Pilot and Feasibility Studies

STUDY PROTOCOL

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Protocol for a feasibility multi-centre randomised controlled trial of a pre-operative two-week very low-calorie diet to reduce steatosis prior to liver resection (RESOLVE)

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Abstract

Background Hepatic steatosis (HS) increases morbidity and mortality associated with liver surgery (LS). Furthermore, patients with HS are more likely to require a blood transfusion, which is associated with worse short and long-term outcomes. Patients with HS requiring LS receive no specific dietary treatment or advice. A very low-calorie diet (VLCD) is commonly used before gallbladder and bariatric surgery to reduce liver volumes and associated intraoperative morbidity. These diets typically provide 800–1200 kcal/day over a 2–4-week period. Limited evidence suggests that a VLCD in patients with LS may result in better outcomes.

Methods This study aims to test the feasibility of delivering a multi-centre randomised clinical trial to compare a dietary intervention (VLCD plus motivational instructions) versus treatment as usual (TAU) in people with HS having LS. This study will provide high-quality data to estimate screening rates, recruitment, randomisation, retention, and intervention adherence. The study will also determine the definitive trial's most clinically relevant primary outcome. The study will also estimate resource use and costs associated with the delivery of the intervention. Seventy-two adults ≥ 18 who are scheduled to undergo elective LS and have a magnetic resonance imaging (MRI) identified HS will be recruited. Acceptability to the dietary intervention will be evaluated with food diaries and focus groups. Clinical and patient-reported outcomes will be collected at baseline, pre- and post-surgery, day of discharge, plus 30- and 90-day follow-up.

Discussion This feasibility study will provide data on the acceptability and feasibility of a dietary intervention for patients with HS having LS. The intervention has been developed based on scientific evidence from other clinical areas and patient experience; therefore, it is safe for this patient group. Patients with experience of LS and VLCDs have advised throughout the development of the study protocol. The findings will inform the design of a future definitive study.

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Keywords Fatty liver, Diet therapy, Intraoperative complications, Postoperative haemorrhage

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Background

Liver surgery (LS) is the primary curative treatment for liver metastases from colorectal cancer, primary liver tumours, and symptomatic benign and pre-malignant tumours. LS offers clear survival benefits. In 2018/19, almost 4000 resections were performed in England alone [1] and between 30 and 50% of these patients are estimated to have underlying hepatic steatosis (HS). HS is associated with a two to three times increased risk of complications, intra-operative bleeding, blood transfusion rate, increased mortality, and a 50% increased risk of readmission rate following surgery [2, 3]. Studies also found a correlation between the degree of fatty liver and the overall complication rate [4]. In a cohort of 485 patients, Kooby et al. 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 the severe steatosis group (43%) compared to mild steatosis (24%) and normal parenchyma groups (14%) [5]. Any intervention that reduces the amount of fat in the liver can potentially reduce these risks.

Low- and very low-calorie diets (LCDs and VLCDs) are routinely used for 2–4 weeks before bariatric 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 restricted regular food with a vitamin and mineral supplement or a commercially produced balanced liquid meal replacement. Studies have also shown that a pre-operative low-calorie diet can result in a liver that may be easier to mobilise [6] and could, therefore, reduce intraoperative blood loss. However, these studies are small, only include obese patients, and no formal prospective HS assessments are conducted before the dietary intervention. Furthermore, there is a lack of clarity on the types of diets they have used and how they measured adherence.

Short-term adherence to pre-operative low-calorie diets in bariatric and gastric cancer surgery is reported to be between 100 and 97%, respectively [7, 8]. In the study by Barth et al. [9], 94% of patients fully adhered to the diet in patients undergoing liver resection. Our patient and public involvement (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.

Most liver resection patients will undergo a magnetic resonance imaging (MRI) scan to characterise the liver tumour/s 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 and is sensitive to changes in HS quantification, so it can be used to identify patients with HS before liver surgery [11]. A meta-analysis by Yokoo et al. concluded that MRI PDFF measurements have excellent linearity, bias and precision across different field strengths, manufacturers, and reconstruction methods [12]. Serai et al. recently demonstrated that the estimation of PDFF using MRI is highly reproducible across different readers. They also showed similar results across different field strengths and imaging platforms [13]. This is paramount for the RESOLVE study as the pre-operative MRI scans will be performed within different hospitals and by different scanners. This protocol describes a multi-centre randomised controlled trial (RCT) with a parallel process evaluation to assess the feasibility and patient acceptability of a VLCD in patients with HS to LS and an economic evaluation assessment of resource use tools to inform the design of a future definitive RCT. The comparator group is treatment as usual (TAU). This was decided after discussions with the clinical teams and patient and public involvement (PPI). There is much inconsistency between units on what is provided to patients as part of usual care; therefore, no treatment was withdrawn for the group not receiving the intervention.

Objectives

To inform the design and delivery of a definitive RCT to compare the effectiveness and cost-effectiveness of the RESOLVE dietary intervention compared with treatment as usual (TAU), this randomised feasibility trial has the following objectives (please see Table 1. Objectives and outcome measures).

Trial feasibility objectives

- To estimate the rates of screening, recruitment, randomisation, and retention
- To ascertain adherence to a VLCD and study requirements before LS and any possible contamination
- Ascertain completeness of data collection at baseline, day of surgery, day of discharge, plus 30 and 90 days post-operatively
- To allow a preliminary assessment of the VLCD intervention.

Secondary objectives

- In a full trial, estimate the resource use and costs associated with intervention delivery and pilot methods for the cost-effectiveness framework

Table 1 SPIRIT Figure: Tabulated summary of the study data collection by time point

	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	X						
chemo history							
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			←	—	—	—	→

Table 1 (continued)

*at time of diet commencing

**routine bloods taken

***bloods reported on eCRF

- To identify whether there is a need to modify the VLCD and its delivery within the NHS and, if so, identify methods for improvement
- 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) [14] (overall Clavien-Dindo grade I–V postoperative complications [15]), length of stay and readmission rate within 90 days, or 90-day mortality

Design

This is a multi-centre feasibility randomised controlled trial of RESOLVE (VLCD) versus TAU.

Study setting

The study aims to include five secondary care trusts in the UK. For more information, contact the author. Participating units must have dietetic support available. The protocol does consider any differing clinical pathways at each trust.

Participant eligibility criteria

Inclusion criteria

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

- Adult patients ≥ 18 years
- Able to provide informed consent
- Patients with HS with or without non-alcohol steatohepatitis 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 who meet any of the following criteria will be excluded from study participation:

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

Recruitment and consent

Site principal investigators (PIs) will promote the study locally. The Trial Management Group (TMG) will closely monitor recruitment performance at each site. The stages of the recruitment process are illustrated in Additional file 1.

Participant identification and eligibility screening

The clinical teams will screen for potential patients at the hepato-pancreatico-biliary multi-disciplinary team meeting (HPB MDT). Patient-identifiable information will not be used by anyone other than the clinical team.

Participant recruitment and consent

After identifying patients with fatty liver requiring surgery at MDT, clinicians will check their eligibility for RESOLVE study, including pregnancy, allergy, or intolerance to the ingredients or whether they are vegan. If the patient is interested, they will receive a patient information sheet (PIS). The patient will receive a phone call from a member of the RESOLVE research team to discuss the study requirements in more detail and have an opportunity to ask questions, at least 24 h after receiving the PIS.

The researcher will review the eligibility criteria with the patient before obtaining telephone consent. The only eligibility criteria not verified until the baseline measure appointment are BMI in addition to whether the patient has had unintended weight loss (reported unintentional weight loss of > 5% in 0–3 months or > 10% in up to 6 months). All researchers taking consent have been trained in the relevant principles of Good Clinical Practice and have detailed work instructions and training in the study protocol requirements.

The researcher will collect the details of screened patients in a secure bespoke online system created by the Peninsula Clinical Trials Unit (PenCTU). Once a participant is provisionally eligible and consents to the

study, their name and study number will be automatically transferred into REDCap Cloud. A copy of the consent form will be provided to the participant at the baseline appointment.

The following sections detail each study and data collection time point (see also Table 1. SPIRIT Figure).

Pre-baseline

Once a participant has provided consent, their pre-baseline data can be entered into REDCap Cloud before the patient attends their baseline appointment. Pre-baseline data consists of relevant comorbidities, details of previous surgery and chemotherapy, details of diagnosis, tumour characteristics, and intended liver surgery details (see Table 1).

Baseline

Patients will attend the hospital for their baseline appointment on the same day as their pre-operative appointment. A study visit will be arranged if their usual care involves a virtual pre-operative appointment. Height and weight will be measured to determine BMI; if < 20 kg/m^2, the patient will not be eligible to continue. Once eligibility has been confirmed, further baseline data will be collected, including hand grip strength, quality of life (EQ-5D-DL), and demographics.

Randomisation

After all baseline data collection, a minimisation procedure with a random element will be used to allocate participants to receive very low-calorie diet (VLCD) or treatment as usual (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. [16] (grade I, grade II, and grade III)

Treatment allocation will be achieved using a web-based randomisation service provided by the UKCRC-registered PenCTU. Automatically generated emails will inform the local site team and the PI that randomisation has occurred.

The very low-calorie intervention

Dietitians at each recruiting site are provided with an online 3-h training session with the senior lead dietitian on the RESOLVE research team. This has been developed and tested with onsite NHS dietitians and will be recorded for repeated access if required.

Suppose a participant is randomised to the intervention group. In that case, the baseline appointment will take up to 30 min longer (compared to the control group) as the participant will receive the VLCD instructions. During this appointment, participants will rate their chances of success in adhering to the VLCD.

The intervention group will undertake a VLCD 2 weeks before surgery. The VLCD will be in the form of liquid meal replacement (4 sachets (Tesco slim shake) per day), providing 800 kcal and 80 g protein. Participants will be given a list of permitted low-starch vegetables (up to 100 kcal per day) and zero-calorie drinks that can be consumed freely during the study. Participants whose protein requirements, calculated by the study dietitian, are more than 80 g per day will be advised to take and provided with an additional protein powder supplement.

Participants in the intervention group will be given a diet information booklet along with a food and mood diary with instructions on how to complete it for the 2 weeks. The diary may be digital or paper-based, as they choose. Participants will be required to record all food and fluids consumed daily for 2 weeks and record perceived adherence and mood, hunger, and energy levels. These self-reported factors may change with VLCD and may influence motivation. Participants will be educated on the dietary requirements of the study and the need to sustain the diet for 2 weeks before surgery.

Potential complications/side effects will be listed and explained in the diet information booklet, and guidance will be provided on coping strategies to support maintenance. Participants will receive daily email reminders to complete the food diary. To support adherence and provide motivational support, the dietitian will contact participants by phone 2–3 days into the diet. 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. Completed 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 provided, and their dietitian will contact them to provide more phone support in 2 weeks.

Treatment as usual

At their site, participants allocated to the TAU arm will receive 'treatment as usual'. Those participants who consent but do not have an in-person pre-operative appointment as part of usual care will attend the hospital for a research visit to collect baseline information.

Adverse event reporting

The likelihood of participants being harmed by either the VLCD intervention or trial procedures is very low. The

Table 2 Objectives and outcome measures for the RESOLVE study

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	Success of blinding surgeons
Adherence to VLCD	Discussions in qualitative interviews and focus groups Difference in weight between baseline and day of surgery (pre-operation) VLCD diary analysis and collection of empty sachets
Data completeness	Completeness of data capture and outcome measures to include pre-baseline, baseline, day of surgery, day of discharge, 30- and 90-day follow-up, 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
Identification of a primary outcome for the definitive trial	Operating time (calculated from knife to skin and wound closure time), ease of liver surgery (score of 1 to 5 by operating surgeon), blood loss (estimated using fluid in suction canisters, weighing of swabs, fluid in the CUSA irrigation and from blood on the floor), blood transfusion requirements, time to functional recovery, Comprehensive Complications Index (CCI) [14] (overall Clavien-Dindo grade I-V postoperative complications [15]), length of stay and readmission rate within 90 days, or 90-day mortality
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

collection and reporting of adverse events is restricted to only those severe events. 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. The 30- and 90-day follow-ups involve collecting health and social care resource utilisation. Site researchers should ensure any (non-elective) hospitalisations or emergency department visits reported by participants when recalling resource utilisation are reported as serious adverse events.

Outcome measures

Outcomes collected in this feasibility trial are listed below in Table 2. This feasibility study will determine the ability to successfully collect the planned participant data items. Patient-reported measures include the validated EQ-5D-5L and a bespoke Resource Use Questionnaire (for more information, contact the senior author).

Blinding

Surgeons will be blinded to treatment allocation. To assess the success of blinding, surgeons will be asked whether they have been unblinded to a participant's allocation at any point and if not to record the treatment group they believe the participant to be in post-surgery. Unblinding is permissible if a serious adverse event is reported. It is not possible to blind participants, dietitians, or research staff collecting data. The trial statisticians undertaking the analyses will not be blinded to treatment allocation.

Participant withdrawal

Participants enrolled in either study group retain the right to withdraw from the trial at any point. The VLCD poses minimal risks; however, potential withdrawal may occur due to dietary intolerance, general discomfort, or hunger. Data collected from participants before their withdrawal will be retained and included in the subsequent analyses. Regardless of withdrawal, all patients will continue to receive treatment as per TAU.

Participants may choose to cease the VLCD while expressing interest in continuing other aspects of the study, such as data collection on the day of surgery, postoperative assessments, 30- and 90-day follow-up, and qualitative focus groups or interviews.

Target sample size and justification

Seventy-two patient participants will be recruited over 6 months, 36 in each group, providing sufficient data to answer our feasibility and desirability questions. Adherence to the VLCD will be monitored using the food diaries and returned empty sachets. Participants will have adhered if they have complete daily adherence for at least 10 out of 14 days or 75% of all the sachets over the intervention period. To assess the adherence rate with a confidence interval of ± 10% and an estimated expected adherence rate of 75%, the minimum sample size for this feasibility study is 72 participants. Data from five UK-based centres that regularly perform liver resections will be collected. Most large HPB units would expect to perform 75–100 liver resections per year (30–50% with fatty liver), so this will provide a large enough sample for this feasibility study.

Statistical analysis plan

The trial will be reported in accordance with the CONSORT 2010 statement extension to pilot and feasibility trials [17]. The statistical analysis plan (SAP) will be signed off by the TMG and Trial Steering Committee (TSC) before the end of recruitment. 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. The trial arm will summarise baseline data and candidate primary and secondary outcomes. 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. 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. Statistical analysis will be undertaken once the final group of participants has completed the final assessment at 90 days (± 7 day window) post-randomisation and the database is locked. The statistical analyses will be undertaken using StataSE version 16 or later [18] and R [19]. The Medical Statistics Group at the University of Plymouth will have access to the final trial dataset.

Qualitative sub-study

All participants will be given the opportunity to take part in a focus group or interview to discuss their experience of participating in the feasibility study. 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

Six to seven focus groups will be conducted: one for usual care, one for any dropouts, and four to five for the intervention arm [20]. Semi-structured questionnaires will guide discussions, ensuring key areas are covered across the groups and interviews.

The clinicians from the four 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 VLCD and diary's acceptability, identify barriers and facilitators to intervention delivery, and identify methods to improve delivery and implementation within the NHS.

Fidelity of intervention

Ensuring that intervention delivery is consistent over time and between organisations is essential. Consent will be sought from those delivering the VLCD intervention at each site to allow the audio recording of their initial appointment, the ones after several participants, and one near the end of recruitment. The qualitative researcher will then analyse these.

Analysis of qualitative data

The six-phase framework described by Braun and Clarke [21] will be applied to transcribed data and thematic analysis undertaken.

Economic evaluation

Data on the utilisation of health and social care services and broader 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 [22]. Participant-level QALY weights will be estimated in accordance with current guidance from the National Institute for Health and Care Excellence [23]. Preliminary results on intervention costs, resource use and associated costs, and QALYs will be produced. 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.

Progression criteria

Red, Amber, Green (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 complete trial application if minimum success criteria for key feasibility aims/objectives are achieved:

- Target population recruited within a 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

End of trial definition

Participants will complete their involvement in the trial after 90 ± 7 days post-surgery at the follow-up telephone assessment. The trial will end on completion of all data collection.

Data management and confidentiality

Data are collected and stored per the Data Protection legislation, including the UK Data Protection Act 2018 and the General Data Protection Regulation 2018. Participants are allocated unique study numbers and are identified in all study-related documentation by their study number and initials only.

A suite of web-based applications developed by PenCTU is used to record participant data and manage the trial. This consists of a bespoke, cloud-based system for screening, randomisation, and participant management, which is integrated with REDCap Cloud, an electronic data capture system used to capture electronic case report form (eCRF) data.

Data quality and completeness

PenCTU data management staff will monitor the completeness and quality of data recorded in eCRFs. It will correspond regularly with site PIs (or their delegated team member) to capture any missing data where possible and ensure continuous, high-quality data. Data quality and completeness checks will be defined by the data manager through consultation with the chief investigators (CIs), trial statisticians, trial manager, and other members of the Trial Management Group as required. Checks will be described in the Data Management Plan (available from PenCTU). Throughout the trial, the data manager will report the quality and completeness of accumulating data to the Trial Management Group.

Governance

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 are not directly involved in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The CIs and co-applicants designed the trial with support from the NIHR Research Design Service and the PenCTU. The PenCTU has been allocated tasks associated with overall trial and data management, including monitoring. The TMG will meet monthly to review trial progress and ensure appropriate trial management.

The TSC will meet every 6–7 months per an agreed set of terms of reference to review the trial's progress and any serious adverse events and will report to the sponsor. A Data Monitoring Committee was not convened as the study is low-risk, and only surgeons are blinded.

Ethics

Approvals

Approval has been obtained from the UK Health Research Authority (HRA) and West Midlands—The Black Country Research Ethics Committee (REC). The CIs 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 has its basis in the Declaration of Helsinki. Data will be collected and retained in accordance with the UK Data Protection Act 2018 and the General Data Protection Regulation (GDPR) 2016.

Patient involvement

VLCD has an excellent safety profile as opposed to the significant risks associated with liver surgery in patients with underlying fatty liver disease (FLD). The evidence-based intervention has been developed involving patients from the start who had either been patients on the liver surgery pathway or have had experience of a VLCD due to requiring bariatric surgery. Their advice included the VLCD instructions, supplements used, required support, PIS and consent processes, and the design of the study processes and data collection.

The group led by the PPI lead will continue to meet and advise on the study design and review patient-facing documents as required. 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.

Discussion

The RESOLVE study is a multi-centre feasibility randomised controlled trial of a very low-calorie diet (VLCD) versus treatment as usual (TAU) in patients with underlying hepatic steatosis (HS) undergoing liver surgery (LS). This feasibility study will provide data on the acceptability and feasibility of a dietary intervention for patients with HS having LS.

A VLCD could prove to be a low-cost and effective treatment for reducing HS before liver resection surgery. The literature base has demonstrated poorer outcomes in patients with HS in terms of intra-operative complications, mainly in the form of blood loss and reduced survival parameters. The intervention has been developed based on scientific evidence within published literature and is safe and effective. However, the safety within a specific cohort of cancer surgery patients has a limited research base. Therefore, this study has placed strict inclusion/exclusion criteria regarding pre-operative nutritional status.

The findings of this feasibility study will inform the design of a future definitive study to test the effectiveness and cost-effectiveness of the intervention. Feedback from the study sites will be utilised to improve the study processes. In addition, the qualitative feedback obtained from participants will be paramount in ascertaining the intervention's challenges. The feasibility trial will inform the design and delivery of a definitive trial and provide any signals of efficacy. The definitive trial will be processed if the progression criteria are met according to the 'stop–go' green-amber-red criteria.

Abbreviations

BMI	Body mass index
CI	Chief investigator
CTU	Clinical Trials Unit
eCRF	Electronic case report form
HRA	Health Research Authority
HS	Hepatic steatosis
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
LCD	Low-calorie diet
LS	Liver surgery
MRI	Magnetic resonance imaging
PenCTU	Peninsula Clinical Trials Unit
PDFF	Proton density fat fraction
PI	Principal investigator
PPI	Patient and public involvement
PIS	Participant information sheet
RCT	Randomised controlled trial
REC	Research Ethics Committee
T2DM	Type 2 diabetes mellitus
TAU	Treatment as usual
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
VLCD	Very low-calorie diet

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40814-024-01544-x.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions

HN developed and prepared the protocol and manuscript. VL, LS, and JC have provided all the statistical expertise. MB and PA have developed the study software. TP has provided dietary and qualitative expertise. AK supported the development of the protocol. SA is the chief investigator who conceived the work. All authors have contributed to the writing of the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Approval has been obtained from the UK Health Research Authority (HRA) and West Midlands—The Black Country Research Ethics Committee (REC). All patients have provided informed consent to participate in the study.

Consent for publication

Not applicable. There is no patient data or identifiers in this publication therefore consent is not required.

Competing interests

The authors declare they have no competing interests.

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