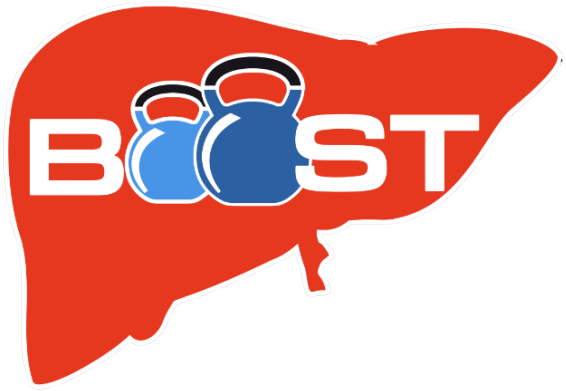
β -hydroxy-β-methylbutyrate (HMB) supplementation to improve functional status in people with advanced liver cirrhosis: a phase IV multicentre double-blind placebo-controlled randomised trial with embedded qualitative study: BOOST



PROTOCOL

Version 3.1, 06 MAY 2026

IRAS ID: 1010060

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Funder's reference: NIHR206170

Sponsor: University Hospitals Plymouth NHS Trust

Sponsor Protocol Number: 23HEP856

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 will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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; and that 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: 

Date: 13th May 2026

Name (please print): Dr Corinna Mossop

Position: Research and Development Operations Director

Chief Investigator:

Date: 06 MAY 2026

Signature:

Name: (please print): Prof Ashwin Dhanda

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Signature:

Date: 06 MAY 2026

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	Independent members: Dr Muhammad Riaz (Research Fellow in Statistics, Cardiff University). riazm3@cardiff.ac.uk Dr Richard Parker (Consultant Hepatologist, Leeds Teaching Hospital NHS Trust). richardparker@nhs.net Jenny Towey (Specialist Dietitian, University Hospitals Birmingham). jennifer.towey@uhb.nhs.net Russell Spiller (Independent PPI representative) Simon Remington (Independent PPI representative)
Data Monitoring Committee	Chair: Dr Vishal Patel (Consultant Hepatologist, King's College Hospital NHS Foundation Trust. vishal.patel@researchinliver.org.uk Independent members: Prof Michael Dewey (Emeritus Professor of Statistical Epidemiology, King's College London). michael.dewey@kcl.ac.uk Dr David Vauzour (Associate Prof in Molecular Nutrition, University of East Anglia). d.vauzour@uea.ac.uk

i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BMI	Body Mass Index
CA	Competent Authority
CI	Chief Investigator
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case Report Form
CT	Computed Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DIBD	Developmental International Birth Date
DMC	Data Monitoring Committee
DMP	Data management Plan
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HMB	β -hydroxy β-methylbutyrate
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INR	Internation Normalised Ratio

IRAS	Integrated research Application System
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
LFI	Liver Frailty Index
LBP	Lipopolysaccharide-binding protein
LPS	Lipopolysaccharide
MA	Marketing Authorisation
MAR	Missing at random
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-stage Liver Disease
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MS	Member State
NCI	National Cancer Institute
NHS R&D	National Health Service Research & Development
NIHR	National institute for Health and Care Research
NIMP	Non-Investigational Medicinal Product
PAG	Patient Advisory Group
PenCTU	Peninsula Clinical Trials Unit
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RfPB	Research for Patient Benefit
RSI	Reference Safety Information

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCFA	Short Chain Fatty Acids
SD	Standard Deviation
SDV	Source Data Verification
SF-36	Short Form 36
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UHPNT	University Hospitals Plymouth NHS Trust
UOP	University of Plymouth
USM	Urgent Safety Measure
WEMWBS	Warwick-Edinburgh Mental Wellbeing Score

iii. TRIAL SUMMARY

Trial Title	**β**-hydroxy-β-methylbutyrate (HMB) supplementation to impr**o**ve functi**o**nal **st**atus in people with advanced liver cirrhosis: a phase IV multicentre double-blind placebo-controlled randomised trial with embedded qualitative study: BOOST.	
Short title	A randomised controlled trial of a nutritional supplement (HM**B**) compared to placeb**o** (maltodextrin) to impr**o**ve muscle **st**rength and function in people with advanced liver cirrhosis: BOOST	
Lay title	HM**B** to impr**o**ve functi**o**nal **st**atus in people with liver cirrhosis - BOOST	
Trial acronym	BOOST	
Clinical Phase	IV	
Trial Design	Multicentre two-arm, individually randomised, double-blind placebo-controlled superiority trial of β -hydroxy β-methylbutyrate (intervention) versus maltodextrin (comparator), with qualitative study and internal pilot.	
Trial Participants	Adults with advanced cirrhosis diagnosed by clinical, radiological or histological features or by fibrosis assessment.	
Planned Sample Size	124 (1:1 randomisation to HMB 3 g daily or matched placebo)	
Treatment duration	12 weeks	
Follow up duration	Week 24 (12 weeks after treatment ends)	
Planned Trial Period	12-month set-up period 12-month recruitment period (internal pilot phase comprises first 4 months) 6-month follow-up period	
	Objectives	**Outcome Measures**
Primary	Determine the clinical effectiveness of HMB supplementation to improve physical function as measured by the Liver Frailty Index (LFI).	Measured by change in LFI at 12-weeks post-baseline
Secondary	1. Determine the effect of HMB supplementation on:	
	i. LFI category ii. Quality of Life and mental wellbeing	i. LFI categories: 'Frail', 'Pre-frail', 'Robust' ii. Short Form-36 questionnaire,

	iii. Liver disease severity iv. Rate of hospitalisation v. Rate of infections vi. Cognitive function vii. Serum Short Chain Fatty Acid (SCFA) concentrations viii. Markers of gut permeability ix. Muscle mass	Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) iii. Child Pugh and MELD scores iv. Number, duration and diagnosis of any hospital admissions v. Infections (self-reported and by primary/secondary care records) vi. Hepatic encephalopathy (by Animal Naming Test) vii. Blood test to measure serum SCFA concentrations viii. Blood test to measure Lipopolysaccharide (LPS), Lipopolysaccharide-binding protein (LBP) and D-lactate concentrations ix. Calf circumference, corrected for BMI and oedema
	2. Evaluate participant engagement with: i. trial procedures ii. adherence to the intervention	i. Attendance to and completion of final study visit (week 24) ii. Pill count and self-report of medication adherence
	3. Assess for contamination	HMB supplement use
	4. Safety of intervention	Adverse Reactions and Serious Adverse Events

	5. Monitor changes in macronutrient intake	24-hour dietary recall (Intake24 tool)
Investigational Medicinal Product(s)	β-hydroxy-β-methylbutyrate (HMB)	
Formulation, Dose, Route of Administration	3 g HMB taken daily for 12-weeks. Administered orally (2 x 750 mg capsules twice daily).	

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) Programme **Email:** manager@ccfrms.org.uk	Total research costs: £508,403.00

v. ROLE OF FUNDER, TRIAL SPONSOR AND COORDINATING CLINICAL TRIALS UNIT

This study is funded by the National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) Programme.

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

The Sponsor for this study, University Hospitals Plymouth NHS Trust, assumes overall responsibility for the initiation and management of the study in accordance with the current UK policy for conduct of health and social care research. The Sponsor has allocated tasks associated with overall trial management and data management to the Peninsula Clinical Trials Unit (PenCTU) at the University of Plymouth (UoP). A detailed breakdown of tasks undertaken by PenCTU on behalf of the CI and Sponsor is described in a formal written Sponsor agreement including a full task allocation matrix. Briefly, the Sponsor's main duties include review of the research protocol and other essential trial documents, authorisation of applications for regulatory review, contracting external parties, review of protocol deviations, permitting/performing audits and management of data sharing requests. As such the Sponsor retains the final decision regarding trial design, conduct, data analysis and interpretation, manuscript writing or dissemination of the results, other than those requirements stipulated in the agreement between the funder and UoP.

The trial was designed by the Chief Investigator, co-applicants and the Peninsula Clinical Trials Unit.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS

The Trial Management Group (TMG) is chaired by the Chief Investigator and includes representation from the Sponsor, co-applicants, statistics team, PenCTU and patient representatives. 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.

Trial oversight will be provided by an independent Data Monitoring Committee (DMC) and a Trial Steering Committee (TSC).

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 (Dr Louise China), independent experts (Dr Richard Parker and Jenny Towey), PPI representatives (Russell Spiller and Simon Remington) and an independent statistician (Dr Muhammad Riaz). The TSC will meet at least annually in accordance with an agreed set of terms of reference, to review the progress of the trial and will report to the Sponsor and Funder.

DMC meetings will be scheduled to precede TSC meetings so that DMC recommendations can be considered by the TSC as appropriate. The DMC has an independent Chair (Dr Vishal Patel), independent statistician (Prof Michael Dewey) and independent experts (Dr David Vauzour). The DMC will meet every 6 months/at least yearly in accordance with an agreed set of terms of reference, detailed in the DMC Charter, to monitor study data and make recommendations to the TSC regarding any ethical or safety issues.

The roles, constitution, and composition of the two committees is in accordance with NIHR Research Governance Guidelines and will be described in committee-specific charters produced by the CTU. Independence of committee members will be as defined in the NIHR Research Governance Guidelines.

vii. KEY WORDS

Liver cirrhosis; β -hydroxy-β-methylbutyrate; liver frailty index

viii. Protocol contributors

Several contributors have been involved in the development of this protocol; these include the CI (Prof Ashwin Dhanda), trial statisticians (Prof Victoria Allgar, Dr Joanne Hosking, Dr Crispin Musicha), Co-applicants (Dr Lynne Callaghan, Prof Phillip Calder, Prof Mary Hickson, Dr Paula Murphy, Prof Mark Thursz, Ms Lesley Manning), as well as members of the PenCTU trial management (see key trial contacts for full staff list) and data management teams (Dr Paigan Aspinall, Mr Mark Warner).

ix. TRIAL FLOW CHARTS

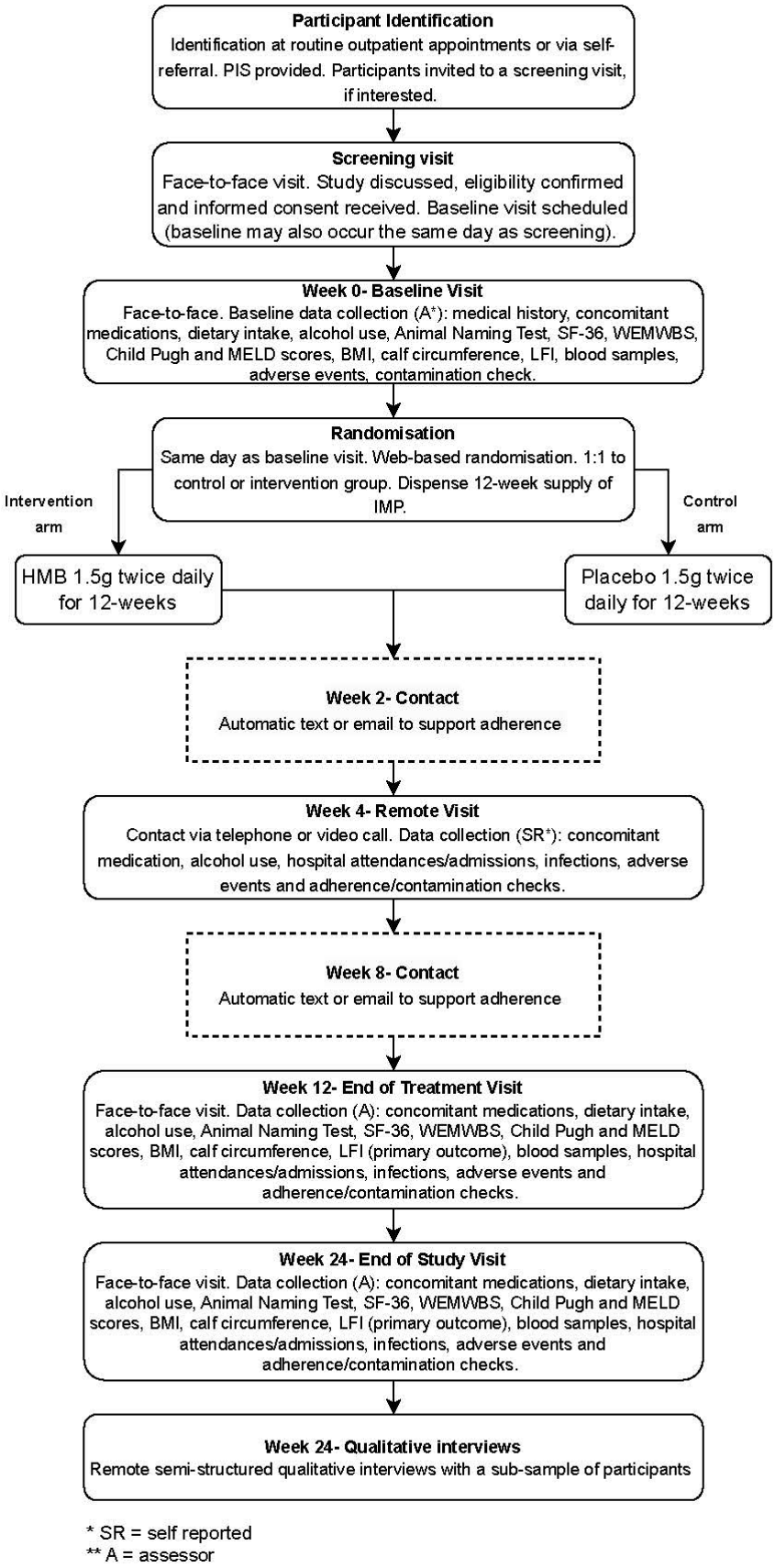

Figure 1a. Detailed participant flow chart

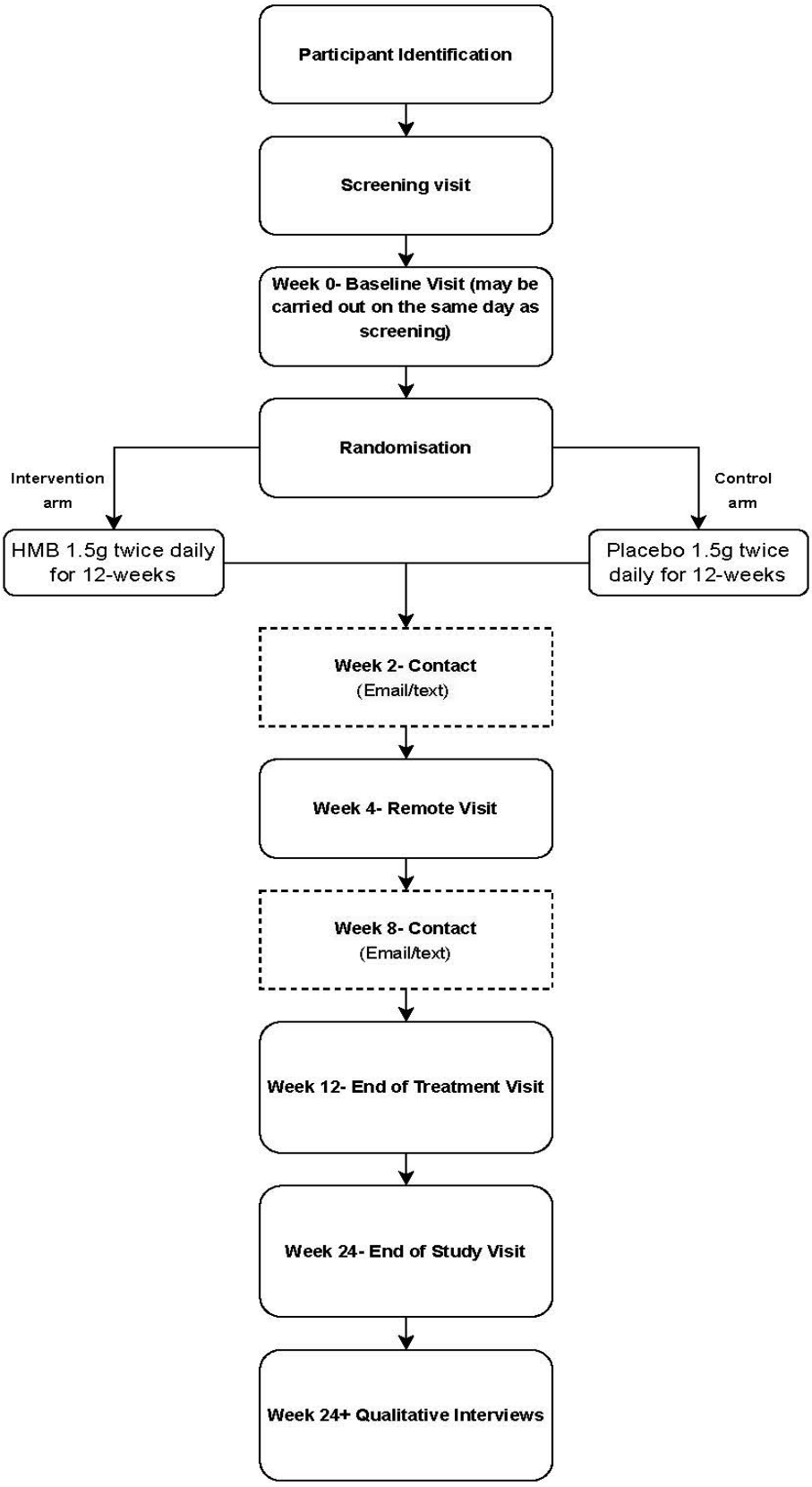

Figure 1b. Simplified participant flow chart

1. BACKGROUND AND RATIONALE

1.1. Problem Addressed

This project aims to address the lack of treatment options for people with liver cirrhosis by testing the clinical effectiveness of the nutritional intervention, beta-hydroxy beta-methylbutyrate (HMB).

Cirrhosis is the third leading cause of premature death in England[1], the fourth in Europe[2] and results in over 1.3 million deaths globally per year[3,4]. Over 100 million people have cirrhosis; 10 million of these suffer from advanced disease[5]. In England, people with cirrhosis had over 75,000 unplanned hospital admissions in 2020/21 mainly due to complications of cirrhosis (advanced cirrhosis), which has been increasing steadily every year for more than two decades[6].

Cirrhosis is estimated to cost the NHS £17 billion annually, largely due to hospital attendances and admissions[7].In patients with advanced cirrhosis, the estimated mean cost of the last year of life was £21,113 mostly due to multiple unplanned hospital admissions[8].

People with cirrhosis report reduced health-related quality of life (QoL) compared to healthy controls and caregivers. Those with advanced cirrhosis report significantly worse QoL in domains of pain, sleep, fatigue, and social and physical function[9,10]. Poor nutritional status is the strongest predictor of lower perceived QoL[11].

Cirrhosis is scarring of the liver, most frequently caused by harmful alcohol use and fatty liver (due to obesity and metabolic risk factors) in the UK[12]. Irrespective of the aetiology, once established, cirrhosis is rarely reversible even when the underlying cause has been removed e.g. through alcohol cessation. In many, cirrhosis progresses to more advanced disease. Scarring disrupts blood flow through the liver, increasing blood pressure within the portal circulation (portal hypertension), resulting in abdominal fluid (ascites), large veins in the stomach and gullet at risk of bleeding (gastro-oesophageal varices) and disordered mental function (hepatic encephalopathy). Ongoing damage is mainly driven by impaired gut barrier function[13-17]. Microbes and their components enter the portal circulation, which drains directly into the liver, causing inflammation and scar formation. International clinical guidelines and position papers recommend targeting the impaired gut barrier as a novel therapeutic strategy for advanced cirrhosis[18,19].

There are no effective therapies targeting inflammatory processes or scar formation within the liver with many negative clinical trials[20,21]. Only obeticholic acid has been approved for primary biliary cholangitis, an uncommon cause of liver disease[22]. It is not licenced for use in advanced cirrhosis or for other causes of liver disease. Furthermore, the drug development pipeline is restricted to pre-cirrhotic and early cirrhotic fatty liver disease[23]. There is some evidence that non-selective beta-blockers, currently indicated to reduce the risk of bleeding from varices, may reduce the risk of decompensation or mortality in people with early cirrhosis[24]. Rifaximin, a non-absorbable antibiotic, indicated for treatment of hepatic encephalopathy, may also modulate the gut microbiome with possible long-term benefits in people with advanced cirrhosis[25]. However, both these therapies have well-documented side effects and require large prospective randomised trials to confirm their clinical effectiveness; furthermore, rifaximin is expensive. A search of clinicaltrials.gov found no trials of beta blockers and only one active trial of rifaximin

(NCT05863364) in the patient population with advanced cirrhosis. We therefore need to test alternative cost-effective strategies to treat people with advanced cirrhosis.

1.2. Research Importance

People with cirrhosis have a poor QoL and high levels of health service utilisation. As well as being identified as a high priority research area, this project is important both for people with cirrhosis and healthcare services. Firstly, the primary objective of the trial is to test whether HMB improves patients' physical function, which will have impact on perceived QoL and may improve clinical outcomes such as liver disease severity and number of hospital admissions. Secondly, we will evaluate the effect of the intervention on health related QoL and mental wellbeing.

New treatment strategies to reduce mortality and morbidity and to increase QoL in this patient cohort are urgently needed[19,26]. Patients, caregivers and healthcare professionals have identified as a high priority the need for new interventions (including dietary) in priority setting partnerships in alcohol-related liver disease[27] and other liver diseases[28]. Recent guidelines from the European Association for the Study of the Liver identify a need for interventions to delay cirrhosis progression[19]. Furthermore, the importance of our study has been confirmed by our PPIE group of people with lived experience of advanced cirrhosis.

In light of several large but negative pharmacological trials in advanced cirrhosis[29,30] and the absence of effective drugs targeting cirrhosis, the importance of nutritional interventions is increasingly being recognised and international guidelines recommend further study in this field[31]. However, there is a lack of well-designed nutritional intervention trials in patients with cirrhosis; no active trials of nutritional intervention to treat cirrhosis are registered on clinicaltrials.gov, the EU Clinical Trials Register or ISRCTN.

The chosen intervention (HMB) is cheap and readily available online or from health food shops. Should the trial demonstrate clinical effectiveness, there are unlikely to be barriers to wide adoption due to cost, availability or acceptability.

1.3. Review of Existing Evidence

There is established evidence that gut barrier dysfunction drives cirrhosis[24] and worsens as cirrhosis progresses[32,33]. People with cirrhosis develop gut barrier dysfunction due to changes in gut flora (microbiome). As cirrhosis progresses, the gut microbiome becomes less diverse and there are changes in relative abundance of bacterial species with overexpression of pathogenic species and under-expression of beneficial species (dysbiosis)[34]. Specifically, there is loss of bacteria capable of fermenting non-digestible dietary carbohydrates to produce short chain fatty acids (SCFAs)[15]. SCFAs, a critical energy source for cells lining the gut, are integral to gut barrier health and function[35].

Increasing the gut concentration of SCFAs reduces gut inflammation and permeability[36], which may break the cycle of liver inflammation and fibrosis. People with advanced cirrhosis, who have the highest degree of gut dysbiosis and barrier dysfunction, have the most to gain from therapies targeting the gut-liver axis[7]. However, few studies targeting gut SCFA levels have been conducted in the context of liver disease. Our systematic review identified only 17 studies (with only two in humans) investigating the effect of increasing SCFA on gut permeability and liver injury[37]. All studies demonstrated a significant reduction in liver injury and 14 reported improved

gut barrier function. However, studies were of low quality and heterogeneous in design. We need a well-designed study in people with liver disease to test the clinical effectiveness of an intervention that increases gut SCFA concentration.

One candidate therapy is a compound related to the SCFA butyrate, β-hydroxy β-methylbutyrate (HMB)[38]. HMB is a metabolite of the branched-chain amino acid, leucine, which plays an important role in muscle protein turnover[39]. It has well established benefits in improving muscle function and strength in patients with muscle wasting in a range of chronic illnesses[40,41].

HMB supplementation also increases SCFA-producing bacteria[42]. In a pig model of inflammation, HMB supplementation improved the gut microbiome reducing dysbiosis, restored gut barrier function and increased SCFA concentration[43]. Therefore, HMB supplementation in patients with cirrhosis may increase SCFAs, thus reducing gut permeability and liver damage.

To date, three pilot trials of HMB treatment of people with liver disease have been conducted (table 1)[44-46]. HMB supplementation was associated with improved muscle mass and strength compared to controls after liver transplantation (in the context of post-operative recovery, not cirrhosis)[44]. In 24 people with early cirrhosis, HMB resulted in increased muscle function and mass[45]. There was also a significant improvement in the Liver Frailty Index® (LFI), a validated tool to measure physical function in people with cirrhosis[47]. In a third RCT, 43 people with early-moderate cirrhosis either received an oral nutritional supplement containing HMB (also containing vitamin D, calcium and fibre) or one that did not contain HMB, vitamin D, calcium or fibre[46]. The intervention group had increased fat mass index and a trend to improved muscle strength, but it is not possible to conclude whether HMB or another constituent of the supplement was responsible for the observed effects. There were no serious adverse events related to HMB in any of these trials and the intervention was well tolerated with only four discontinuations due to gastrointestinal side-effects in the latter study[46].

These trials assessed the benefit of HMB on muscle strength and function and demonstrated that it is well tolerated in people with liver disease. None were conducted in people actively consuming harmful levels of alcohol or in those with advanced cirrhosis and none evaluated patient-reported outcomes. There is a need to test the clinical effectiveness of HMB supplementation on physical function, QoL and liver-related outcomes in people with advanced cirrhosis. The use of a comparator (placebo) in this randomised trial will provide high quality evidence of the clinical effectiveness of HMB; Maltodextrin is a generally inert substance frequently used as placebo in trials of prebiotics. At high doses of maltodextrin changes in gut microbiome and permeability have been demonstrated[48] but this is highly unlikely at low doses as used in this trial. Prebiotics require a dose of more than 3 g to have an effect.[49]

Reference	Design	Population	Intervention	Comparison	Outcomes	Findings	Adverse events
Lattanzi, Nutrients 2019[44]	Placebo controlled RCT	Post-liver transplant (n=22)	1.5 g HMB powder dissolved in juice twice daily for 12 weeks	Placebo	Muscle mass and function at 6 months	HMB: increased muscle mass and strength	None
Lattanzi, Nutrients 2021[45]	Placebo controlled RCT	Early cirrhosis (n=24)	1.5 g HMB powder dissolved in water twice daily for 12 weeks	Placebo	Muscle mass and function; LFI; cognitive function at week 12	HMB: Increased muscle mass and strength; reduction in LFI	None
Espina, Nutrients 2022[46]	Double blind RCT	Early-moderate cirrhosis (n=43)	1.5 g HMB in an oral nutritional supplement twice daily for 12 weeks	Oral nutritional supplement without HMB twice daily	Muscle mass and function; MELD at week 12	Both: Improved MELD HMB: Increase fat mass index; trend to increased strength	2 deaths 4 early discont-inuations

Table 1: Comparison of the 3 randomised trials of HMB in people with liver disease.

1.4 Plain English Summary

Background Cirrhosis is liver scarring, caused mainly by alcohol or fatty liver in the UK. People with cirrhosis have poorer quality of life than healthy people. As cirrhosis worsens, they develop more symptoms and require hospital admissions. Cirrhosis causes over 75,000 hospital admissions and costs the NHS £17 billion annually. A leaky gut, due to breakdown of the gut lining, drives liver damage in cirrhosis. Changes in gut bacteria mean there are fewer bacteria that can break down fibre into short chain fatty acids (SCFAs).

SCFAs are important for the proper function of cells lining the gut. Without them the gut becomes leaky, letting parts of bacteria into the bloodstream leading directly to the liver. This triggers liver inflammation and scar formation. There are no treatments for liver scarring or the leaky gut.

Increasing gut SCFAs may be effective to treat cirrhosis by restoring the gut lining. HMB, a naturally occurring substance that is already available as a dietary supplement to increase muscle strength, also increases SCFA levels in the gut.

In small test trials, HMB was safe and had only minor side-effects in people with cirrhosis.

Aim To address the lack of treatment options for people with liver cirrhosis by testing whether HMB improves their physical function and quality of life.

Design and methods We will compare HMB, to dummy treatment (placebo) in 124 patients with cirrhosis from approximately eight NHS sites. Additional sites will be sought where required to achieve the total recruitment target. Patients will be randomly allocated to receive HMB or placebo twice daily for 12 weeks and followed up for another 12 weeks. At the start and during the trial we will measure the Liver Frailty Index, a combination of strength and function tests, and measures of liver disease, quality of life and mental wellbeing. We will consider the treatment effective if there is meaningful improvement in the Liver Frailty Index after 12 weeks of HMB

compared to placebo. We will also interview approximately 8 people who took HMB and 4 people who took placebo to learn about their experience of this as well as taking part in the trial.

If the trial shows HMB is effective, we will work with national societies and healthcare professionals to encourage the regular use of HMB in routine patient care without delay as it is cheap and widely available.

2. RISK ASSESSMENT AND MANAGEMENT

HMB is a nutritional supplement that is available to the public for purchase without prescription or restriction at health food shops or online vendors. It has been extensively evaluated in clinical trials in people with chronic disease and frailty. A systematic review assessing its impact on muscle mass and function identified five trials that reported adverse events[41]. One reported fewer gastrointestinal adverse events in those receiving HMB than placebo, and four reported similar numbers of adverse events between groups.

Three studies have tested HMB in people with liver disease[44-46]; two did not report any adverse events and one reported gastrointestinal side effects resulting in dropout in patients receiving HMB (numbers not reported clearly). There were no differences in serious adverse events, including deaths, between groups.

This trial is categorised as: Type A: No higher than the risk of standard medical care.

3. OBJECTIVES AND OUTCOME MEASURES

The aim of this study is to determine the clinical effectiveness of HMB supplementation to improve physical function as measured by the Liver Frailty Index® (LFI) in people with advanced liver cirrhosis.

3.1. Primary objective

To determine the effect of HMB supplementation on the LFI, the primary clinical research question of interest is: what is the mean difference in change in LFI from baseline to 12 weeks post-baseline in adults with advanced liver cirrhosis assigned to HMB supplementation compared to placebo (regardless of adherence to the intervention or discontinuation for any reason).

The primary estimand has the following attributes:

- **Population**: adults with advanced liver cirrhosis (as defined by trial inclusion/exclusion criteria)
- **Endpoint**: change in LFI between baseline and 12 weeks post baseline
- **Treatment condition**: HMB supplementation (1.5 g taken twice a day for 12 weeks) compared to placebo (1.5 g Maltodextrin taken twice a day)
- **Key intercurrent events**: non-adherence/discontinuation of treatment for any reason and independently accessing HMB supplementation – addressed in the treatment condition and handled with the treatment policy strategy
- **Population-level summary**: difference in mean LFI change from baseline to 12 weeks post-baseline between treatment conditions

Rationale for estimand: to estimate the effectiveness of HMB supplementation compared to placebo as would be observed in routine practice.

3.2. Secondary objective

- To determine the effect of HMB supplementation from baseline to week 24 on:
    - Liver disease severity measured by model for end-stage liver disease (MELD) score and Child Pugh score
    - Quality of life and mental wellbeing measured by Short Form-36 (SF-36) and Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)
    - Rate of hospitalisation
    - Rate of infections
    - Cognitive function, measured by the Animal Naming Test
    - Serum SCFA concentrations
    - Markers of gut permeability (LPS, LBP and D-lactate)
    - Muscle mass measured by calf muscle circumference
- To evaluate participant engagement with trial procedures and adherence to the intervention
- To assess for contamination, measured by HMB supplement use
- To assess safety of intervention
- To monitor changes in macronutrient intake via 24-hour dietary recall (Intake24)

3.3. Primary outcome measure

The LFI is a validated and reproducible measure of physical function in patients with advanced cirrhosis[47,50]. It combines measurements of muscle strength (hand grip strength) with function (sit to stands and balance assessment). In over 1,000 patients with advanced cirrhosis the median (interquartile range) of the LFI was 3.9 (3.5-4.5)[51]. Previous studies have suggested a change of 0.2 and 0.5 to define moderate and substantial clinically important differences in the LFI, respectively[52,53]. Small changes in each physical function measure are significantly associated with mortality while on the liver transplant waiting list[54]. An improvement of LFI by 0.2 is also associated with an improvement in QoL score[52]. The LFI is an excellent predictor of clinical outcomes in people with advanced cirrhosis and is associated with stage of disease, mortality, hospitalisation and QoL[51,55-57]. It is a stronger predictor of mortality than either subjective clinical opinion[47] or the MELD score[46]. Patients with improved frailty measured by LFI had better outcomes than those with stable or worsening LFI score[51].

Choice of primary outcome measure was discussed with the PPIE group of people with lived experience of cirrhosis. Members of the group were familiar with the measure, as they had experienced it personally as part of their clinical care. From experience, they found the LFI measurement and classification as frail, pre-frail or robust, useful to measure changes in their health. They described the measure as simple for participants to complete. The PPIE group confirmed that for them a small improvement in LFI of even 0.2 would be important and that our chosen clinically relevant minimally important difference of 0.4 was meaningful.

3.4. Secondary outcome measures

- Quality of life assessed by the SF-36 questionnaire

- Mental wellbeing assessed by WEMWBS
- Child Pugh score calculated by blood test (bilirubin, albumin, INR), abdominal exam to determine fluid build-up (ascites) and assessment of hepatic encephalopathy grade
- MELD score calculated by blood test (bilirubin, INR, creatine).
- Number, duration and diagnosis of any hospital admissions
- Infections (self-reported and by primary/secondary care records)
- Animal Naming Test
- SCFA concentrations in blood serum
- LPS, LBP and D-lactate concentrations in blood serum
- Calf circumference, corrected for BMI and oedema
- Attendance to and completion of final study visit (Week 24)
- Pill count and self-report of medication adherence
- Dietary intake by a 24-hour food recall (total macronutrient intake/24hr - protein, carbohydrate, fat, and fibre)
- HMB supplement use (contamination check)
- Adverse reactions and Serious Adverse Events

3.5. Summary of objectives and outcome measures

	Objectives	**Outcome Measures**	**Timepoint(s) of evaluation**
Primary	Determine the clinical effectiveness of HMB supplementation to improve physical function as measured by the LFI.	Change in LFI between baseline and 12-weeks post-baseline.	Baseline, Weeks 12 and 24
Secondary	1. Determine the effect of HMB supplementation on:	1. Change from baseline in:	Baseline, Weeks 12 and Week 24
	i. LFI category	Category of LFI ('frail', 'pre-frail', 'robust')	
	ii. Quality of Life and mental wellbeing	Participant self-reported SF-36 and WEMWBS	
	iii. Liver disease severity	Child Pugh and MELD scores	
	iv. Cognitive function	Animal Naming Test	
	v. Serum SCFA concentration	Blood test to measure serum SCFA concentrations	
	vi. Markers of gut permeability	Blood test to measure LPS, LBP and D-lactate concentrations	

	vii. Muscle mass	Calf circumference, corrected for BMI and oedema	
	viii. Rate of hospitalisation	Participant self-reported number, duration and diagnosis of any hospital admissions	Weeks 4, 12 and 24
	ix. Rate of infections	Infections (self-reported and by primary/secondary care records)	
	2. To evaluate participant engagement with trial procedures (i) and adherence to the intervention (ii).	Attendance to and completion of final study visit (i) Self-report of medication adherence (ii) Pill count (ii)	Week 24 Weeks 4 and 12 Week 12
	3. Assess for contamination	HMB supplement use	Baseline, Weeks 4, 12 and 24.
	4. Safety of intervention	Adverse reactions & Serious Adverse events	Baseline, Weeks 4, 12 and 24
	5. Macronutrient intake	24-hour dietary food recall (Intake24 tool)	Baseline, Weeks 12 and 24.

Table 2. Study objectives, outcomes and timepoints

4. TRIAL DESIGN

This study is a multicentre two-arm, individually randomised, double-blind placebo-controlled superiority trial of β -hydroxy β-methylbutyrate (intervention) verses maltodextrin (comparator), with process evaluation and an internal pilot, conducted in secondary care acute NHS Trusts in the UK. This study is a randomised double-blind placebo-controlled trial, which has been identified as the gold standard and most efficient trial design to provide the highest quality evidence of clinical effectiveness for the research question.

5. TRIAL SETTING

This study will be conducted in approximately eight secondary care acute NHS Trusts in the UK. Inequalities in cirrhosis is well established, with increased prevalence in males, lower socioeconomic groups and in certain ethnic groups, such as South Asians. The sites have been specifically selected to ensure a spread of patient demographics including age, sex, social deprivation status, ethnicity and aetiology of liver disease. These sites have large liver units that

treat above average numbers of patients with liver cirrhosis. All have rates greater than the UK average of hospital admissions and mortality due to liver disease. To assist with recruitment of participants from ethnic minorities, translations of patient-facing materials in common first languages at each site will be provided and support with telephone-based interpreters will be provided, as required.

6. PARTICIPANT ELIGIBILITY CRITERIA

6.1. Inclusion criteria

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

- Cirrhosis diagnosed by any of the following:
  - Clinical features of cirrhosis as determined by an experienced clinician;
  - Radiological features on ultrasound or cross-sectional imaging;
  - Histological evidence of cirrhosis;
  - Fibrosis assessment by transient elastography with stiffness > 15 kPa.
- Advanced cirrhosis defined as Child Pugh score of 7 or more (based on laboratory values and clinical assessment within the previous 3 months)[54].
- Evidence of portal hypertension within the previous 6 months defined by
  - Presence of ascites;
  - Presence of oesophageal or gastric varices;
  - Splenomegaly > 13 cm in maximum diameter;
  - Episode of hepatic encephalopathy.
- Ability to provide informed consent to participate.
  Participant is ≥ 18 years and ≤ 85 years of age.

6.2. Exclusion criteria

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

- Estimated prognosis limited to less than 6 months.
- Advanced hepatocellular carcinoma.
- The consumption of HMB, or products containing HMB, within the previous 4 weeks.
- Inability to complete the Liver Frailty index.
- Liver transplant recipient.
- On the liver transplant waiting list.
- Participant in any other interventional trial within previous 4 weeks.
- Previous history of poor engagement with clinical services, at the discretion of local PI.
- Previous history of hypersensitivity reactions or allergy to exogenous HMB supplements or any of its excipients.

7. TRIAL PROCEDURES

Please refer to the schedule of events in Table 3 below for a summary of the study visits and the procedures and data collected at each visit.

Procedures and data collected	Screening visit	Baseline visit	Treatment phase		Follow-up
			Week 4 Remote Visit	Week 12 End of Treatment	Week 24 End of study visit
Eligibility assessment	X				
Informed consent	X				
Demographics		X			
Medical history		X			
Randomisation		X			
Provision of capsules		X			
LFI		X		X	X
Child Pugh & MELD scores		X		X	X
Dietary intake (24-hr food recall)		X		X	X
Animal Naming Test		X		X	X
SF-36		X		X	X
WEMWBS		X		X	X
BMI (Weight and height to derive BMI at baseline; weight only at week 12 and week 24)		X		X	X
Calf circumference		X		X	X
Adverse events		X	X	X	X
Alcohol use in last 7 days		X	X	X	X
Contamination check		X	X	X	X
Concomitant medications		X	X	X	X
Blood samples (biochemistry, haematology and clotting)		X		X	X
Blood samples (LPS, LBP, D-lactate)		X		X	X
Blood samples (SCFA)		X		X	X
Engagement & medication adherence check (engagement at week 24 only)			X	X	X
Hospital attendances/ admissions			X	X	X
Infections			X	X	X

Table 3. Schedule of events. In addition to the visits, participants will have a contact point at Week 2 and Week 8; they will receive a text/email to encourage adherence and to contact the clinic team if they are having any issues.

7.1. Recruitment

7.1.1. Participant identification and approach

There are two main routes in which participants could be identified:

(1) Screening of local hospital databases / clinic lists.
Potentially eligible participants may be identified through screening of hospital databases or inpatient and outpatient clinic lists by the Principal Investigator or appropriately delegated individuals. As part of standard clinical management, the target population of patients with advanced liver cirrhosis are reviewed regularly (every 1-6 months depending on the severity of cirrhosis) in outpatient clinics. At the time of their routine appointment, potentially eligible patients will be approached by the PI or delegate and provided with verbal information about the study and the Study Summary and Participant Information Sheet (PIS). Potential participants will be asked if they wish to receive a follow-up call from a member of the research team. If so, a member of the local research team will make contact (see Section 7.1.2. Confirmation of initial eligibility). The follow-up call will take place after potential participants have had sufficient time to consider participation. Usually, this will be at least 24 hours after provision of the study information but may be sooner if the participant wishes.

If, at the routine appointment, the patient does not wish to receive a follow-up call at that time, they will be advised that, should they re-consider thereafter, they can use the contact information on the PIS to make contact with the research team or register their interest via the study website.

Participant Identification Centres (PIC) may also be used to identify and approach patients about participation in the study. PICs will make use of existing routes to access and contact patients, e.g. liver clinics. If patients are interested in taking part and consent to being contacted about the study, the PIC will forward the contact details to the local research team. If the patient does not consent to be contacted, they will be advised that they may self-refer to the study at any time (see below). Responsibilities of the PIC will be documented via a PIC agreement.

2) Patient self-referral.
Via promotional materials, such as posters and leaflets displayed in clinics, and promotion on social media, patients in the target trial population will be directed to the BOOST webpage on the PenCTU website. The BOOST webpage comprises a lay summary of the study (which includes a description of the eligibility criteria and the location of the participating sites), a downloadable PIS and an expression of interest form. In submitting a completed expression of interest form via the webpage, the patient agrees that: (i) they have read the PIS, (ii) they are happy for a member of the site research team to contact them on the telephone number and/or email address provided and (iii) the local research site and PenCTU will receive their expression of interest form.

7.1.2. Confirmation of initial eligibility (both routes)

A member of the local clinical team will pre-screen patient medical notes to confirm the patient meets the following initial eligibility criteria:

- Diagnosis of cirrhosis, defined by the criteria in section 6.1

- Child Pugh score 7 or more
- Evidence of portal hypertension
- Age is ≥ 18 years and ≤ 85 years of age.
- Not received a liver transplant.
- Not on the liver transplant waiting list.
- History of hypersensitivity reactions or allergy to exogenous HMB supplements or any of its excipients.

If initially eligible, a member of the research team will contact the patient to discuss the study further and answer any questions they may have and ascertain whether they are interested in participating. Patients who are interested in participating will be invited to attend a face-to-face screening visit at the participating site, for confirmation of eligibility and to provide informed consent.

A record (i.e., age, sex at birth, ethnicity, date of screening) of all patients considered for the trial will be recorded, by the researcher, on a study-specific screening log. De-identified information will be provided to PenCTU for CONSORT reporting.

If it is not possible to contact the patient after three telephone calls, the researcher will document on the screening log that the patient was ‘not contactable’. If a patient approached at the routine appointment did not wish to receive a follow-up call and they do not contact the research team within four weeks, the patient will be documented as ‘not interested’.

7.2. Screening

Initially eligible and amenable patients will attend a face-to-face screening visit at their local participating site. No specific trial-related screening tests are required. A medical doctor in the research team will confirm eligibility using the eligibility criteria checklist via routinely collected data recorded in the participant’s NHS record, including:

- Results from imaging (ultrasounds, CT, MRI), endoscopy, pathology and transient elastography
- Laboratory results
- Clinic consultation records

Once eligibility has been confirmed, informed consent will be obtained from the patient (see Section 7.4). Each participating centre should keep a separate enrolment log linking trial ID and identifiable patient data, i.e. patient name.

Following this, the baseline visit (see Section 7.8.1) can be merged with the screening visit where feasible, otherwise, the baseline assessment date should be scheduled with the participant.

7.3. Payment

Payments to participants will not be made to compensate for their time during the study. Participants will be reimbursed for reasonable travel expenses for research visits.

7.4. Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the receiving of informed consent of participants at their site. They must

ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. Informed consent may be obtained by associate PIs, Sub-Investigators and Research Nurses (grade 5 and above), where delegated by the local PI.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site, including the collection of identifiable participant data.

The informed consent form will include optional consent to be contacted by a researcher to discuss participation in the qualitative sub-study (see section 7.10),

The participant remains free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment and will be provided with a contact point at site where they may obtain further information about the trial. Data collected up to the point of withdrawal will be retained and used in analysis as outlined in the participant information sheet. Any intention to utilise such data will be outlined in the informed consent form. Where a participant is required to re-consent, or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

If a patient meets the eligibility criteria and wishes to take part in the study, they will be asked by the researcher to complete a study-specific consent form. The original consent form must be filed in the Investigator Site File. A copy must be provided to participants and a copy filed in the participant's medical notes. The researcher will document the consent process on the study database and in the patient's medical notes.

Where a participant provides informed consent but later in the study becomes incapacitated, the original consent given endures the loss of capacity, providing that the trial has not significantly altered since the initial consent was obtained.

7.4.1. Consent of non-English speaking patients

Where patients are identified as being non-English speakers, translated versions of the main Participant Information Sheet and Informed Consent Form will be provided. To identify translation requirements, potential sites will be provided with an expression of interest form and asked to list the top two languages spoken within their catchment areas. Non-English-speaking participants will be encouraged to bring an English-speaking family member or friend to all subsequent appointments to assist with data collection, and this requirement will be stated in the PIS. Sites should also use the translation/interpreter services available to them as part of standard care in the NHS. Local research team members who speak the relevant language may also act as interpreter at these visits. Where support from an interpreter is not available, i.e., a patient attends a visit without a family member/friend or staff member does not speak the language, at a minimum the primary outcome measure should be collected. The LFI is commonly used in clinical practice with this patient group and therefore patients are likely to already be familiar with this measure. The SF-36 and WEMWBS will also be obtained in the required languages, where possible.

7.5. Randomisation

After providing informed consent and completing screening and baseline assessments (see Sections 7.2, 7.4 and 7.8), participants will be individually randomised 1:1 to HMB versus placebo, stratified by alcohol use (Alcohol units per week: >50 units for men, >35 units for women (high risk), <= 50 units for men, <= 35 units for women (low risk))[58] and for severity of liver disease (Child Pugh score from screening: 7-9 (moderate) and 10+ (severe)). Randomisation should occur on the same day as the baseline assessment to allow the capsules to be dispensed at the end of the appointment.

The randomisation sequence, using variable block sizes, will be generated by a statistician independent to the trial team and implemented through a secure web-based system on REDCap, ensuring allocation concealment. Only site staff who have been delegated the role of randomisation on the delegation log will be able to access the randomisation system.
A blinded, automated confirmation email will be generated when a participant is randomised and sent to the PI, participant, and other delegated members of the study team. An unblinded confirmation email will be sent to the pharmacy representative when a participant is randomised with the treatment allocation.

7.6. Blinding

This is a double-blind trial where neither investigators nor participants are aware of treatment allocation. PenCTU will hold the key to the allocation.

Blinding will be maintained by the use of identically packaged and labelled placebo so that trial participants and all trial staff (including the research team and outcome assessors) are unaware of treatment allocation throughout the duration of the trial. Pill bottles will be provided to dispensing pharmacies with flag labels that detail the bottle contents (HMB or Placebo). After randomisation and as part of dispensing, locally delegated pharmacy staff will tear off the label with the treatment allocation and affix the label to an unblinded accountability log.

The statistician preparing reports for the DMC and local pharmacy teams who are delegated to dispense the allocated the treatment will be unblinded. The Co-applicant leading on the qualitative component (Dr Lynne Callaghan) will also be unblinded to enable recruitment of appropriate numbers of participants from each treatment arm.

7.7. Emergency Unblinding

The emergency unblinding procedure will be detailed in the Pharmacy manual, which will be available at all times in the Pharmacy department of each recruiting site and in the Investigator Site File.

Unblinding will only take place if a suspected unexpected serious adverse reaction (SUSAR) is reported or, if any Investigator has clinical concerns that might be related to the intervention and breaking the blind is necessary for the appropriate medical management of the participant. In the event unblinding is required, the responsibility at the local site resides with the Principal Investigator (PI). The PI will not be required to discuss unblinding with the Chief Investigator if they feel the emergent unblinding is necessary.

If the person requiring the unblinding is not the PI, then the attending clinician will follow local procedure to unblind: the clinician should request to unblind with the local PI, where this is not possible (the PI is not contactable), an emergency unblinding procedure will be held in the local site file with specific instructions to follow.

If a decision is made to unblind, the allocation details will be obtained from the REDCap database via completion of a code break request CRF. Only the PI at each centre will have access to this form. For out of hours cover, an emergency unblinding log-in will be provided to sites and should be stored securely in the ISF.

The PI will document the code break and reasons for doing so on the eCRF, in the site file and participant medical notes. Once a code break eCRF is completed, an automated blinded email will be sent to the local research team, PenCTU and the Sponsor to inform them an unblinding has occurred. The PenCTU will notify the regulatory authorities and other relevant parties as required.

7.8. Trial visits

7.8.1. Baseline Visit (Week 0)

After screening, eligible and consented participants will attend a face-to-face baseline assessment at their local participating site (within 1 month from initial screening visit).

Baseline demographic data will be collected including age, sex assigned at birth, ethnicity, education, socioeconomic status (measured using Multiple Deprivation decile), and preferred language.

Medical history will be collected, including aetiology of cirrhosis, and relevant medical and surgical diagnoses.

The following data will be collected by the researcher, as per the schedule in Table 3 (Section 7), and entered onto the study database:

- Functional status using the Liver Frailty Index® (primary outcome measure)
- Severity of liver disease (Child Pugh and MELD scores via blood test and abdominal exam)
- Dietary intake (by 24-hour food recall using Intake24 online tool)
- Cognitive function using the Animal Naming Test
- Health-related QoL using the Short Form (SF)-36 questionnaire
- Warwick-Edinburgh Mental Wellbeing Score (WEMWBS)
- Body Mass Index (Height cm and Weight kg).
- Calf circumference corrected for BMI and oedema as a measure of skeletal muscle mass
- Adverse events (if baseline occurs on different day to screening)
- Alcohol use over previous 7 days using timeline follow back
- Use of supplements containing HMB (contamination check)
- Concomitant medication (pre-specified and relevant to liver disease).

The following blood samples will be collected:

- Blood sample for sodium and creatinine (urea and electrolytes), INR (clotting screen), albumin and bilirubin (liver function test) to calculate Child Pugh and MELD scores. If routine bloods have been obtained to calculate Child Pugh and MELD scores within 4 weeks of the visit, these results may be used if available, otherwise a new blood sample will be required for research purposes. Haematology testing should also be performed on this sample (Full Blood Count: haemoglobin, White Blood Cells and Platelets).
- Research blood sample for serum SCFAs and gut permeability markers (LPS, LBP and D-Lactate).

The participant will be randomised to a treatment arm and provided with a 12-week supply of HMB or Placebo (see Section 7.5). The Week 4 visit will be scheduled.

At the suggestion of our PPI group, participants will be contacted at Weeks 2 and 8 by text message or email to support engagement in the trial and provide contact information as a prompt for participants to ask any questions. Participant contact details (mobile number/email) will be collected at this visit to facilitate this.

7.8.2. Week 2 Contact

Contact via text message/ email only.

7.8.3. Week 4 Remote Visit (+/- 4 days)

Participants will be contacted by telephone or video call, depending on the participant's preference. The following data will be collected by the researcher and entered onto the study database:

- Adverse events
- Alcohol use over previous 7 days by timeline follow-back
- Use of supplements containing HMB (contamination check)
- Concomitant medication (pre-specified and relevant to liver disease).
- Treatment adherence check (self-report)
- Self-reported hospital attendances and admissions including number, duration and diagnosis
- Self-reported infections

The week 12 visit will be scheduled with the participant.

7.8.4. Week 8 Contact

Contact via text message/ email only.

7.8.5. Week 12 End of Treatment Visit (+/- 4 days)

Participants will attend a face-to-face End of Treatment visit. Excluding demographics and medical history, this will be a repeat of the data collected at the baseline visit, with the addition of the below:

- Treatment adherence check (pill count and self-report)
- Weight to calculate BMI (not height)

- Self-reported hospital attendances and admissions including number, duration and diagnosis
- Self-reported infections

The data will be collected and entered onto the study database by the researcher. The bloods collected at the baseline visit will be repeated. The Week 24 visit will be scheduled with the participant (if applicable, see Section 7.8.6).

7.8.6. Week 24 End of Study Visit (+/- 4 days)

Participants will attend a face-to-face End of Study visit. This will be a repeat of the Week 12 visit. The data will be collected and entered onto the study database by the researcher. The bloods collected at the baseline visit will be repeated. This will be the final study visit for those not participating in the qualitative component.

Participants recruited after a specified date will not complete the final study visit, and their participation will conclude at the Week 12 visit. This is due to an extension to the recruitment period only for the study. The follow-up period for the study is scheduled to end on 30Nov2026, therefore any participants recruited on or after 16Jun2026 will not have a Week 24 visit. This will be clearly explained to affected participants at the point of consent via a cover sheet accompanying the Participant Information Sheet.

7.9. Long term follow-up assessments

No long-term follow-up assessments are planned for this study.

7.10. Qualitative sub-study

The aim of the qualitative study is to understand participant experience of trial methods and engagement with intervention/placebo. This will inform the implementation strategy and the development of future trials in other patient populations.

Participants will have an optional consent point on the main RCT informed consent forms where they can consent to being contacted to take part in the qualitative sub-study following completion of their last study visit. The researcher (LC) will attempt to make contact with each consenting participant, firstly via email, attaching the qualitative sub-study PIS and ICF and follow this up with up to three telephone calls in order to discuss if the participant would like to take part in a semi-structured interview about their experience of taking part in the trial. Qualitative interviews will be carried out with 12 participants (2 intervention/1 control from each of 4 sites selected to ensure a spread of patient demographics), following completion of trial data collection.

Interviews will primarily be carried out via telephone or online (Zoom, Microsoft Teams) with an option to take part in a face-to-face interview if required by the participant. Interviews will be audio recorded using the record function on Microsoft Teams or Zoom or using a digital recorder if conducting the interview via the telephone or in person. Semi-structured topic guides have been co-produced with the PPIE representatives to understand patient experience of trial methods (e.g. reason for participation, experience of recruitment & retention) and intervention/placebo engagement (e.g. facilitators and challenges to adherence). The topic guides will be used flexibly to allow participants to talk about issues of importance to them in relation to their experience of taking part in the study.

Interviews will be transcribed verbatim, organised using NVivo 12 and analysed using thematic analysis[59].

7.11. Early discontinuation and withdrawal criteria

A participant can choose to discontinue the intervention/placebo or withdraw from the trial at any time, without providing an explanation. Their standard clinical care will not be affected. If a participant chooses to discontinue the intervention/placebo, they should always be followed up providing they are willing, and they should be encouraged to not leave the whole trial. If a participant does not wish to participate in any study follow-up, sites should request consent from the participant to allow data from their medical records to be collected for the study during the follow-up period (up to Week 24), including hospital admissions (primary and secondary diagnoses, treatment and duration of hospital stay), attendance to emergency departments (diagnoses and treatment), and encounters with primary/secondary care where infection is diagnosed (infection type and treatment). Study intervention/placebo should be discontinued if there is an occurrence of an AE or SAE that suggests an unacceptable risk to the participant, in the judgement of the investigator, including worsening of cirrhosis.

Withdrawal from the study may take place if the participant requests to withdraw or the Sponsor decides to terminate the study and/or the internal pilot progression rules are not met and the study is terminated on that basis. Full study withdrawal may also occur if a participant becomes ineligible according to the criteria specified by the trial protocol during study participation (see Section 6.2), e.g., if a patient receives a liver transplant, they will be instructed to stop the intervention and will be withdrawn from the study.

Data and samples already collected during the participant's participation in the trial will be kept for analysis. If a participant withdraws from the study but has provided consent for their blood sample to be transferred to the Inflammatory Liver Disease Biobank at the University of Plymouth for use in future research, sites should ask the patient if they still consent to their sample being transferred. If they do not, the sample should not be transferred and destroyed in line with local procedures. If a participant withdraws and cannot be contacted to confirm the scope of withdrawal, it will be assumed they have withdrawn consent for all optional consent points, including donation of samples to the Biobank.

Participants who stop trial follow-up early will not be replaced. If a participant consents to the qualitative interview, but withdraws before the interview occurs, they will be replaced.

Withdrawals will be recorded by completing a digital withdrawal form in REDCap Community. This form allows the collection of withdrawal, partial withdrawal, loss-to-follow up and participant death events.

7.12. Loss to follow-up

The follow-up protocol has been designed to ensure high levels of participant engagement. At the baseline visit, contact details will be obtained from all participants to include mobile phone number, home landline number, email address and postal address. Participants will confirm the best method of communication with them. At each visit, contact details will be checked and updated.

At weeks 2 and 8, participants will receive a text message or email to check their status and remind them to take the HMB/placebo twice daily.

The week 12 and 24 visits should take place in-person at site but if a participant is unable to attend and where resources exist, a community-based visit should be offered in a suitable location convenient to the participant where visit procedures including phlebotomy can be safely conducted. Examples include GP practice, mobile research unit, alcohol service.

If a participant is no longer contactable and has missed at least one follow-up visit, site staff should attempt to contact the participant at least three times using at least two methods e.g. text message, phone and letter. If the participant remains uncontactable, site staff should contact the participant's GP to gain further information and check contact details.

7.13. Storage and analysis of clinical samples

Blood samples will be drawn at baseline, Week 12 and Week 24. Clinical samples for biochemistry and haematology will be collected, processed and analysed in local laboratories according to local protocols.

Research samples to measure serum SCFA and markers of gut permeability will be processed according to a separate Laboratory Manual. In brief, blood (approx. 3.5 ml) will be collected into a serum separating collection tube. The tube will be stood at room temperature for 20 to 30 minutes. It will then be centrifuged at 1500 rpm for 10 minutes at room temperature. The upper serum layer will be transferred (without disturbing the lower cell layer) as two 0.5 ml aliquots into pre-labelled (e.g. sample ID, visit number) endotoxin-free Eppendorf tubes; endotoxin-free pipettes/pipette tips must be used. The Eppendorf tubes will be stored at -80°C at each site and transferred in one batch on dry ice to the designated central laboratory at the University of Southampton at the end of the trial period. These samples will be analysed for SCFAs, LPS, LBP and D-lactate.

SCFAs will be measured by mass spectrometry. LPS will be measured using the Pierce™ Chromogenic Endotoxin Quant Kit. LBP will be measured using the Antibodies Online LBP ELISA Kit. D-lactate will be measured using the abcam D-Lactate Assay Kit (Colorimetric). In all cases the manufacturers' instructions will be followed.

Participants will be asked to consent to the storage and retention of samples for use in future research. Where consent has been provided, any serum remaining after completion of the assays will be transferred from the analytical lab at the University of Southampton to the University of Plymouth for storage in the Inflammatory Liver Disease Biobank.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

7.14. Internal Pilot

An internal pilot 4-months after recruitment commences will be used to decide whether the trial will progress. The criteria will be Red, Amber and Green rates (Red, stop; Amber, modify; Green, go). The status at 4 months will be reviewed by the Trial Steering Committee. Guidance will be sought for remedial action with Amber ratings. With no obvious mitigating factors, Red ratings will terminate the project. Please see Table 4 below for details of the progression criteria.

Progression criteria after 4 months of recruitment	Green band (progression of trial)	Amber band (progression of trial with remedial action)	Red band (likely termination of trial)
Sites open	7-8	5-6	0-4
Proportion of expected recruitment	100%	≥80% and <100%	<80%
Consent rate (defined as number of eligible patients who consent)	≥50%	≥30% and <50%	<30%

Table 4: Internal Pilot Progression Criteria after 4 months of recruitment

7.15. End of Trial

The end of the trial is defined as the last visit of the last participant or upon completion of any follow up and data collection. This timepoint is defined as when the final participant has completed their week 24 visit, or the qualitative component (where relevant), whichever occurs later.

The study may be terminated early if the internal pilot progression criteria are not met, as detailed in Section 7.14. If any of the progression criteria are in the red banding, it is likely that the trial will be terminated early. If any of the progression criteria are in the amber banding, the trial may progress with remedial action.

The Sponsor delegate will notify the MHRA and REC of the end of the trial within 90 days of completion. The final report will be written within 12 months of the end of the trial.

8. TRIAL INTERVENTION

The study intervention is Calcium β-hydroxy β-methylbutyrate (CaHMB), a dietary supplement which is sold over the counter in the UK. (Ca)HMB is the chemical product after the break down of the amino acid leucine. The matched placebo is maltodextrin, a type of carbohydrate commonly used as a food additive.

The intervention will consist of twice daily, oral administration of 1.5 g HMB (2 x 750 mg capsules), or matched placebo (Maltodextrin). Participants will be provided with pill bottles of their allocated treatment immediately following randomisation.

8.1. Regulatory status of the drug

HMB is sold as an over-the-counter dietary supplement and does not have Marketing Authorisation (MA) in the UK to treat any medical conditions.

The clinical trial data collected by the current study will not be used to support a MA. HMB is a long established and widely available dietary supplement which can be purchased at a relatively cheap price, from numerous vendors and in various doses and formulations.

8.2. Product Characteristics

An Investigator Brochure (IB) has been developed for the current trial by PenCTU and the literature will be reviewed annually to ascertain whether any updates need to be made to the document. The IB will be used as the Reference Safety Information. A simplified IMP dossier (sIMPD) has also been provided by Nottingham University Hospitals NHS Foundation Trust.

8.3. Storage and supply

Nottingham University Hospitals NHS Foundation Trust (NUH) is responsible for sourcing, manufacturing (packaging), labelling, Qualified Person (QP) release, storage and distribution of the study intervention/placebo to participating centres.

CaHMB 750 mg capsules and Maltodextrin 750 mg capsules will be sourced from TSI Group Co. Ltd. and used in this clinical trial (see sIMPD for detailed information on IMP supply and manufacturing process).

NUH will remove the CaHMB and Maltodextrin capsules from their bulk containers and pack into suitable pill bottles. NUH will package the matched Placebo (Maltodextrin) to visually match the IMP (see sIMPD for further details).

There are no special precautions for storage. The study capsules should be kept at room temperature (15-25°C) in a cool dry place, out of direct sunlight.

Detailed information regarding IMP storage, shipment, receipt, distribution, return and destruction of the IMP is available in the Pharmacy manual.

Trial intervention/placebo will be provided by NUH and requested by the study team in accordance with the Pharmacy Manual.

Accurate records for IMP dispensed and returned must be maintained and a record available for inspection.

8.4. Preparation and labelling of Investigational Medicinal Product

QP services will be provided by the Pharmacy Production team at Nottingham University Hospitals NHS Foundation Trust, who will provide the relevant certification and trial labelling. This will be conducted in accordance with Annexe 13 requirements.

The HMB and Placebo will be packaged identically, but labelled with a primary label which contains a tear off portion of the label identifying the bottle as either IMP or Placebo. Therefore, the IMP/Placebo must be handled only by unblinded personnel until the distinguishing feature is removed at the point of issue to blinded researchers or dispensing to the patient.

Upon randomisation, an unblinded alert will be sent to the local Pharmacy team specifying the treatment allocation for each participant. A delegated and appropriately trained Pharmacy team member will select pill bottles from the allocated arm (HMB/Placebo), tear off the portion of the labels identifying the bottle contents, affix these to the unblinded accountability log, before dispensing the medication to the trial team to provide to the participant.

8.5. Dosage schedules

Participants will be provided with a 12-week supply of study treatment at the baseline visit, with instructions to take 2 x 750 mg capsules by oral administration twice daily (morning and evening). There are no restrictions for dose timings, but participants will be encouraged to follow a 12-hour schedule to promote consistency and adherence. Capsules do not need to be taken with food.

Participants will be provided with the exact number of capsules required for the 12-week treatment period. In the event of a missed dose, i.e., due to forgetting, losing or damaging a capsule, and/or vomiting, the participant should carry on with the treatment as instructed.

No dosage modifications are permitted. See section 9.8 for information about overdoses.

If a participant develops clinical evidence of a significant adverse reaction during the intervention, then the administration can be stopped at the direction of the treating clinician. If a product recall should occur, the medication will be quarantined, and the trial will temporarily halt recruitment until the matter is resolved.

8.6. Known drug reactions and interaction with other therapies

There are no known drug interactions or interactions with other therapies or situations for HMB or maltodextrin.

8.7. Concomitant medication

Only pre-specified concomitant medications taken by the participant during study participation which are relevant to liver disease will be recorded:

- Rifaximin
- Beta-blockers (Carvedilol, Propranolol)
- Lactulose
- Antibiotics (Co-trimoxazole, Ciprofloxacin)
- Zinc sulphate

Other than supplements which contain HMB, all other medications may be taken as clinically indicated.

8.8. Trial restrictions

There are no restrictions related to involvement in the trial other than those covered by the exclusion criteria.

Pregnant persons, and those of child-bearing potential, will not be excluded from taking part. As a result, there are no contraception requirements in this trial. This decision is based on this being a low-risk trial, HMB being available to buy over the counter as a supplement, and evidence from

pre-clinical studies in animals which indicate a potential beneficial impact in pregnancy (see Investigator Brochure). If pregnancy occurs during trial participation, outcomes will be recorded for completeness and to add to the limited evidence base (see section 9.7). The limited data regarding exposure to HMB in human pregnancy and breastfeeding will be included in the PIS so patients are fully informed before consenting to take part.

8.9. Assessment of compliance with treatment

Compliance with treatment will be assessed at the Week 4 and 12 visits via participant self-report and pill count (latter at Week 12 only). Information will be recorded on the eCRF by the study team. Non-adherence with the treatment with be recorded as a protocol non-compliance (see section 13.5 for details on non-compliance reporting). Automated text/email reminders will be sent to participants at weeks 2 and 8 to support treatment adherence. Participants will be reminded of the importance of adhering to the treatment schedule at each study visit.

9. PHARMACOVIGILANCE

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect

	Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information (IB).

9.2. Operational definitions for (S)AEs

The safety reporting period will commence from the point of consent until the final study visit (Week 24).

All AEs occurring on the trial should be recorded in the patient’s medical notes. Given the nature of liver cirrhosis, it is anticipated that participants will experience a high number of AEs related to their condition which, if reported, risk masking any important safety signals. HMB is a widely available dietary supplement, and the overall risk of the intervention is low (Type A; no higher than risk of standard medical care) with no known adverse reactions. In other clinical trials of HMB, no SAEs have been reported and in patients with liver cirrhosis, a similar number of AEs have been reported compared to placebo (see IB for further details). The aim of the current study is not to support a Marketing Authorisation application, but to encourage the use of HMB in patient care, if successful. Participants will be asked to provide a reason if they did not take the dispensed IMP as per protocol to ensure any potential impact of AEs on treatment adherence is being captured. The outcome measures of rate of hospitalisation and infections will also capture any notable adverse events. Therefore, a pragmatic approach will be taken whereby only events deemed to be serious in nature (SAEs) and / or related to the study drug (AR/SAR/SUSARs) will be subsequently reported via the eCRF.

Pre-existing conditions (documented in the medical notes) do not qualify as an AE unless they worsen during trial participation. This includes routine treatment or monitoring of the studied indication, and admission to hospital or other institution for general care with no deterioration in condition.

Any reported adverse events which are ongoing at the point of the final visit, must be followed up until the event has resolved, stabilised or has been fully investigated to the satisfaction of the PI and Sponsor. This may require contact with the participants general health practitioner (GP), or other healthcare providers involved in the ongoing clinical care of the patient. The GP will be notified of the patient’s study participation and will be provided with a copy of the completed consent form.

Any new ARs or SAEs which occur after the final visit will not be sought or captured in the eCRF. If the Investigator becomes aware of any SARs that occur after the end of the safety reporting period (week 24), these should be reported to PenCTU as per section 9.3.

Events should be recorded using V5.0 of the Common Terminology Criteria for Adverse Events (CTCAE) provided in the National Cancer Institute (NCI).

9.3. Recording and reporting of SAEs, SARs AND SUSARs

Serious adverse events and reactions occurring from the time of written informed consent until the week 24 face-to-face study visit must be reported by the Investigator within the eCRF as per the work instruction for reporting safety events. The PI / PI delegate is responsible for checking for AEs and ARs at each in-person and telephone study visit. SAEs must be reported using the digital PenCTU SAE reporting form **within 24 hours of the research team first becoming aware of the event,** even if not all information is available at the time of reporting.

For each **SAE & SAR** the following information will be collected:

- Full details of the event, including a diagnosis
- MedDRA coding (system organ class and preferred term)
- Duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to trial drug), in the opinion of the investigator
- Expectedness

Any change of condition or other follow-up information should be entered on the digital SAE resolution form as soon as it is available or at least **within 24 hours of the information becoming available**.

CTU contact information	
Email	boost.penctu@plymouth.ac.uk
Telephone	01752 439831

All SAEs both suspected to be related to IMP and unexpected as per the approved RSI will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA) by the Sponsor. Fatal or life-threatening SUSARS will be reported within 7 calendar days of first awareness of the reaction. Any additional relevant information will be sent within the following 8 calendar days. All other SUSARs will be reported within 15 calendar days of first awareness. Once a report has been made to the MHRA, PenCTU in collaboration with the CI will inform all participating sites.

9.4. Assessment of AEs and SAEs

9.4.1. Severity

The investigator should determine the severity of the AE as per NCI CTCAE (V5.0):

	Severity	Definition
1	*Mild*	Aware of sign/ symptom but easily tolerated
2	*Moderate*	Discomfort enough to cause interference with usual activity
3	*Severe (or medically significant)*	Incapacitating, unable to work or perform usual tasks
4	*Life-threatening*	Risk of death at the time of the event, urgent intervention required
5	*Death*	Death related to AE

NOTE: to avoid confusion or misunderstanding the term “severe” is used to describe the intensity of the event, which may be of relatively minor medical significance, and is NOT the same as “serious” which is described in the safety definitions.

9.4.2. Causality

Clinical judgement should be used to determine the relationship between the IMP and the occurrence of each AE.

- Not related: There is no evidence of a causal relationship between the event and IMP.
- Related: There is evidence of a causal relationship between the event and IMP i.e., a relationship to the IMP cannot be completely ruled out.

A medically qualified doctor (usually the principal investigator) must assess causality. If a doctor is unavailable, initial reports should be submitted to PenCTU without the causality assessment, but they must be followed up with a medical assessment as soon as possible (and within 3 working days).

9.4.3. Expectedness

The assessment of expectedness is only required if the event is deemed to be related to the IMP.

- Expected: Reaction previously identified and described in the reference safety information (RSI) and/or protocol.
- Unexpected: Reaction not previously described in the protocol or RSI.

The expectedness assessment is delegated to the Principal Investigator(s) and Chief Investigator who will perform a clinical review. The RSI for this trial is the approved Investigator Brochure.

9.5. Responsibilities

Principal Investigator (PI) / delegate:

1. Checking for AEs and ARs at each study visit.
2. Using medical judgement in assigning severity, seriousness, causality and whether the event was anticipated using the Reference Safety Information approved for the trial.
3. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and whether the event was anticipated using the Reference Safety Information approved for the trial.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor: (NB where relevant these can be delegated to CI or PenCTU)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. The unblinding of a participant for the purpose of expedited SUSAR reporting.
7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial. This will be performed via literature review of the existing data.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):
In accordance with the TSC Charter, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):
In accordance with the DMC Charter, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. To facilitate this, total numbers of SAEs reported per month will be sent to the DMC chair, along with a line listing of SAEs grade 4 and 5.

9.6. Notification of deaths

All deaths should be reported to PenCTU within the eCRF. 'Death' is not an SAE, but the outcome of an SAE, and should be reported in line with section 9.3.

9.7. Pregnancy reporting

If a participant becomes pregnant or is suspected to be pregnant during trial participation, the investigator must notify the PenCTU **within 24 hours of first becoming aware** of the pregnancy using the PenCTU digital pregnancy notification form.

If a confirmed pregnancy occurs during study participation, the participant will not be withdrawn from trial treatment. This decision is based on this being a low-risk trial, HMB being a widely available supplement, and animal studies which indicate a beneficial impact in pregnancy. The Sponsor and IMP manufacturer (where required) will be informed of any reported pregnancies by PenCTU within 1 working day of being notified. Follow-up information will be transmitted within the same timelines.

Whilst not considered an AE, pregnancy occurring in a CTIMP requires monitoring and follow up by the Investigator. The pregnancy must be followed up no less than 10 months after study participation ends and the Investigator must complete the PenCTU digital pregnancy outcome form.

Any negative or consequential outcome for the mother or child/foetus should be reported as an SAE as per section 8.3, if the outcome meets the serious criteria.

9.8. Overdose

An overdose will be determined by patient self-report and pill count at the week 4 and 12 visits and is defined by more than 12 g of HMB administered in 1 calendar day (16 capsules). This definition has been determined by the existing evidence in the literature. The highest studied dose of HMB administered to humans, 6 g per day for 8 weeks, reported no adverse events[60]. In addition, very high doses of HMB have been studied in animal models (2g/kg) and have not demonstrated any acute toxicology[61]. Deviations to the dosage schedule which are less than 12 g per day will be recorded as a protocol non-compliance.

Any instance of an overdose regardless of whether this results in an adverse event must be reported to PenCTU **within 24 hours of first becoming aware** of the overdose using the digital deviation form in REDCap. The overdose should also be recorded in the medical notes. If the overdose results in an SAE, this must also be reported according to the PenCTU procedure described above. In the instance of an overdose all responsible parties will review and rectify systems and processes to prevent reoccurrence and all details/findings will be reported to the PenCTU, Sponsor and regulatory bodies as appropriate.

9.9. Reporting urgent safety measures

If any urgent safety measures are required, the CI/Sponsor will telephone the MHRA's Clinical Trial Unit immediately (i.e., within 24 hours of measures being taken) to discuss the issue with a medical assessor. The Sponsor will submit a written notice of the USM(s) to the MHRA and the relevant REC via the IRAS, within 3 days of the measures being implemented. A substantial amendment covering the changes made as part of the USM will also be submitted within 2 weeks of the written notification to the MHRA.

If an USM is implemented at site, PenCTU should be notified **immediately** by telephone or emailing boost.penctu@plymouth.ac.uk. The PenCTU will notify all participating sites within 24 hours of USM(s) being implemented and acknowledgement of receipt from each site PI will be recorded.

9.10. Type and duration of the follow-up of participants after adverse reactions.

All adverse reactions which occur on the trial will be followed up until resolution, stabilisation, or Sponsor satisfaction.

Any SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred and followed up until resolved.

9.11. Development safety update reports

The PenCTU will provide DSURs once a year throughout the clinical trial, or as necessary, to the Competent Authority (MHRA in the UK), and where relevant, the Research Ethics Committee.

The report will be submitted by the Sponsor within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample size calculation

A pilot trial of HMB in people with advanced cirrhosis found that the LFI reduced from a baseline of 4.1 (SD: 0.4) to 3.7 (SD: 0.4) after 12 weeks of treatment[45]. To detect a moderate to substantial clinically relevant minimally important difference of 0.4 between groups at Week 12, with a conservative estimate of SD of 0.6, with 90% power and alpha of 0.05, a sample of 98 participants is required. Assuming 20% attrition to follow-up, we intend to recruit 124 participants.

10.2. Planned recruitment rate

An outpatient follow-up waiting list audit in Plymouth identified over 100 patients with advanced cirrhosis of which more than 75 did not have ongoing alcohol use. Other participating centres have similar or larger outpatient lists, suggesting the pool of eligible participants for this trial in these eight centres is conservatively 600, but likely more suggesting our recruitment target over 12 months is feasible.

10.3. Statistical analysis plan

A detailed statistical analysis plan (SAP) will be drafted by the trial statisticians and approved by an independent statistician prior to database lock. The study will be reported following the

relevant Consolidated Standards Of Reporting Trials (CONSORT) guidelines. The statistical significance level for hypothesis tests will be two-sided at the 5% level and between-group differences will be presented with two-sided 95% confidence intervals, for both primary and secondary outcomes. Primary analyses for the primary and secondary outcomes will be adjusted for the stratification factors and where relevant the baseline measure of the outcome under consideration. Simple unadjusted analyses will also be presented alongside the adjusted estimates. No adjustments for multiple analyses will be made as the trial has a clearly specified primary outcome. Model assumptions will be visually checked and bootstrapping implemented as required e.g. to handle substantial deviations from normality.

10.3.1. Summary of baseline data and flow of patients

Baseline characteristics of participants will be summarised descriptively using means (standard deviation), median (inter-quartile range) or number (percentage). The summarized data will be used to assess for any marked baseline differences in demographics or outcome measures between the two allocated groups. Loss to follow-up after randomisation will be reported separately for each group, summarised visually via a CONSORT flow diagram. Baseline characteristics will be subjectively examined to assess for potential differences between participants who withdraw, discontinue HMB, and those who complete the trial.

10.3.2. Primary outcome analysis

The primary analysis will compare the change in LFI between allocated groups at 12 weeks using a linear mixed effects model, with adjustment for stratification factors and baseline LFI. The model facilitates inclusion of participants who provide at least one post-baseline measurement of liver frailty index, which is a valid and unbiased approach when these data are missing at random (MAR) or missing completely at random (MCAR). The changes between baseline and the follow-up time points (12 weeks and 24 weeks) will be modelled on allocated group, time point and the interaction between allocated group and time point, with adjustment for stratification factors and baseline LFI. The model will provide estimates of the between-group difference (and confidence intervals) at the primary endpoint of 12 weeks and at 24 weeks. For the primary estimand, intercurrent events related to adherence to treatment (i.e. discontinuation/independent initiation of additional HMB supplementation) will be handled using the treatment policy strategy. Participant data collected prior to death will be included in the analyses. Therefore, primary analyses will be programmed and undertaken following the intention-to-treat principle.

10.3.3. Secondary, sensitivity and subgroup analyses of the primary outcome

The SAP will contain full details of all additional planned analyses. These will include:

(i) A hypothetical strategy whereby observations after an intercurrent event of interest has occurred are excluded, used to estimate the treatment effect assuming intercurrent events do not occur (i.e. if participants do not discontinue the intervention, or they independently initiate HMB supplementation).

(ii) A secondary analysis of the primary outcome which considers adherence with allocated treatment, i.e., based on participants who meet a minimum threshold of adherence with their allocated trial treatment (in particular usage of HMB).

(iii) Exploratory analysis of the treatment*alcohol use interaction to assess whether the effect of the intervention on change in LFI is modified by alcohol use (high risk or low risk).

10.3.4. Secondary outcome analysis

The analysis of secondary outcomes will follow the principles outlined for the primary outcome, i.e primarily on an intention-to-treat basis, using treatment policy strategy to handle the key intercurrent events of interest.

Continuous secondary outcomes will be descriptively summarised and analysed following a similar approach for the primary outcome using linear mixed effects models. The changes between baseline and each follow- up time point (12 weeks and 24 weeks) will be modelled on allocated group, time point and the interaction between allocated group and time point, with adjustment for stratification factors. Binary secondary outcomes will be analysed using logistic regression models, with adjustment for stratification factors.

Safety outcomes will be descriptively summarised on an as-treated basis

10.4. Interim analysis and criteria for the premature termination of the trial

There will be a review of progress against the pre-specified progression criteria at the end of the internal pilot phase, to assess evidence to support continuation of the trial. The decision to continue will be informed by the progression criteria proposed in Section 7.14 and discussion with the TSC, Sponsor and Funder.

The trial may end early if there is evidence that HMB is harmful. The DMC will meet at pre-specified intervals and will monitor safety by review of SAE data and make recommendations to the TSC regarding any safety or ethical issues.

No formal interim analyses of primary and secondary outcomes are planned.
In the event that the TSC or Sponsor recommends early termination of the study for any reason, the Sponsor will notify the Ethics Committee and MHRA. Supported by PenCTU, the Sponsor will be responsible for informing all the sites running the study of the early termination. The sites will be responsible for informing participants of the early termination of the study.

10.5. Participant population

The primary analysis population will include all participants, as randomised, for whom the primary outcome, Liver Frailty Index (LFI) at 12 weeks or 24 weeks, can be derived. The safety outcomes will be considered on an as treated basis thus the safety set will include all participants who have had at least one dose of HMB.

10.6. Procedure(s) to account for missing or spurious data

Reasons for being unable to collect data during an assessment will be recorded on the electronic case report form (eCRF), where appropriate. eCRFs will be assessed for missing data by the CTU and sites will be regularly chased for missing data. The CTU will maintain a record of site compliance with eCRF completion. If data completion is poor, a monitoring visit may be scheduled.

The eCRFs will include mandatory fields; if a form is saved without these fields being completed an automatic flag will be displayed to the user. Where questions may need to be left blank, options such as ‘Not applicable’ or ‘Prefer not to say’ will be available, to differentiate these from missing data. Validations will be written into the study database, to raise queries with particular data field, such as flagging if the date of a visit does not correspond to the correct timepoint.

Periodic reminders will be sent out to participants to complete questionnaires, if they have selected to complete these electronically.

The PenCTU data manager will write a series of R scripts to perform data tasks to aid data completeness, including checking overall completeness by field of all CRFs, checking all visits have been recorded in a logical order and checking SAE forms have been completed. The scripts will be run on a weekly basis and any concerns will be raised individually with sites.

11. 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.

11.1. Data collection tools

The REDCap database will be used to collect participant screening and outcome data, as well as to perform IMP tracking. It will be a web-based, fully validated system, compliant with MHRA guidance and ALCOA+ principles. Data will be captured in accordance with the best principles of clinical data management and the relevant standard operating procedures on Clinical Data Management System Specification and Validation. PenCTU will be responsible for the database build and system validation. Inbuilt validation features will be utilised alongside post-entry monitoring, performed using validated R scripts to ensure data quality and completeness.

Data will be hosted externally by AIMES on MS Azure datacentres located within the UK (Liverpool, England). AIMES are NHS DSP Toolkit compliant and hold ISO27001 and Cyber Essentials Plus certifications. Microsoft Azure datacentres are Service Organisation Control (SOC) type 1 and 2 compliant. Data will be stored on hardware dedicated to PenCTU's instance of REDCap. All electronic data are regularly backed up and stored with a full audit trail.

11.2. Source data

Source data will include participants' medical records (e.g. for medical history), participant-completed documents (e.g. informed consent forms, patient-reported outcome measures), paper worksheets provided by PenCTU/electronic data capture forms (eCRFs), laboratory result outputs and data captured in the 24-hour diet recall software. 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 participant's health record should be updated to include:

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

Source data should be compliant with ALCOA CCEA guidance (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available). The CTU will

verify source data and source documents as stipulated in the study monitoring plan (see Section 12 Trial Monitoring). Study data will be recorded on the eCRF or on paper forms which will then be entered into the REDCap eCRF.

Participant questionnaires will be completed on eCRFs. Paper-based options will be available on request and entered onto the eCRFs by site staff.

The investigator should keep a record of all participating patients and all original signed informed consent forms. Any paper forms completed by site staff or participants should be retained in the ISF.

The investigator and trial team will ensure that the participant's identity is protected at every stage of their participation in the trial, according to the Caldicott principles. If any patient information needs to be sent to a third party the trial team will adhere to maintaining pseudo-anonymous participant parameters in correspondence.

11.3. 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.

11.4. 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 5 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, so as 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).

12. MONITORING, AUDIT & INSPECTION

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

PenCTU will perform ongoing central monitoring, outputs from which will be discussed by the TMG, and used to identify areas of poor performance at participating sites. 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 and calendar checks (to identify deviations from participants' visit schedules). Remote monitoring will also be performed and will include consent process checks (through collection of completed de-identified consent forms) and appropriateness of delegated duties at investigator sites (through collection of site delegation and training logs). Poor performance at sites may trigger on-site

monitoring visits, hosted by the investigator site PI and relevant members of the PI's team. On-site monitoring (if applicable) will be conducted by PenCTU staff according to established PenCTU SOPs. The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the REC or regulatory authority inspectors. Authorised representatives of the Sponsor and competent authority may visit the participating sites to conduct audits/ inspections.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee (REC) review & reports

Prior to the start of the trial, the Sponsor/delegate will obtain approval from the UK Health Research Authority (HRA), Research Ethics Committee (REC) and Medicines and Healthcare products Regulatory Agency (MHRA) for the trial protocol, informed consent forms and other study documentation (e.g. Participant Information Sheets, GP letter and study advertisements).

Substantial amendments that require review by the REC, HRA and MHRA (where applicable) will not be implemented until a favourable opinion is received from each of the relevant regulatory bodies. NHS R&D departments have up to 35 days upon notification of an amendment to raise an objection, after which point the amendment will be implemented at sites. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. The Sponsor delegate (PenCTU) will notify the REC and MHRA of the end of trial, including the reason for termination where the trial is ended prematurely. Within one year after the end of the trial, the Sponsor delegate (PenCTU) will submit a final study report, including a lay summary, to the REC.

13.2. Peer review

This study has been peer reviewed and approved as part of the NIHR RfPB funding application process, by 4 independent reviewers consisting of Healthcare Professionals and a PPI representative.

13.3. Public and Patient Involvement

During study design, four meetings were held with a Patient Advisory Group (PAG) which consisted of 10 people with lived experience of liver cirrhosis. Their input and assistance was sought during project development, including which type of HMB would be acceptable to test and which outcome measures were important for patients, which included function and quality of life. A patient representative is part of the Trial Management Group and will have regular input throughout the duration of the study. The PAG group will meet regularly throughout the duration of the study (at least once yearly) to review participant facing study documentation, study progression and support the development of dissemination materials.

13.4. Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and a favourable REC opinion is received. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol patients into the study, PenCTU will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, PenCTU, following authorisation from the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. PenCTU 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.

13.5. Protocol compliance

Non-compliance with protocol will be captured on study specific non-compliance report forms, according to instructions provided by PenCTU and in accordance with PenCTU standard operating procedures. Protocol non-compliances will be reviewed periodically by the Trial Management Group as part of central monitoring, 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 will immediately inform the PenCTU QA Manager and CI 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, PenCTU will ensure that a completed non-compliance report form is provided to the Sponsor immediately (i.e., within 1 working day of first awareness)

13.6. Notification of Serious Breaches to GCP

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 notification of serious breaches of GCP or the trial protocol report form to the MHRA (via GCP.SeriousBreaches@mhra.gov.uk) within seven days of becoming aware of the event. Reports should be forwarded to the REC (via breaches.nres@nhs.net) cc’ing the HRA within the same timeframe. If the CI/PI (or delegate) is unsure if non-compliance meets these criteria, they should consult the Sponsor and MHRA for further guidance.

Complete investigations of breaches will be fully documented, filed in the TMF and a copy provided to the Sponsor.

13.7. 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. questionnaires) for capturing source data will remain at investigator sites. Investigator site staff will enter participant data into purposed designed data capture systems. 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 pseudonymised by the use of 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.

In order 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 pseudonymised and will not contain any direct identifiers or participant contact details.

Audio data from qualitative interviews 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.

13.8. Financial and other competing interests

The Chief Investigator, PIs at each site and TSC/DMC 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 the may impact on academic promotion.

Declaration forms will be filed in the Trial Master File (TMF). At the time of protocol writing, there are no known financial or other competing interests of the Chief Investigator or team.

13.9. Indemnity

This study is sponsored by an NHS/HSC organisation (University Hospitals Plymouth NHS FT) and no additional insurance for design or management of the research is required. The NHS indemnity scheme will apply.

13.10. Amendments

If changes to the study are required, these must be discussed with the Sponsor, who is responsible for deciding if an amendment is required and the substantiality of the amendment. Substantial amendments will be submitted to the relevant regulatory bodies (MHRA, REC, HRA) for review and approval by PenCTU via Combined Review. The amendment will only be implemented upon receipt of approvals from the HRA and MHRA, and a favourable opinion from the REC. Non-substantial amendments will be submitted to the HRA via the same process as above and will not be implemented until acknowledgement or approval is received from the HRA. PenCTU will notify the relevant stakeholders of any substantive amendments, including the Funder, trial registries, external vendors, where contractually required. PenCTU will maintain an amendment history log documenting changes to trial documents and implementation date(s).

13.11. Post trial care

All participants will continue to receive the standard care for their condition post-trial, and their participation in this study will not affect or delay this care. Participants will not receive any further IMP from the study team once their treatment is complete, however, HMB can be purchased by patients over the counter at a low cost from UK vendors.

13.12. Access to the final trial dataset

During the study, the PenCTU data team will have access to the trial 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 for analysis.

After the trial has been reported, the anonymised 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.

14. COMMUNICATION AND DISSEMINIATION POLICY

In collaboration with the Media and Communications Team at the University of Plymouth, a strong communication and dissemination plan has been developed. This team includes experts in media and communications, marketing, website design and maintenance, social media, photography and multimedia and they have a variety of channels at their disposal through which the outcomes of the research – and its benefits or otherwise for the wider public – will be

communicated. The Media and Communications team has a positive and long-lasting relationships with regional, national and international health correspondents, in addition to international science communication platforms (eg. EurekAlert) and sector/trade publications. They are well versed in the writing and issuing of press releases and the generation of other proactive and reactive media opportunities. In conjunction with the project partners and funders, this team will look for opportunities to showcase the research through these channels. Media training will also be provided to those involved in the research, as a means of upskilling but also to ensure the greatest benefit is gained from work to generate these opportunities.

A dedicated study webpage hosted by Peninsula Clinical Trials Unit will highlight the project aims, objectives, methods and partners and provide a location for potential participants to view the Participant Information Sheet, register their interest in participating and view regular study updates. The study webpage will provide a platform with potential to generate a range of written, visual and video content to showcase and promote the study and will be promoted by utilising the University of Plymouth's extensive following on various social media platforms.

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 publicly available. 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 relevant 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, with support from the PAG group, and published on the PenCTU website, social media and sent to patient liver groups. Trial participants will receive a notification via email (if provided) or post when the results are available. The CI and study team will hold a virtual dissemination event that will be widely publicised through patient groups and professional societies with the aim to explain the results of the study and involve participants in considering future studies and further research priorities.

An anonymised participant level dataset will be produced and held within PenCTU.

If study results indicate that HMB is effective, the study group will work with national societies and healthcare professions to encourage regular use of HMB in routine patient care without delay, as it is cheap and widely available.

14.1. Authorship eligibility guidelines and any intended use of professional writers

Authorship of all manuscripts and papers 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. There is no intention to use professional writers.

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16. APPENDICES

16.1. Appendix 1 – Animal Naming Test

Instructions for administering the ANT:

Introduction: “I’d like to ask a question to check your cognitive performance.”

Instruction: “Tell me the name of as many animals as you can think of, as quickly as possible. Are you ready? Let’s begin.”

Procedure:

• Time for 60 seconds and record all responses.

• If the person stops before 60 seconds, say “Any more animals?”

• If the person says nothing for 15 seconds, say “A dog is an animal. Can you tell me any more animals?”

Scoring: Count the total number of animals (NOT including repetitions or non-animal words).

Source: Campagna F, Montagnese S, Ridola L, et al. The Animal Naming Test: An Easy Tool for the Assessment of Hepatic Encephalopathy. Hepatology. 2017;66(1):198-208.

16.2. Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NA	1.0	16Jan2025	Various	NA – First edition.
NA	1.1	14Apr2025	Kayle-Anne Sands	- Addition of 'Willing and able to provide informed consent' as inclusion criterion. - Addition of 'History of hypersensitivity reactions or allergy to exogenous HMB supplements or any of its excipients' as exclusion criterion. - Removal of option to recruit patients with reduced capacity. - Clarification and guidance about emergency unblinding added (section 7.7). - Guidance about withdrawal of samples added (section 7.11). - Rationale for proportionate safety reporting added (section 9.2). - Change to 2 x 750 mg capsules and subsequent correction to overdose definition (section 9.8). IMP and Placebo supplier confirmed.
AM02	2.0	12Aug2025	Kayle-Anne Sands	- Update to key trial contacts: CI title, PenCTU postal address. - New secondary objective 'Monitor changes in macronutrient intake' added. '24-hour dietary recall' changed from an outcome measure for contamination, to an outcome measure for macronutrient intake. - LFI instructions not to be provided in alternate languages (section 7.4.1 updated). - Minor wording/grammatical changes throughout.
AM03	2.1	17Oct2025	Kayle-Anne Sands	- Addition of Participant Identification Centres as recruitment method (section 7.1.1). - List of prespecified concomitant medications added (section 8.7).

				- Clarification that Haematology is required as part of clinical blood sample (section 7.8.1). - Measures required to calculate CHILD Pugh and MELD scores added (sections 3.4 and 7.8.1).
AM04	3.0	27Nov2025	Kayle-Anne Sands	- Exclusion criteria updated to remove 'those being considered for or under assessment for liver transplant'. - Guidance added to section 7.11 regarding study withdrawals.
AM05	3.1	14May2026	Kayle-Anne Sands	-Sponsor contact address updated. -W24 visit removed for participants recruited on or after 16Jun2026.