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The effects of a 2-week very low-calorie liquid diet prior to liver surgery for patients with fatty liver

Submission date
08/03/2023

Recruitment status
No longer recruiting

Registration date
20/03/2023

Overall study status
Completed

Last Edited
23/01/2026

Condition category
Surgery

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Fatty liver (steatosis) occurs when too much fat builds up in liver cells. Although it is normal to have a tiny amount of fat in these cells, the liver is considered fatty if more than 5% of it is fat. Patients with tumours that have spread to the liver may have part of their liver removed in an operation. Having a fatty liver can lead to more difficulties when operating and may lead to more complications, particularly bleeding during the operation. This can impact a patient's recovery after surgery and may cause long-term problems. The aim of this study is to determine if a very low-calorie diet (VLCD) for 2 weeks before surgery is tolerated and acceptable to patients in several hospitals in the UK. A planned larger future study will test whether the diet is effective in reducing the complications of surgery.

Who can participate?
Patients aged 18 years and over who are scheduled to have liver surgery and have been found to have a fatty liver on an MRI scan

What does the study involve?
Participants will be randomly allocated (like the toss of a coin) to a VCLD for 2 weeks before the operation, or to usual treatment. VCLD has been used successfully for many years before for gallbladder and weight loss surgery. Participants will have four sachets per day of commercially available liquid meal replacements and be able to eat vegetables and drink sugar-free drinks. They will complete a food diary to evaluate adherence and mood, supervised by a qualified dietitian. All participants will complete quality-of-life measures before surgery and 1 and 3 months after. Some will participate in focus groups to discuss their involvement (optional).

What are the possible benefits and risks of participating?
The researchers are unable to guarantee direct benefits for taking part in the study. It is possible that during the time on the VLCD some patients may experience lower energy levels, feelings of hunger and irritability/low mood.

Where is the study run from?
University Hospitals Plymouth NHS Trust and the Peninsula Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
November 2022 to December 2024

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
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Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
323252

ClinicalTrials.gov (NCT)
Nil known

Central Portfolio Management System (CPMS)
55454

Study information

Scientific Title
A feasibility multi-centre randomised controlled trial to test if a pre-operative 2-week very low-calorie diet reduces intra-operative blood loss and improves postoperative outcomes following liver surgery, compared with a control group: Reducing Steatosis prior to Liver Resection (RESOLVE)

Acronym
RESOLVE

Study objectives
Patients with hepatic steatosis who undergo a very low-calorie diet plus education and support will have better patient and surgical outcomes during and after liver surgery than those who do not.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/03/2023, West Midlands - Black Country Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8010; blackcountry.rec@hra.nhs.uk)

Study design

Randomized; Interventional; Design type: Treatment, Dietary, Imaging, Psychological & Behavioural, Management of Care, Surgery

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Liver surgery

Interventions
In the future definitive trial, the primary research question will be: In patients with a diagnosis of hepatic steatosis (fatty liver) who are having elective liver surgery, does VLCD with dietitian education and support compared to Treatment as Usual at each site 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 postoperative complication rates, readmission rate within 90 days, and 90-day mortality.

At this point, the researchers 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.

Identification of potential participants:
All patients requiring elective Liver Surgery have an MRI. The clinical teams meet weekly at the Multi-Disciplinary Team meeting and will identify the patients that are eligible for the study.

Approach:
All patients have a face-to-face meeting with their surgeon to discuss the surgery. At this meeting, the study will be discussed with eligible patients. If they are interested then they will be provided with a Patient Information Sheet to read. This will be emailed or posted if the meeting is virtual. The patient will be asked by their surgeon if they are willing to be contacted by a member of the research team to discuss this further. If patients have further questions after speaking with the research team they will be able to speak with a member of their surgical team again prior to providing consent.

Consent:
Patients will be given at least 24 hours to consider the PIS before being contacted by a member of the RESOLVE research team (only if the patient has given permission for direct contact). The researcher will review eligibility criteria with the patient and explain the study in further detail, addressing any queries raised by the patient. If the patient has questions better responded to by a clinician they will be put in contact with their clinical team before they are consented. If the patient is willing to participate, informed consent will be taken either during the course of the telephone call or rescheduled for a further call if preferred. Researchers will follow a Work Instruction to guide them.

Baseline assessments:
After consent 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. For most patients this is a routine appointment. At this appointment the baseline physical assessments will be taken:
1. Weight
2. Height
3. Hand grip strength
Participants will also be asked to complete the Health-related Quality of Life questionnaire measure. Demographic and co-morbidity information will also be collected by the dietitian or Healthcare Professional at the appointment.

Randomisation:
Randomisation to either group will be conducted once all the above data is collected. Participants will be allocated to either:

Treatment as Usual:
Participants will receive the usual care provided at their organisation.

Receiving VLCD:
Participants will receive the VLCD Intervention at this appointment. The dietitian or trained Healthcare professional will provide motivational instructions, a diet information booklet and liquid meal replacement sachets (enough for two weeks). This will take approximately 20 to 30 minutes to deliver.

Intervention period:
Two weeks prior to surgery, participants in the VLCD start their liquid diet following the written instructions. During the diet they will be asked to complete a daily food and mood diary (online tick boxes). They will be sent a daily reminder to help them. If they prefer this can be a paper and pencil diary.

Two days after starting the diet, the dietitian or Healthcare professional responsible will call at a pre-arranged time to make sure that the participant is coping with the diet and to answer any questions they may have.

If the surgery is postponed, participants may remain on the diet for a further two weeks at the most before recommencing a normal diet. However, data collection will continue if they are satisfied to remain in the study. In this case, a further phone call will be made by the dietitian or Healthcare professional.

Day of Surgery:
On the day of surgery, the physical measurements will be repeated:
1. Weight
2. Hand grip strength
They will be asked to repeat the health-related quality of life measure.

Clinical measurements will be taken from the notes.

Surgical outcomes:
All surgical outcomes and assessments will be taken from the notes post-surgery, day of discharge and at 30 and 90 days.

30- and 90-day follow-up:
Participants in both groups will be telephoned at 30 and 90 days to complete measures:

1. Health-related quality of life
2. Health resource use questionnaire
These phone calls should take 5 to 10 minutes at most.

Qualitative research:
Participants who consented to be contacted for the qualitative component of the study will be contacted a couple of weeks after surgery and a more detailed PIS will be provided. 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.

The 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.

PPI Involvement:
Patients have informed during the protocol development on all aspects of the above in terms of consent, timings of any interventions, outcome measures and follow-ups.

Evaluation of VLCD from a Dietitian/Healthcare Professional perspective:
An objective of the study is to evaluate the intervention. Those responsible for delivering it will be invited to take part in a focus group at the end of the intervention period to discuss their experience. This will take approximately 1 hour. Those taking part will follow a consent process.

Fidelity of the intervention:
Consent will be sought from those delivering the VCLD intervention at each site to allow the audio recording of their initial appointment, and once after several participants and one near the end of recruitment. Patient participants will also be informed of potential audio recordings and consent obtained.

Intervention Type
Behavioural

Primary outcome(s)
The feasibility of a future definitive trial, assessed using:
1. Rates of screening at MDT meeting, recruitment at consent, and randomisation numbers (as a proportion of patients screened) at randomisation
2. Retention measured as the number of patients completing measures on the day of surgery and the number of patients completing the food diary over the period of VLCD
3. Adherence to VLCD and study requirements prior to liver surgery and any possible contamination assessed by measuring changes in body weight, food diary reports and numbers of empty sachets returned pre-operatively. In addition, qualitative interviews and focus groups will explore further at 1-month post-surgery
4. Completeness of data collection measured at baseline, day of surgery plus 30- and 90-days postoperatively
5. Preliminary assessment of the VLCD intervention by audio recording some of the intervention sessions at the start of the recruitment period, halfway through and nearer the end. Also feedback is obtained from qualitative interviews with staff delivering the intervention post-recruitment.
6. Resource use and costs associated with the delivery of the intervention, and pilot methods for the cost-effectiveness framework in a full trial using the EuroQoL 5-Dimension 5 level (EQ-5D-

5L) at baseline, day of surgery, 30 and 90 days postoperatively and a bespoke Resource Use Questionnaire at 30 and 90 days postoperatively
7. Identify if there is a need to modify the VLCD and its delivery within the NHS and if so, methods for improvement including exploring barriers and facilitators to delivering the intervention in focus groups with staff post recruitment and qualitative work with the participants post-surgery
8. Identify the most clinically relevant primary outcome for the definitive trial: operating time, ease of liver surgery, blood loss, blood transfusion requirement, time to functional recovery, Comprehensive Complications Index (CCI), overall Clavien-Dindo grade I-V postoperative complications, length of stay and patient-reported outcomes, which will be collected in the form of a questionnaire post-operatively.

The researchers shall progress to a full trial application if minimum success criteria for key feasibility aims/objectives are achieved:
1. Target population recruited within the 12-month recruitment window (<60% stop, 60-80% discuss and modify, >80% go)
2. In participants randomized to the intervention group, adherence with diet (<50% stop, 50-70% discuss and modify, >70% go)
3. Completion of key outcome measures (including 3-month follow-up) (<60% stop, 60-80% discuss and modify, >80% go)
4. Evidence to suggest efficacy, i.e., that the VLCD holds promise as an effective intervention (demonstrated by an 80% confidence interval that indicates plausibility of the between-group difference) at 3 months follow-up
5. Collection of data required to conduct cost-effectiveness analysis alongside a future full trial

Key secondary outcome(s))

The outcome measures that will be evaluated within this feasibility study are as follows:
1. Surgical outcomes:
1.1. Intra-operative blood loss, blood transfusion requirements, duration of surgery (in minutes), and ease of liver surgery measured using a subjective measure of 1 to 5 peri-operatively
1.2. Intra-operative complications assessed using Clavien-Dindo grade III (bleeding, injury to surrounding structures, cardiovascular events, cerebrovascular events, anaesthetic-related complications)
1.3. Length of stay (in days), postoperative complications (CCI score), readmission rate and mortality within 30 and 90 days, overall, in-hospital blood transfusion requirements measured in units postoperatively
2. Time to functional recovery measured using the number of days between surgery and the date of proposed discharge

Patient-reported and other clinical outcomes will be measured:
1. Total energy and protein intake measured by self-report in diary (number of sachets per day + any additional food/fluids consumed) over the 2-week preoperative period
2. Weight and hand grip strength measured using a hand grip dynamometer pre and post diet
3. Mood assessed using a self-report four-point scale in the diary daily over the 2-week diet period
4. Side effects of VCLD assessed using self-report to the research team at any point during the diet
5. Health-related quality of life measured using the EuroQoL 5-Dimension 5 level (EQ-5D-5L) at baseline, day of surgery, 30 and 90 days postoperatively
6. Use of health, social care and wider societal resources measured using a bespoke Resource Use Questionnaire at 30 and 90 days postoperatively

Completion date
31/12/2024

Eligibility

Key inclusion criteria
1. Adult patients ≥18 years
2. Able to provide informed consent
3. Patients with hepatic steatosis (fatty liver) with or without non-alcohol steatohepatitis (NASH) requiring liver resection
4. Patients selected for liver resection surgery for treatment of metastases, hepatocellular carcinoma, gallbladder cancer, peripheral cholangiocarcinoma, or pre-malignant hepatic tumours

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
29

Key exclusion criteria
1. Patients with normal background liver on pre-op MRI
2. Patients with cirrhosis with or without signs of portal hypertension
3. Pregnant women
4. Patients that cannot tolerate low fat diet or are allergic or intolerant to components of VLCD sachets
5. Patients who are unable to complete a food diary
6. Patients who are underweight (BMI <20 kg/m²)
7. Patients who are lactose intolerant
8. Patients who follow a vegan diet
9. Patients who report unintentional weight loss of >5% in 0-3 months or >10% in up to 6 months

Date of first enrolment
17/04/2023

Date of final enrolment

30/09/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Aintree University Hospital
Lower Ln
Fazakerley
Liverpool
England
L9 7AL

Study participating centre
Derriford Hospital
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Plymouth
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PL6 8DH

Study participating centre
Southampton General Hospital
Tremona Road
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SO16 6YD

Study participating centre
Royal Surrey County Hospital NHS Foundation Trust
Egerton Road
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GU2 7XX

Sponsor information

Organisation
University Hospitals Plymouth NHS Trust

ROR
https://ror.org/05x3jck08

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: NIHR203632

Results and Publications

Individual participant data (IPD) sharing plan
For access to the data send a request to Matthew Bailey (matthew.bailey@plymouth.ac.uk), Victoria Allgar (victoria.allgar@plymouth.ac.uk) and PenCTU data (penctudata@plymouth.ac.uk).

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 study 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.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		30/09/2024	02/10/2024	Yes	No
Basic results		23/01/2025	23/01/2026	No	No
Protocol file	version 1.5 version 1.0	17/06/2024	20/06/2024	No	No

Statistical Analysis Plan	14/08/2023	20/06/2024	No	No