-5L

10.6 Day of Surgery (post-op)

Clinical assessments

- Type of surgery
- Surgical approach
- Classification of surgery (G-K stratification of liver surgery)
-
- Ease of liver surgery (1-5)
- Surgicalcomplications
- Blood loss
- Blood transfusion requirements
- Use of haemostatic agents: yes/no; if yes, type of product and number of products used
- Intra-operative complications apart from blood loss: Conversion to an open operation/injury to surrounding structures/cardiovascular events/cerebrovascular events/anaesthetic-related complications/other
- Bloods (FBC, LFTs, Creatinine, Urea, GFR, CRP)
-

10.7 Day of Discharge

Clinical assessments

- Post-operative blood transfusion requirements
- Post-operative complications
- Total HDU/ITU stay
- Total hospital stay
- Time to functional recovery
- FBC
- LFTs
- Renal function: Creatinine/Urea/GFR/CRP
- Clavien-Dindo post-operative complications

10.8 30 and 90-day (within 7 days either way) post-surgical follow-up

- Clinical outcomesData on readmission
- Mortality
- Histology data Follow up diagnosis, Tumour locations, number of tumours, tumour sizes
- Complication rates including Clavien dindo grades
- Blood transfusion requirements at 30 days

Self-report measures

- EQ-5D-5L questionnaire
- Health resource use questionnaire

10.9 Procedures

Post-operative clinical follow-up for all participants will take place according to usual care as determined by the treating clinician.

Follow-up research assessments will be conducted by a research nurse at the time periods stated by telephone or email (if preferred).

11. QUALITATIVE EVALUATION

11.1 Participant focus groups

The focus groups aim to explore participants' perspectives and experiences in the study. Our PPI group advised that interviews should also be offered to patients who may not be comfortable in a group setting but wish to take part in the qualitative data collection. Therefore, participants who do not wish to take part in focus groups but would like to feedback, will be offered the opportunity of an online interview, maximising opportunities for the patient experience to be heard[53]**.**

The key objectives are:

- to examine perspectives around the acceptability of VLCD and trial procedures
- barriers and challenges encountered and their solutions
- perceived impact of motivational support on their ability to manage the diet.

Purposive sampling will ensure that participants from the intervention and usual care arm who did and did not complete the diet are invited to attend online focus groups (consisting of between 4-6 Participants) or individual interviews lasting between 30-60 minutes.

Six to seven focus groups will be conducted: one for usual care, one for any dropouts, and four to five for the intervention arm[54]**.** Semi-structured questionnaires will guide discussions, ensuring key areas

covered across the groups and interviews (see Topic guides for participants). Prompts will help facilitate fuller discussion of topic areas.

11.2 Patient participant consent process

Participants will have indicated their willingness to be contacted after surgery for a qualitative interview or to take part in a focus group about their experience of participating in the study during initial consent (RESOLVE Participant ICF). A researcher will contact the participant by telephone a couple of weeks after surgery and a more detailed PIS and consent form will be provided at least 48 hours prior to the interview or focus group (see PIS Qualitative Participants and ICF Qualitative Participants respectively). There will be an opportunity to discuss this aspect of the study in more depth with the researcher before consent is obtained over the telephone.

11.3 Dietitian and Healthcare Professional Focus group

An objective in the feasibility study is to evaluate the VLCD intervention from the perspective of the dietitians and healthcare professionals delivering it. At the end of the study the clinicians from all participating sites will be invited to take part in a focus group to discuss their experience and perspectives of.

- The study process and data collection
- The VLCD intervention
- The training

The aim is to explore the acceptability of the VLCD and diary, to identify barriers and facilitators to intervention delivery, to identify methods to improve delivery and implementation within the NHS. Semi-structured questionnaires will guide discussions, ensuring key areas covered across the groups and interviews (see Topic Guide for Staff).

11.4 Fidelity of Intervention

It is important to ensure that intervention delivery is consistent over time and between organisations. Consent will be sought from those delivering the VLCD intervention at each site to allow the audio recording of their initial appointment, and ones after several participants and one near the end of recruitment. These will then be analysed by the qualitative researcher. Patient participants will also be informed of potential audio recordings (see RESOLVE Participant Information Sheet).

11.5 Dietitian and Healthcare Professional consent process

Prior to being trained on the aspects of motivational interviewing, the clinicians will be provided with a PIS (See PIS Qualitative Staff) and the evaluation of the training and intervention aspects discussed with them. If they consent to recording of a selection of their intervention appointments and participation in the focus group, they will be asked to complete a Consent form (see ICF Dietitian qualitative interviews). One of the research team will contact the dietitians or Healthcare professionals to arrange the audio recordings for the fidelity checks at each site.

Once all sites have completed clinical data collection on all their participants, the research team will contact them again to arrange the focus group at a convenient time for all. The meeting will be held on Microsoft Teams.

11.6 Analysis of qualitative data

Focus groups and interviews will be audio-recorded and then transcribed verbatim. The six-phase framework described by Braun & Clarke[55], will be applied to transcribed data and thematic analysis undertaken. Identified themes from focus groups and interviews will be reviewed, then a process of peer debriefing undertaken to maximise credibility and dependability of identified themes. This will be further strengthened by inviting participants to review draft themes to ensure accurate representation

of views and experience. Data will then be shared with the wider team and PPI representative before a final consensus of findings is made.

Fidelity of intervention audio recordings will be analysed for consistency across the sites. Main themes of the training will be identified, and usage scored to measure training effects don't decrease or change over time.

12 ECONOMIC EVALUATION COMPONENT

This study will be used to develop and test methods for assessing the cost-effectiveness of the intervention alongside a future full trial. Intervention resource use will be collected by the healthcare professionals who are delivering the intervention, using individual-level electronic case report forms (eCRFs). Data on the utilisation of health and social care services, and on wider societal resource use, will be collected using a self-report, Resource Use Questionnaire. Health-related quality of life will be measured using the EQ-5D-5L questionnaire[56]**.** Participant-level QALY weights will be estimated in accordance with current guidance from the National Institute for Health and Care Excellence[57].

12.1 Suggested approach for health economic analysis

This feasibility study will be used to test the methods for a subsequent, policy-relevant, cost-effectiveness analysis (CEA) of VLCD plus support to reduce hepatic steatosis before liver resection, compared to usual care. The objectives of the health economics component of this feasibility study are:

- to identify, measure, and value intervention costs
- to assess the feasibility of collecting data on health, social care, and wider societal resource use
- to assess the feasibility of collecting participant-level data on health-related quality of life to inform a future cost per quality-adjusted life-year (QALY) analysis
- to present the costs/outcomes associated with the intervention and the control groups separately
- to conduct a preliminary health economic evaluation and develop a framework for estimating cost-effectiveness in a future full trial.

Using the data collected in the feasibility study, we will produce preliminary results on intervention costs, resource use and associated costs, and QALYs. This will be undertaken against a primary perspective of the NHS/Social Care, with the participant and broader societal perspectives considered in sensitivity analyses. Results will be presented in a disaggregated format, i.e., cost and outcome data will not be synthesised.

12.2 Intervention costing

The resources required to deliver the VLCD plus support intervention will be assessed via participant-level case records and discussion with the intervention developers and providers. This will include staff time, travel, materials, documentation, and consumables. Staff time will be documented in terms of per-participant contact, non-contact time, and any additional time in relation to the delivery of the intervention. Training and supervision resources will also be documented. Nationally recognised UK unit costs for health and social care services[58] will be applied to this resource use data. Where national costs are not available, costs will be identified in consultation with the intervention developers and providers. The mean cost per participant of the intervention will be estimated.

12.3 Health, social care, and wider societal resource use

We will use a modified version of the Client Service Receipt Inventory (CSRI)[59] to measure resource use. Relevant items will be identified from the Database of Instruments for Resource Use Measurement (DIRUM)[60] and recent literature. Participants at baseline and follow-up will complete the questionnaire. Unit costs will be applied to the resource use data using the approach outlined for the intervention costing above.

12.4 Health outcomes and quality-adjusted life-years

Participants will complete the EQ-5D-5L[56] at baseline and at follow-up. Participant-level QALY weights will be estimated in accordance with current guidance from the National Institute of Health and Care Excellence (NICE): responses to the EQ-5D-5L will be mapped to the UK tariff of health state values for the EQ-5D-3L using an 'approved' crosswalk algorithm[61-62].

13 PARTICIPANT WITHDRAWAL

13.1 Withdrawal from intervention phase

There is very little risk associated with the VLCD however there is potential risk of withdrawal due to lack of tolerance of the diet; general feeling of unwellness or hunger. Participants may request withdrawal at any time during the intervention.

Participants may wish to stop the diet but may still be interested in taking part in the data collection (food diary, mood scores, 30 and 90-day follow-up) and/or qualitative focus groups or interviews. They will be presented with these options.

13.2 Withdrawal from research

In addition to participants in the VLCD group, participants in the TAU group may also wish to withdraw from the study at any stage.

Any participant who withdraws will be asked to provide a reason but will be made aware that they are under no obligation to provide one, and that their withdrawal from the study shall in no way affect their access to ongoing treatment. Participants who withdraw will be offered the opportunity to take part in a focus group or interview to discuss in more detail

Withdrawal from RESOLVE, and reason if provided, will be documented in the participants' clinical records reported to the CTU using a specific eCRF. Patients will continue to be recruited if within study timeframes.

Data collected prior to withdrawal will be included in the analysis. All patients will continue to be treated as per usual care.

13.3 End of study

Participants will complete their involvement in the trial after approximately 90 days post-surgery at the follow-up telephone assessment. The trial will end on completion of all data collection.

14 SAFETY MONITORING

Whilst participants are unlikely to experience any harm as a direct result of taking part in this trial, processes will be implemented to ensure that such harms are detected and monitored appropriately. The safety of participants will be monitored throughout the trial, from the time that consent is obtained until the 90-day follow up.

14.1 Definitions

An **Adverse Event (AE)** is any unfavourable sign, symptom, or disease in a participant, regardless of severity and regardless of cause.

An **Adverse Reaction (AR)** is an adverse event which is considered to have been definitely, probably or possibly caused by either the trial intervention or the trial procedures.

A **Serious** Adverse Event (SAE) or **Serious** Adverse Reaction (SAR):

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

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

Hospital admissions for elective procedures **will not be reported as SAEs. All unplanned hospital admissions will be reported as SAEs, regardless of duration of hospital stay. This includes visits to ED departments.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is an event which:

- is serious, as defined above, **and**
- is considered to have been definitely, probably or possibly caused by either the trial intervention or the trial procedures, **and**
- is deemed ‘unexpected’ i.e. the reaction is one which has not been foreseen by the Chief Investigator.

Guidance on assessing events against these definitions is described later in this section.

14.2 Adverse event reporting in the RESOLVE Study

The likelihood of participants being harmed by either the VLCD intervention or any of the trial procedures is very low. As such and acknowledging that post-operative complications are collected in all participants as an outcome measure, the collection and reporting of adverse events in the RESOLVE trial is restricted to only those events which are serious, as defined above. In the context of clinical care and in accordance with local practice, adverse events should be recorded by investigator site staff in the participants’ medical records. For the purposes of the trial, only serious adverse events (including serious adverse reactions) will be collected and entered the eCRF.

14.3 Detecting and recording reportable adverse events

Detailed instructions for the recording and reporting of serious adverse events will be provided to Investigator Sites by PenCTU. The primary means of detecting serious adverse events will be the interactions between the research team member(s) and the trial participant at each of the data collection timepoints. At each visit or telephone call, participants will be asked to describe any adverse events they have experienced.

Participants in the VLCD group will also be able to report any adverse events to their dietitian or Healthcare Professional.

Any events meeting the criteria for seriousness (defined in section 14.1) must be recorded by the research team member in the participant's health record and in the eCRF. SAEs are subject to expedited reporting so must be processed in a timely manner (see section 14.5).

The Day 30 and 90 follow-up involves collection of health and social care resource utilisation. Site researchers should ensure any (non-elective) hospitalisations or ED visits reported by participants when recalling resource utilisation are reported as serious adverse events.

14.3.1 Serious Adverse events detected by dietitians or HCPs delivering VLCD intervention

Dietitians or HCPs may also become aware of hospitalisations, or of concerns for the participants' wellbeing during the VLCD period. If a dietitian or HCP believes a participant has suffered a serious adverse event caused by participating in the VLCD intervention or by any trial procedures, they must report immediately to the site Principal Investigator, who will enter the event into the eCRF according to instructions provided by CTU. This applies to those in the TAU group also.

14.4 Assessing causality of (serious) adverse events

For serious adverse events, the PI (or authorised delegate) will assess the causal relationship between the SAE and trial participation. For participants in the intervention group, the PI will record their opinion on whether the SAE was caused by participating in the VLCD, and whether the SAE was caused by any trial procedures. For participants in the control group, the PI will record their opinion on whether the SAE was caused by any trial procedures. Causal relationship will be recorded in the participant's health record and in the eCRF. SAEs caused by the intervention or trial procedures in the opinion of the PI will be regarded as serious adverse reactions (SARs).

14.5 Reporting Serious Adverse Events and Serious Adverse Reactions

All SAEs and SARs must be reported to PenCTU within 24 hours of the research staff becoming aware of the event, according to instructions provided by PenCTU.
For each SAE/SAR the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causal relationship

PenCTU will immediately notify the CI of any reported SAEs / SARs and the CI will record a second assessment of causal relationship. The CI may upgrade the causality assessment (e.g. from not related to related) but may not downgrade the assessment (e.g. related to not related).
Where a causal relationship is suggested, the CI will record an assessment of expectedness. Expectedness will be judged on a case-by-case basis.
An event deemed to be unexpected will be regarded as a SUSAR and will be subject to expedited onward reporting as described in section 14.6 and will be followed up until the event has resolved or an outcome has been reached.

14.6 Onward reporting of SAEs / SARs / SUSARs

Onward safety reporting activities and responsibilities are summarised in Table 3. Onward safety reporting activities and responsibilities

Table 3: Onward safety reporting activities and responsibilities

Event	Reported by	Reported to	Reported when	Reported how
SUSARs	PenCTU	Sponsor	Within* 24 hours	Email to plh-tr.rdgovernance@nhs.net
SUSARs	PenCTU	REC† & TSC‡	Within* 7 or 15 days¶	Using non-CTIMP safety report form (available on HRA website), by email.
All SAEs/SARs	PenCTU	Sponsor & TSC	Quarterly	Line listing, by email
Overall safety concerns	PenCTU	REC	Annually	Using annual progress report form (available on HRA website), by email

**of the CI becoming aware of the event*
†REC - Research Ethics Committee
‡TSC - Trial Steering Committee
¶7 days for fatal or life-threatening events. 15 days for others

14.7 Coding of adverse events

PenCTU will maintain a register of all recorded serious adverse events. Events entered into the eCRF will be coded by designated members of PenCTU staff using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 23.1. Events will be coded at two levels - the 'preferred term' (PT) and 'System organ class' (SOC). The same version of the MedDRA dictionary will be used throughout the trial.

14.8 Safety oversight

The Trial Management Group (TMG) will discuss any SUSARs and any emerging safety concerns at monthly TMG meetings. Line listings of SAEs/SARs, produced by PenCTU, will be reviewed quarterly by the Trial Steering Committee (TSC) in accordance with the details set out in the agreed TSC Charter.

15 STATISTICS AND DATA ANALYSIS

15.1 Target sample size and justification

As the trial is a feasibility study, a formal sample size calculation has not been performed. Seventy-two patient-participants will be recruited over six months, 36 in each group, providing sufficient data to answer our feasibility and desirability questions. 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. This feasibility study will include data from seven UK based centres that regularly perform liver resections. Most large 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 seven UK based centres that will take part in this study (Liverpool, Surrey, Southampton and Plymouth, Leeds,), 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. Seventy-two patient-participants will be recruited over 12 months (6 per month).

15.2 Statistical analysis plan

The trial will be reported in accordance with the CONSORT 2010 statement extension to pilot and feasibility trials[63]. The Statistical Analysis Plan will be signed off by the TMG and TSC prior to the end of recruitment. The SAP will be reviewed by the TSC and signed off by an independent statistician prior to database lock.

In brief, descriptive statistics will be reported for the feasibility outcomes: recruitment, retention, and adherence rates (with 95% confidence intervals), quality of data collection, intervention delivery and fidelity. Baseline data and candidate primary and secondary outcomes will be summarised overall and by trial arm. Data will inform a potential definitive study with variability in candidate primary measures calculated and a sample size (power calculation) for the definitive trial estimated for each. Serious adverse events will be summarised descriptively. Missing data will be described but not imputed. No statistical comparisons between treatment groups will be undertaken on baseline or follow-up data as the trial is not designed to test effectiveness.

15.2.1 Summary of baseline data and flow of patients

The analysis and reporting of this feasibility study will follow the CONSORT guidance for pilot and feasibility studies. The flow of participants through the study will be presented in a CONSORT-style diagram with reasons for discontinuation or withdrawal given where available. Descriptive statistics of participants' demographic and baseline characteristics will be presented by allocated groups and overall. No formal between-group comparisons of baseline data will be undertaken.

15.2.2 Progression criteria

RAG stop-go criteria will be used to assess the key feasibility objectives of recruitment and intervention adherence to inform whether a main trial is possible and whether the design or other issues need modification to conduct it successfully. Process data will be used to describe interpreted timelines to identify "fixable", "manageable" and "insurmountable" challenges to site opening, training, data collection and intervention fidelity, regarding both the future main trial and clinical implementation in the event of a positive trial.

We shall progress to a full trial application if minimum success criteria for key feasibility aims/objectives are achieved:

- target population recruited within 12-month 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 (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.

15.3 Interim analysis and criteria for the premature termination of the trial

There is no planned interim analysis for this pilot trial.

15.4 Participant analysis population(s)

Primary analysis (in the form of summary statistics, not hypothesis testing/inferential analysis) will be undertaken on an Intention To Treat (ITT) basis, where participants are analysed according to their allocated group, regardless of adherence to the protocol or lack of participation or completion of VLCD if allocated to the intervention group.

The safety population will include all participants who consent to participate in the study, with safety data collected from the time of recruitment until a participant completes or withdraws from the study.

15.5 Procedure(s) to account for missing or spurious data

One of the objectives of this pilot trial is to assess the completeness of potential outcome measures for the definitive trial, at the level of both item and outcome measure. Missing outcome data will be noted and used to inform the likely pattern of missing data in a full-scale trial. If a considerable amount of outcome data is missing, this may suggest a need to reconsider the choice of outcome measures and inform the choice of primary outcome measure for any future definitive trial. This may also provide an insight into how missing data can be minimised in any subsequent full-scale trial.

15.6 Other statistical considerations.

Statistical analysis will be undertaken once the final group of participants has completed the final assessment at 90 (±14) days post-randomisation and the database is locked.

The statistical analyses will be undertaken using StataSE version 16 or later, supplemented where required by R.

16 DATA MANAGEMENT

Data management activities are summarised in this section. Detailed data management activities are described in a separate Data Management Plan (DMP).

The main study database will be developed by PenCTU, using the commercial electronic data capture system, REDCap Cloud. The system uses validation and verification features to monitor study data quality and completeness.

16.1 Data collection tools and source document identification

A web-based application developed by PenCTU will be used for trial management and for recording participant data. Source data will include participants' medical records (e.g. for certain eligibility criteria) MRI scans, participant-completed documents (e.g. informed consent forms, food diaries), worksheets provided by PenCTU and the eCRF. In the context of clinical care, investigator site staff must ensure that details of a patient's participation in the trial are recorded in the participant's health record. As a minimum, the health record should be updated to include:

- Consent and eligibility for study
- Dates of all study visits and follow ups
- Adverse events
- Completion or discontinuation of study

16.2 Data handling and record keeping

Any electronic data captured in PenCTU's bespoke web-based system will be stored on Microsoft Azure servers located in the UK. The servers are certified to Cyber Essentials PLUS standards. PenCTU staff develop applications in the Azure environment according to the requirements of the UK NHS Health and Social Care Cloud Security - Good Practice Guide.

The eCRF is built in REDCap Cloud. eCRF data is stored in the REDCap Cloud production infrastructure, hosted in Amazon Web Server (AWS) datacentres located in the European Union. AWS datacentres are Service Organization Control (SOC) type 1 and type 2 compliant. Data will be stored on hardware dedicated to REDCap Cloud. In both systems, all electronic data are backed up and stored with a full audit trail.

16.3 Data quality and completeness

PenCTU Data Management staff will monitor completeness and quality of data recorded in eCRFs and will correspond regularly with site PIs (or their delegated team member) with the aim of capturing any missing data where possible and ensuring continuous high quality of data. Data quality and completeness checks will be defined by the Data Manager through consultation with the CI, trial statistician, trial manager and other members of the Trial Management Group as required. Checks will be described in the Data Management Plan. Throughout the trial, the Data Manager will report on the quality and completeness of accumulating data to the Trial Management Group.

16.4 Access to Data

Direct access to investigator site records will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections- in line with participant consent.

16.5 Archiving

Following completion of trial data analysis, the Sponsor will be responsible for archiving the study data and Trial Master File in a secure location for at least five years after the end of the trial. PenCTU will prepare the Trial Master File for archiving in accordance with the requirements of the Sponsor's SOP. PenCTU will prepare a copy of the final dataset for archiving according to the requirements of the CTU's SOP.

Principal Investigators at sites will be responsible for archiving Investigator Site Files and trial data generated at the site according to local policy. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so. Medical records containing source data or other trial related information should be labelled, physically or electronically, to ensure retention until the Sponsor gives authorisation to destroy. e.g. "Keep until dd/mm/yyyy" (where the date given is five years after the last participant's final visit).

17 TRIAL OVERSIGHT, MONITORING AND AUDIT

17.1 Trial Management Group

A Trial Management Group (TMG) comprising the CI, co-applicants, trial statisticians, PPI representatives, CTU staff and Sponsor representatives will meet monthly throughout the trial to review overall trial progress, protocol compliance and data quality and completeness, identifying and addressing any issues with trial conduct as they arise.

17.2 Trial Steering Committee

A Trial Steering Committee (TSC) comprising an independent chairperson (clinician), two independent clinicians (surgeon and dietitian), an independent statistician, two PPI representatives and designated members of the TMG will meet six monthly throughout the trial to provide overall supervision of a trial on behalf of the Sponsor and funder and to ensure that the trial is conducted in accordance with the protocol and governance guidelines. The full composition, role, and function of the TSC will be described in a separate charter. TSC meetings will be guided by progress reports compiled by the TMG in advance of TSC meetings.

17.3 Trial monitoring

In accordance with CTU standard operating procedures for risk assessment and monitoring, a specific monitoring plan will be generated by the CTU, based on the CTU's risk assessment, with input from the TMG. The monitoring plan will be signed off by the CI and Sponsor before implementation.

CTU will perform ongoing central monitoring, outputs from which will be discussed by the TMG. Central monitoring will include close supervision of participant recruitment rates, attrition rates, data completeness (missing data), data quality (using range and consistency checks), protocol non-compliance, calendar checks (to identify deviations from participants' visit schedules), consent process checks (through collection of completed de-identified consent forms) and appropriateness of delegated duties at investigator sites (through collection of site delegation logs). Central monitoring will be used to identify areas of potential poor performance at individual investigator sites. Poor performance at sites may trigger on-site monitoring visits (subject to any COVID-restrictions), hosted by the investigator site PI and relevant members of the PI's team. On-site monitoring (if applicable) will be conducted by CTU staff according to established CTU standard operating procedures.

17.4 Audit

Independent audits may be conducted by the trial Sponsor, funder, or regulatory bodies. Site PIs, the CI and CTU will permit access to all records required by auditors to fulfil their audit duties.

18 PUBLIC AND PATIENT INVOLVEMENT

The PPI group has been vital in planning this trial and in particular the design of the intervention. Two groups of patients that would be important to engage with were identified. People who had either been patients on the liver surgery pathway or have had experience of a very low-calorie diet due to requiring bariatric surgery.

Patient representatives who had a cancer diagnosis and had or were intending to undergo liver surgery told us that diet was important to them at the time and would have done/would do anything to help improve their health and surgical outcomes. Those that had already been through the pathway had not received any specific pre-operative dietary advice, although they had asked. All wanted to do something actively and would have accepted a special diet to give them some control over their treatment.

PPI discussions are reflected in this feasibility trial methods;

1. In terms of the importance of the study, the PPI group's experience illustrated that there is little or no dietary advice leading up to surgery, even when they have asked for it.

2. The individuals in the group would have done anything to improve the outcomes of their surgery. Their advice led us to decide on the liquid diet as it was something they felt they could control and wouldn't deviate from and from the experience of some had adhered to well.

3. They helped the study team decide which brands were the most tolerable whilst offering some flexibility in terms of meal replacement shakes and soups. They also wanted vegetables as an option.

4. Clear information was identified as integral to the success of the intervention, and they proposed that an information/support booklet providing the diet details should be provided.

5. The patient group advised on the practical processes of the study, including the diet intervention and the 'treatment as usual' to ensure that participants engage with the study and found both arms acceptable. A scheduled phone call after one week, a contact telephone number for questions and food diaries were all suggested and considered acceptable by the group as methods of monitoring diet and providing support for participants pre-surgery on trial.

6. The group also advised on the collection of data including the qualitative component, specifically on the use of virtual meetings for focus groups and the flexibility of an interview for participants if preferred. It was emphasised that participants would be more likely to engage in a virtual environment as they may still be recovering from surgery or other treatments and entering a social environment may put them at risk of infection.

The group led by the PPI Lead will continue to meet and advise on the study design and review patient-facing documents as required. One representative has agreed to continue as a co-applicant and will attend the Trial Management meetings.

If this feasibility trial is successful, the PPI group will play a central role in designing the definitive RCT proposed and supporting a new funding application.

Two independent PPI representatives are members of the Trial Steering Committee.

19 ETHICAL AND REGULATORY CONSIDERATIONS

19.1 Research Ethics Committee (REC) review

The Chief Investigator (CI) has obtained approval from the UK Health Research Authority (HRA) and Research Ethics Committee (REC). The Chief Investigators will ensure that this study is conducted in full conformity with relevant regulations and with the UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki.

19.2 Peer review

The study was funded by NIHR through open competition after independent external peer review was conducted.

19.3 Regulatory Compliance

The trial will not commence until a favourable REC opinion and HRA approval has been obtained. Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. For any amendment to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

19.4 Protocol compliance

Non-compliance with protocol will be captured on specific non-compliance report forms according to instructions provided by PenCTU and in accordance with PenCTU standard operating procedures. Protocol non-compliance will be reviewed periodically by the Trial Management Group as part of central monitoring (see section 17.3), with the aim of identifying and addressing recurrent episodes of non-compliance. Each reported non-compliance is reviewed by the PenCTU trial manager. PenCTU staff must immediately inform the PenCTU QA Manager if they believe that a serious breach has occurred (see below). Where the trial manager and/or PenCTU QA Manger believes that a non-compliance might constitute a serious breach, the trial manager should ensure that a completed non-compliance report form is provided to the Sponsor immediately.

19.5 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(1.a) the safety, rights or physical or mental integrity of the participants of the trial; or

(1.b) the scientific value of the trial

Where a non-compliance meets the above criteria, PenCTU will immediately notify the CI and Sponsor. The Sponsor will email a serious breach report to the REC and to HRA (using the breaches.nres@nhs.net email address) within seven days of becoming aware of the event.

19.6 Data protection and patient confidentiality

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and the General Data Protection Regulation (GDPR) 2016.The trial Sponsor is the Data Controller for the trial data. PenCTU is a data processor, centrally managing trial data generated at investigator sites. The

University of Plymouth is the data custodian since data are stored on databases managed by the University of Plymouth.

Data including the number of patients screened, approached, and interested in taking part will be collected via a log completed by staff conducting screening. Investigator site staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information in accordance with ethics approval.

Any paper-based data collection tools (e.g. worksheets and questionnaires) for capturing source data will remain at investigator sites. Investigator site staff will enter participant data into purposed designed data capture systems (described in section 16). Access to the system for all users (including PenCTU staff) is via a secure password-protected web-interface. Each participant will be allocated a unique system-generated study number. Participants will be identified in all study-related documentation by their study number and initials. Data collected and analysed during the study will be de-identified using this unique identifier. A record of trial participants' names and contact details, hospital numbers and assigned trial numbers will be stored securely in a locked room at the trial site and is the responsibility of the site PI.

To facilitate central coordination of the study and contact between participants and qualitative researchers, participants' contact details will be entered into the data capture system by investigator site staff (after consent). Only limited staff at PenCTU will have access to these details and these details will not be made available in any form to any persons unless needed for study conduct. Datasets prepared for transmission to statisticians (for analysis), co-applicants or Sponsor will be de-identified and will not contain any direct identifiers or participant contact details.

Audio data from qualitative interviews and session delivery audio recording of facilitators will be recorded either via Microsoft Teams or Zoom or using an encrypted digital audio recorder. Data collected using both Microsoft Teams and encrypted digital recorders will be stored on Microsoft SharePoint on the University's secure server using the participant's unique study number. All data will be deleted from digital recorders as soon as it is securely transferred. Audio recordings and transcribed data will only be accessible to the 'designated members of the qualitative evaluation team.

Transcription of audio recordings of interviews or sessions will only be carried out by members of the research team or professional services with confidentiality agreements in place. Audio-recordings will be deleted following transcription of interviews and focus group sessions.

19.7 Financial and other competing interests

The Chief Investigator and TSC committee members will sign a declaration form to disclose any financial or other competing interests including, but not limited to:

• any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
• commercial ties including, but not restricted to, any pharmaceutical, behaviour modification, and/or technology company
• any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

These declaration forms will be filed as part of the Trial Master File.

19.8 Indemnity

This is an NHS-Sponsored research study. If an individual suffers negligent harm because of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an ex-gratia payment may be considered in the event of a claim.

19.9 Amendments

The Sponsor may make a non-substantial amendment at any time during a trial. If the Sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor must submit a valid notice of amendment to the REC for consideration. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amended documents will be allocated a new sequential version number. Once approved by REC, this version will supersede any previous versions.

19.10 Access to the final trial dataset

During the study, the PenCTU data team will have access to the dataset, including identifiable participant data. Other members of the CTU and the wider study team will have restricted access to pseudo-anonymised study data. Access to the dataset will be granted to the Sponsor and host institution on request, to permit study-related monitoring, audits, and inspections. Access will be overseen by the CTU data manager and trial manager. Access to the final dataset will be provided to the trial statisticians and health economist for analysis.

This is a feasibility trial, to plan and assess the feasibility of a definitive RCT. After the programme has reported, the individual participant data that underlie the results will be available on request from the CI and Sponsor, along with supplementary files as required (e.g. data dictionaries, blank data collection forms, analysis code, etc.). Data will be shared with (or access to the data will be provided to) requestors whose proposed use of the data has been approved by the CI and Sponsor, under an appropriate data sharing agreement. It will not be possible to identify participants personally from any information shared.

20 DISSEMINATION POLICY

20.1 Dissemination policy

The data arising from the trial will be owned by the Sponsor. On completion of the trial, the data will be analysed and tabulated, and a Final Trial Report prepared. This report will be submitted to the Trial Sponsor and Funder and will be accessed on request by contacting PenCTU. Participating investigators will not have rights to publish any of the trial data without the permission of the CI and Sponsor.

The trial will be reported in a manuscript that will be submitted to a peer-reviewed medical journal as open access. The trial will be reported in accordance with the Consort Guidelines. All publications arising from this trial will acknowledge the Funder and a copy of all manuscripts will be provided to the Funder for review at the time of submission to a journal. However, the Funder does not have the right to revise any submission prior to publication. The trial protocol will also be submitted for open access publication to a peer-reviewed journal. A lay summary of the trial results will be produced and provided to sites, to pass on to trial participants on request. An anonymised participant level dataset will be produced and held within PenCTU (see section 20.11 for access details).

20.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship of all manuscripts relating to this trial will be determined according to the International Committee of Medical Journal Editors criteria. All members of the TMG who have contributed to trial design, management, analysis, and interpretation will be granted authorship of the Final Trial Report. The CI will retain lead author status on the Final Trial Report.

21. REFERENCES

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