TRIAL PROTOCOL

HOME-BASED EXERCISE AND MOTIVATIONAL PROGRAMME BEFORE AND AFTER LIVER TRANSPLANTATION: ExaLT Trial

A PHASE IIb, RANDOMISED-CONTROLLED, TWO-CENTRE CLINICAL TRIAL ON THE EFFICACY OF A HOME-BASED EXERCISE AND MOTIVATIONAL PROGRAMME IN PATIENTS BEFORE AND AFTER LIVER TRANSPLANTATION

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: 5.0

Version Date: 01 October 2024

IRAS ID: 295426

Sponsor reference: RG_20-065

ISRCTN 13476586

PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
NS-01	21 Mar 2023	**V3.0**	Non substantial	Sections 10.5 and Section 11 have been amended. REDCap an online database will replace paper Case Report forms [CRFs]. The BCTU will not input the CRF data, as originally outlined, instead Sites will enter data directly into the online database. Expedited SAE reporting will also use the REDCap online database. Sites will till email the ExaLT study Office when a SAE form has been entered into REDCap. Section 14 has been amended to bring in line the wording of the statistical analysis methods to that used in the separate more detailed statistical analysis plan. Finally Sponsor Reference number previously quoted on protocol was incorrect. This has now been amended.
SA-01	2 Jul 2023	**V4.0**	Substantial	**1. Changes to the TSC and research team (other than CIs or PIs).** The critical care/transplant specialist of the TSC has changes from Dr Brian Hogan to Dr Tasneem Pirani. William Mckinnon and Dawn Brant from the BCTU have joined the trial management group. **2. Study design: changes to study design** a) Removal of the heart rate monitors (chest straps) due to not functioning as intended. The change does not affect the validity of the study and the adherence tools (patient diary, wrist watch monitor) are more than adequate to enable us to evaluate adherence to the exercise programme.

				b) The time window for visits 2 has changed from (+/-) 3 days to (+/-) 7 days and for visit 5 from (+/-) 7 days to (+/-) 14 days. A time window of (+/-) 1 week has also been created for telehealth call visits. The changes allow more flexibility for sites when performing these visits, therefore avoiding a significant number of future protocol deviations. c) A section on future planning for future viral pandemics, industrial strike action, terrorist/war threat or severe mitigating circumstances (i.e. prolonged hospital admission unable to attend trial visits for prolonged time) has been added to the protocol. This allows for virtual study visits in these events. d) Mechanistic sub-study: Participants in the mechanistic sub-study who reach visit 6 <u>without</u> LT will be given the option of taking part in an additional sub-study assessment visit where visit 6 has an additional 6-week window (i.e. week 48 <u>+ 28 days</u>). e) Mechanistic sub-study: At QEUHB site only, participants taking part in the sub study will be given the option to consent for a small amount of urine (that would otherwise be wasted) to be stored for potential future research. A Urine sample (20-30ml) will be collected at each sub-study visit. f) Mechanistic sub-study: The order of the specialist biomarkers and muscle ultrasound will take place before the CPET/6MWT to ensure that their results are not impacted by acute/strenuous exertion of these functional tests. In addition, the CPET will take priority and precede the 6MWT (with 30 minutes rest in between tests), since the CPET has

				more rigorous data outputs (i.e. VO2 peak, Anaerobic threshold, ramp gradient, maximal heart rate etc.) g) Fidelity testing: To test the fidelity of the behaviour therapy training throughout the entire ExaLT trial study period, an additional four patient video recordings **per physio** will take place at patient 40 (+/-3) and patient 60 (+/-3) (i.e. a total 8 additional recordings per physio). Visit recordings will be identical to those completed at patient 20 (+/-3). h) Additional information regarding sample tracking and storage has been added to the protocol for clarity. i) A typographical error which recorded a telehealth visit post LT at week 10 and not at the correct time of week 16 post LT has been corrected for clarity in section 7.1. j) The time for the trial physiotherapists to review the participant on the post-LT ward, prior discharge from ICU has been extended from 48 hours to within 72 hours. Also, assessments undertaken on the ward within 48 hours will be extended to within 72 hours.
NS-03	01 Oct 2024	V5.0	Non substantial	a) The 52-week cut off for LT has been amended to allow 52 weeks +2 weeks. b) For visit 1 to visit 6 -bloods to be taken on day of visit, however if some results are missing, results from a NHS visit taken within +/-4 weeks of study visit will be accepted. c) For visit 7 to visit 10 - bloods to be taken on day of visit, however if some results are missing, results from a NHS visit taken within +/-4 weeks of visit will be accepted. d) For L1 visit- due to the ad hoc nature of this visit it is recognised that it may

				not be possible to perform these assessments if out of hours. i. Nutritional/physical/functional (including LFI) ii. DASI Questionnaire iii. Blood tests In cases where bloods are not performed- sites can enter bloods from a previous NHS visit if performed within **4 weeks** of this visit. Post LT bloods are not accepted

Funding and support in kind	
Funder(s)/Supporting Organisations	**Financial and non-financial support given:**
National Institute for Health Research Birmingham's NIHR Biomedical Research Centre (BRC)	Fully funded project grant BRC research nurse support; Equipment (including muscle ultrasound machine) and laboratory support including -80 freezer space.
Funding scheme (if applicable)	NIHR EME Programme
Funder's reference number	129318
The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, Health Education England or the Department of Health. The funder had no role with respect to study design; collection, management, analysis, and interpretation of the data; writing of the report; and the decision to submit the report for publication.	

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the 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 study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	ExaLT Trial
Protocol version number:	Version: 5.0
Protocol version date:	**01/OCT/2024**
CI (Birmingham) name:	Dr Matthew Armstrong
Signature and date:	_____ __ __/ __ __/ __ __ __ __
Co-CI (London) name:	Professor Daniel Martin
Signature and date:	_____ __ __/ __ __/ __ __ __ __

Sponsor statement

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the ExaLT trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the ExaLT trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the 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.

Trial name:	ExaLT
Protocol version number:	Version: 5.0
Protocol version date:	**01/OCT/2024**
PI name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

Reference Numbers	
Sponsor number	RG_20-065
ISRCTN reference number	13476586
Clinicaltrials.gov reference number	
IRAS reference number	295426
Sponsor	
University of Birmingham	Birgit Whitman
Contact Details:	Head of Research Governance and Integrity, Research Strategy and Services Central, Birmingham Research Park, Vincent Drive, University of Birmingham Edgbaston B15 2TT Email: Researchgovernance@contacts.bham.ac.uk
Chief Investigator	
Dr Matthew J Armstrong	Consultant in Liver and Transplant Medicine Liver Unit. Honorary Reader at the University of Birmingham.
Queen Elizabeth University Hospital Birmingham Mindelsohn Way, Birmingham B15 2TH	0121 371 4673 matthew.armstrong@uhb.nhs.uk
Co-Chief Investigator	
Professor Daniel Martin	Professor of Perioperative and Intensive Care Medicine
Peninsula Medical School	daniel.martin@plymouth.ac.uk

Trial office contact details	
Birmingham Clinical Trials Unit (BCTU) Institute of Applied Health Research College of Medical and Dental Sciences Public Health Building University of Birmingham, Birmingham, B15 2TT	T: 0121 415 8445 E: EXALT@trials.bham.ac.uk

Trial Management Group	
University Hospitals Birmingham NHS Foundation Trust	
Dr Matthew Armstrong (Chief Investigator)	Consultant in Liver and Transplant Medicine
University of Plymouth	
Professor Daniel Martin, OBE (Co-Chief Investigator)	Professor of Perioperative and Intensive Care Medicine
University of Birmingham	
Mrs Felicity Williams (Principal-Investigator; Birmingham)	Lead Physiotherapist, NIHR Allied Health Professional Clinical Research Fellow
Professor Joan Duda (Co-Investigator)	Professor of Sport and Exercise Psychology
Dr Sally Fenton (Co-Investigator)	Senior Lecturer in Lifestyle Behaviour Change
Royal Free London NHS Foundation Trust	
Dr Clare Melikian (Principal Investigator, London)	Consultant Anaesthetist, Lead for Hepatobiliary Liver Transplant Anaesthesia
The Royal Marsden NHS Foundation Trust	
Dr Don Milliken (Co-Investigator)	Consultant Anaesthetist in Hepatobiliary Surgery
University of Birmingham – Birmingham Clinical Trials Unit	
Professor Peter Brocklehurst (Co-Investigator)	Professor of Women's Health, Director of Research and Development
Gemma Slinn (Co-Investigator) William Mckinnon	Trials Management Team Leaders
Samir Mehta (Co-Investigator)	Senior Medical Statistician
Yongzhong Sun	Trial Statistician
Dawn Brant	ExaLT Trial Manager
Patient and Public Involvement	
Christian Price (Co-Investigator)	PPI Representative
Karen Rockell (Co-Investigator)	PPI Representative

Trial Steering Committee	
Independent Members	
Professor Denny Levett (Chair)	Professor of Critical Care and Perioperative Medicine
Dr Tasneem Pirani	Consultant in Critical Care and Hepatology
Dr Kate Hallsworth	Senior Research Physiotherapist and NIHR Health Education England Clinical Lecturer
Neil Corrigan	Senior Medical Statistician
Mark Lamond	Patient and public involvement representative
Non-Independent Members	
Dr Matthew Armstrong	Consultant in Liver and Transplant Medicine
Professor Daniel Martin	Professor of Perioperative and Intensive Care Medicine

Data Monitoring Committee	
Dr Ian Rowe (Chair)	Academic Fellow and Honorary Consultant Hepatologist
Professor Steve Wigmore	Professor of Transplantation Surgery
Trish Hepburn	Senior Medical Statistician

ABBREVIATIONS

Abbreviation	Term
6MWT	Six-minute walk test
6MWD	Six-minute walk distance
A1AT	Alpha-1 antitrypsin
AASLD	American Association of the Study of Liver Disease
Ab	Antibody
ACSA	Anatomical cross-sectional surface area
AE	Adverse Event
AHP	Allied healthcare professional
AIH	Autoimmune hepatitis
AKI	Acute kidney injury
ArLD	Alcohol-related liver disease
ALP	Alkaline phosphatase
ALT	Alanine transferase
AST	Aspartate transferase
AUROC	Area Under the Receiver Operating Characteristic Curve
BCTU	Birmingham Clinical Trials Unit
BMI	Body Mass Index
BLTG	British Liver Transplant Group
BP	Blood pressure
BREQ-2	Behavioural Regulation in Exercise Questionaire-2
CCI	Comprehensive complication index
CI	Chief Investigator
CLD	Chronic liver disease
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary Exercise Test
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
CVD	cerebrovascular disease
DASI	Duke Activity Status Index
DBD	Donation after Brainstem Death
DCF	Data Clarification Form
DCD	Donation after Circulatory Death
DMC	Data Monitoring Committee
DOB	Date of birth

ECG	Electrocardiogram
FBC	Full blood count
GCP	Good Clinical Practice
GP	General Practitioner
HAT	Hepatic artery thrombosis
HBEP	Home-based exercise programme
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCCQ	Health Care Climate Questionnaire
HCV	Hepatitis C virus
HGS	Hand grip strength
HR	Heart rate
HRA	Health Research Authority
HRS	Hepato-renal syndrome
ICF	Informed Consent Form
ICU	Intensive care unit
IHD	Ischaemic heart disease
IL	Interleukin
INR	International normalised ratio
ISF	Investigator Site File
ISPACOT	Interpersonal Support in Physical Activity Consultations Observational Tool.
FPFV	First patient first visit
LFI	Liver Frailty Index
LFT	Liver function tests
LOS	Length of stay
LPLV	Last patient last visit
LRTI	Lower respiratory tract infection
LT	Liver transplant
LVP	large volume paracentesis
MAFLD	Metabolic associated fatty liver disease
MAMC	Mid-arm muscle circumference
MCS	Mental component score
MDT	Multi-disciplinary team
MELD	Model for end-stage liver disease
MELD-Na	Model for end-stage liver disease - Sodium
MI	Myocardial infarction
NAFLD	Non-Alcoholic Fatty Liver Disease
NHS	National Health Service
NHSBT	National Health Service Blood and Transfusion

NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OGD	Oesopho-gastro-duodenoscopy
PBC	Primary biliary cirrhosis
PCS	Physical component score
PI	Principal Investigator
PPI	Patient and Public Involvement
PIS	Participant Information Sheet
PNSE	*Basic* Psychological Need Satisfaction in Exercise Scale
PSC	Primary sclerosing cholangitis
QoL	Quality of Life
QEUHB	Queen Elizabeth Hospital, Birmingham
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RIR	Repetitions in reserve
RGT	Research Governance Team
RFH	Royal Free Hospital
RoPE	Rate of perceived exertion
RR	Respiratory rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SaO_2	Oxygen saturation
SBP	Spontaneous bacterial peritonitis
SDT	Self-determination theory
SOP	Standard operating procedure
SPARC	Secreted protein acidic and rich in cysteine
TFTs	Thyroid function tests
TIA	Transient ischaemic accident
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
U&E	Urea, creatinine and electrolytes
UKELD	United Kingdom model for End-stage Liver Disease
UK	United Kingdom
UoB	University of Birmingham
UTI	Urinary tract infection

TRIAL SUMMARY

Title

ExaLT: Home-based EXercise and motivAtional programme before and after Liver Transplantation.

Objectives

The primary aim is to investigate whether a remotely monitored 'home-based exercise and theory-based motivation support programme' delivered by physiotherapists before and after liver transplantation (LT) (intervention group) improves quality of life (QoL; physical component score of SF-36v2) in LT recipients compared to a control group using a patient 'exercise' advice leaflet (control group).

The secondary aims are to investigate whether a remotely monitored 'home-based exercise and theory-based motivation support programme' delivered before and after LT (experimental arm) improves:

- Surgical complication after LT (comprehensive complication index (CCI))
- Mental wellbeing/health (mental component score (MCS) of SF-36v2 health-related QoL)
- Clinical markers of physical frailty and fitness (liver frailty index [LFI] ; Duke activity status index [DASI])
- Pre-LT: morbidity (United Kingdom model for end-stage liver disease (UKELD), model for end-stage liver disease – sodium (MELD-Na), hospital admissions) and mortality
- Post-LT: length of intensive care unit (ICU)/hospital stay, hospital re-admissions and mortality (30, 90, 180 day, 1 year)
- Habitual physical activity levels (daily time spent in light, moderate and vigorous intensity physical activity)
- The frequency, intensity and duration of exercise ('dose') completed
- Adherence to home-based exercise programme (HBEP) (*intervention arm only*)
- Perceptions of the health care climate (how need supportive/empowering the physio is)
- Basic psychological need satisfaction (i.e. feelings of autonomy, relatedness, competence)
- Self-determined motivation to exercise

The mechanistic objectives are to investigate:

1. What is the dose-dependent effect of the HBEP on physical fitness, muscle biology (including oxidative stress and inflammation) and their association with QoL?
2. How does the theory-based motivation support affect adherence and engagement with the HBEP?

Trial design

A phase 2b, open-label, two-centre randomised controlled clinical trial (RCT), with 1:1 individual participant randomisation.

Participant population and sample size

Adult patients (aged 18 years and over) who are awaiting a cadaveric, primary LT. Sample size = 266 patients (133 patients in each arm).

Setting

The ExaLT Trial will be based at the LT units of the Queen Elizabeth University Hospital, Birmingham (QEUHB) and the Royal Free Hospital, London (RFH).

Eligibility criteria

Inclusion criteria

- Adult patients (aged 18 years and over)
- Awaiting a cadaveric, primary LT at two LT centres: QEUHB and RFH.
- Being an out-patient at the time of baseline trial visit (consent)

Exclusion criteria

- Patients awaiting super-urgent LT, multi-organ transplantation, live-related donor LT, regraft LT
- Inability to safely comply with the exercise intervention due to:
    - severe hepatic encephalopathy
    - oxygen-dependent hepato-pulmonary syndrome
- Patients without liver failure including:
    - liver cancer in the absence of cirrhosis
    - polycystic liver disease
    - rare metabolic/genetic conditions.
- Patient refuses or lacks capacity to give informed consent to participate in the trial, at the point of study visit 1 (baseline)[1]

Interventions

Eligible participants will be randomised 1:1 to receive either:

Group 1: Intervention group. Remotely-monitored home-based exercise and theory-based motivation support programme whilst on the LT waiting list (max. 12 months) through to 24 weeks post-LT.

Group 2: Control group. Patient exercise advice leaflet before and after LT.

The interventions will be delivered to the participants in two phases: phase 1 pre-LT (maximum 52weeks) and phase 2 post-LT (24 weeks). The study intervention will be of variable duration pre-LT, due to the unpredictable nature of the timing of LT (median waiting time 72 days (95% CI 64-80) registered between 2018-2021). All patients that are transplanted within 52 weeks (+ 2 weeks) of randomisation will receive a fixed 24 week intervention after LT. Group 1 and 2 will contain approximately the same proportion of age groups, disease severity (UKELD), gender, trial site and participation rates in the 'muscle sub-study' as a result of minimisation.

[1] During the course of the trial, some participants may lose capacity because of complications of their liver condition(s), for example hepatic encephalopathy.

Outcome measures

The primary outcome measure is the physical component score (PCS) from the short form-36 version 2.0 (SF-36v2) health-related QoL questionnaire at 24 weeks post LT.

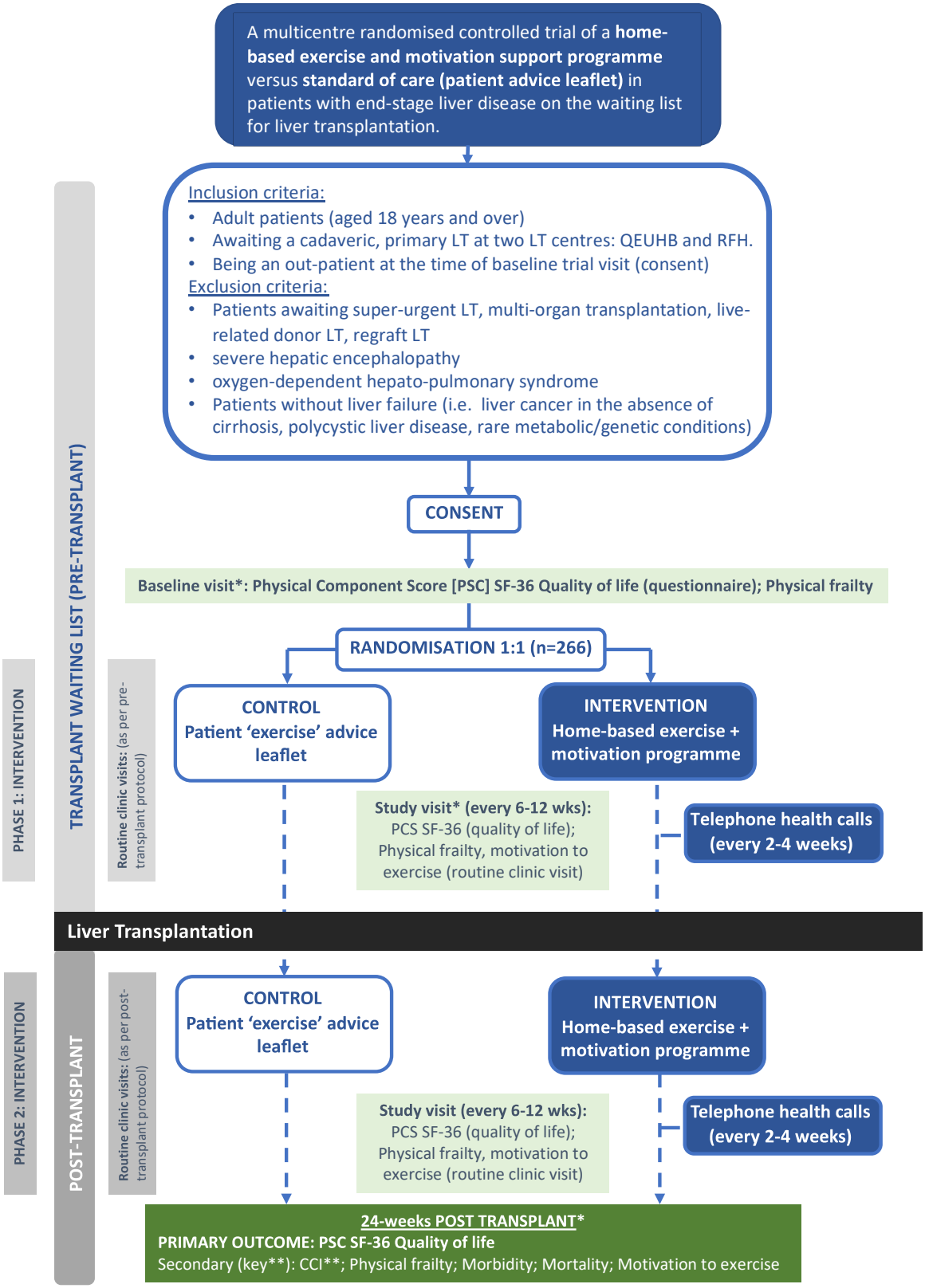
The 'key' secondary outcome measure is the CCI at 24 weeks post LT.

The other secondary outcome measures to be assessed at 24 weeks post LT (**unless stated*) include:

- MCS score of SF-36v2 health-related QoL questionnaire
- Liver Frailty Index (LFI), Duke Activity Score Index (DASI)
- Pre-LT morbidity (UKELD, MELD-Na, hospital admissions) and mortality (**assessed up to day of LT*)
- Post-LT length of ICU/hospital stay and hospital re-admissions (frequency, duration [days])
- Post-LT 30, 90, 180 and 365 day mortality
- Habitual physical activity levels (daily time spent in light, moderate and vigorous intensity physical activity)
- "Dose" of exercise completed (measure of the frequency, intensity and duration of exercise)
- Adherence to HBEP (*intervention arm only*)
- Perceptions of the health care climate (how need supportive/empowering the physiotherapist is)
- Basic psychological need satisfaction (i.e. feelings of autonomy, relatedness, competence)
- Self-determined motivation to exercise

TRIAL SCHEMA

ExaLT trial: study design



* At baseline, at 6-weeks (pre-transplant) and 24-weeks after transplant (mechanistic 'muscle' sub-study; n=100; optional): Cardiopulmonary exercise tests, muscle ultrasound and biomarkers. Key: CCI, Comprehensive complications index; PCS, Physical Component Score

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1. Background

Liver disease, the third commonest cause of death in the UK, predominantly kills between the ages of 18 and 65. This leads to the loss of 62,000 years of working life each year in the UK. Liver transplantation (LT) remains the only curative treatment for patients with liver failure and the number of transplantations in the UK has risen over the past seven years by 50% to 1014/year.(1) LT is a highly resource intensive procedure requiring a large investment of healthcare resources. The average cost per procedure is estimated at over £1.1m, which includes pre-LT work-up, surgery, perioperative care, and an estimated seven year postoperative follow-up.(2) Complications whilst on the waiting list and in the perioperative period contribute substantially to this cost, and their likelihood is increased markedly by the presence of physical frailty.(3-5)

Despite a new organ allocation system and advances in clinical management, 5-7% of patients on the waiting list die before LT, largely as a result of disease severity and physical frailty.(6) LT exerts a phenomenal physiological and psychological stress on recipients who are frail as a result of long-standing liver failure. As a consequence, a further 5% of patients die within 6 months after LT.(6) Among those who survive, readmission rates are around 50% and perioperative complications can lead to prolonged hospital stays and long-term disability.(4, 5, 7) Ultimately, this results in a reduced long-term quality of life (QoL) and delayed/reduced return to productive employment after LT.(8, 9) End-stage liver disease triggers complex pathological changes in skeletal muscle, leading to sarcopenia characterised by low muscle mass and function.(10) Along with poor nutrition and physical inactivity and their close causative relationships, sarcopenia contributes to a high prevalence (70%) of physical frailty.(11) In turn, frailty is associated with poor clinical outcomes, including increased hospitalisation and intensive care unit (ICU) utilisation, (12-14) a 50% risk of severe postoperative complications(15) and a two-fold increase in pre- and post-LT mortality.(3, 16, 17) Frailty both before and after LT is associated with poor psychological and physical health-related QoL,(18-20) which is itself an independent predictor of mortality.(21) QoL post-LT significantly lags behind that of the general population (22) and although the majority are under 65 years old, fewer than 50% return to employment, which is largely attributed to prolonged disability/frailty.(9)

1.2. Trial rationale

Exercise interventions have been shown to be effective in other fields of medicine including prior to elective major surgery. However, due to the life-threatening, multi-systemic effects of end-stage liver disease, patients awaiting LT are often perceived as ‘too sick’ to exercise by healthcare professionals and the patient/carers themselves (PPI/Expert observations); with virtually no published data to support the benefits and safety of exercise in this cohort. Effective exercise interventions that reduce frailty pre- and post-LT have the potential to improve clinical outcomes and long-term QoL for this patient group, leading to cost savings for the NHS. Furthermore, a better understanding of how exercise works (i.e. on the muscular and cardiopulmonary systems) and how it can be effectively delivered (i.e. motivational approach adopted) in this unique cohort, will guide future exercise prescriptions (‘type’, ‘dose’, ‘duration’, ‘motivational strategies’) that are required to maximise the efficiency and longevity of this life-changing surgery. In an environment of substantial NHS resource

limitation, identifying simple, cost-effective and remotely monitored home-based interventions should be a priority in those patients who may benefit the most.

1.2.1. Justification for participant population

For those patients awaiting LT, the benefits of exercise are unknown as traditionally they have been viewed as 'too sick' to exercise. Healthcare professionals and research teams have therefore been reluctant to use exercise as a 'medicine' in this group. What underlies this myth is that due to their underlying liver disease these patients are frequently deconditioned with substantial functional impairment,(23) which tends to be proportional to the severity of disease.(24) End-stage liver disease is a multi-system disorder leading to physical frailty (muscle wasting, weakness, poor functional status, dependence of activities of daily living), cirrhotic cardiomyopathy, malnutrition, ascites, encephalopathy, anaemia and impaired pulmonary gas exchange, all of which limit a patient's ability to exercise. Indeed, patients awaiting LT are some of the sickest and frailest patients in the NHS, to the extent that a 57 year old end-stage liver patient has the predicted physical frailty of >80 year old in the community.(25) Furthermore, there is an innate fear and anxiety (which has been confirmed by our patient feedback workshops) that exercise may actually exacerbate the complications of cirrhosis, thereby worsening a patient's quality of life (QoL) and potentially even preventing them from being eligible for LT. These factors make patients with end-stage liver disease awaiting LT a unique cohort of patients in whom virtually no data exist to support the benefits and safety of exercise (p)rehabilitation. It cannot be assumed that because a preoperative exercise programme improves aerobic capacity in relatively well patients awaiting colorectal/cancer surgery that the same is true for patients with a life-threatening multi-system disease such as cirrhosis. When a patient with end-stage liver disease requires any surgery other than LT, it is highly likely that they would present 'too' high a risk (of postoperative morbidity and mortality) to be operated on. Thus, there is pressing need for detailed studies to answer efficacy and mechanistic questions unique to this patient population that cannot be addressed by simply transferring findings from other conditions.

In order to optimise outcomes from LT these frail patients must survive their illness for an undefined period on the waiting list and then be in the best condition to survive one of the most physiologically and mentally challenging operations in the NHS. There is a theoretical case for the use of exercise therapy to improve outcomes in this cohort but this needs to be tested by rigorous clinical studies that are currently lacking.

The physical hurdles to exercise in liver failure are apparent, however, the psycho-behavioural hurdles are also poorly understood. Little is known about the motivation to engage and adhere to exercise in all chronic medical conditions and such knowledge is crucial in achieving benefits of exercise. Common psychological barriers to exercise in patients with chronic disease, include low self-efficacy (competence) and a lack of individualised support. Both of these factors contribute to low motivation to engage and adhere to exercise, and are amplified in patients awaiting LT due to patient and healthcare professional fear of causing harm. To promote optimal behaviour changes towards exercise adoption, NICE recommends that interventions target recognised determinants of behaviour (such as motivation) and are theoretically grounded.(26) An example of such a theoretical approach is self-determination theory (SDT), which centres on the determinants and positive consequences linked to

autonomous motivation for exercise. SDT has been successfully applied by our research group in patients with chronic arthritis.(27) To date, the efficacy and mode of action of theory-based behaviour change/motivational interventions have not been tested in patients with end-stage liver disease awaiting and/or recovering from LT. Furthermore, training selective members of the pre-existing NHS workforce (i.e. surgery physiotherapists) to deliver the exercise intervention in a more motivationally adaptive manner can be an evolving cost-effective approach and unique to patients awaiting major surgery and/or with severe liver disease.

1.2.2. Justification for design

The ExaLT study is a phase 2b open-label two-centre randomised controlled trial (RCT) of 266 patients with end-stage liver disease evaluating the effectiveness of a unique remotely monitored pre- and post-LT programme of home-based exercise and theory-based motivation support in improving QoL post-LT. Delivering an effective home-based exercise programme that can be monitored and objectively evaluated is essential to patients with end-stage liver disease. Ensuring optimal uptake and adherence to such programmes is critical to realise meaningful improvements in health and wellbeing. The ExaLT trial intervention is designed to promote higher quality of motivation for exercise (i.e., more autonomously motivated), leading to sustained engagement with the home-based exercise program and exercise in general.

To the best of our knowledge there are no other RCTs investigating the combined effect of exercise and targeted behavioural change/motivational strategies before or after LT. Currently an American team are recruiting 500 patients, either pre-LT or post-LT at baseline, to a trial of low-level resistance exercise via a DVD versus standard advice from their physician in clinic, on physical frailty using the liver frailty index (clinicaltrials.gov NCT02367092). The ExaLT study, however, is unique in that it follows the patient through the whole LT journey (pre-LT to post-LT) and assesses key patient-reported outcomes (i.e. physical and mental components of quality of life). In contrast to the American study, it incorporates an individualised resistance and aerobic exercise programme, physiotherapy-led training/monitoring, analysis of the effects of exercise on muscle physiology, and detailed assessment of the theory-based motivation programme and its impact on adherence and engagement with exercise. In addition, there are no directly competing trials regarding lifestyle/exercise/behaviour interventions in patients pre- and post-LT in the recruiting LT units. There are a growing number of interventional trials in LT, most notably donor organ optimisation with machine perfusion techniques (i.e. the Hope trial, NAPLES study). However, we do not feel that co-enrolment will influence the results of the ExaLT trial and most importantly, the use of machine perfusion will be captured in the trial database, as will other donor factors (age, type of organ, cold ischaemic time, intra-operative complications etc.).

Currently in the UK, there is a lack of standardisation for exercise/physical advice across the 6 LT units; confirmed by a national LT audit we carried out in 2018 on behalf of British Liver Transplant Group (BLTG). The national audit highlighted that clinical guidance regarding physical activity can vary between exercise advice leaflets, verbal encouragement to keep active from clinicians and, at most units, no advice at all. Whilst provision of an exercise advice leaflet is not standard of care for all clinicians, advice about exercise is recognised as “best practice” by the NHS. Consequently, increased

emphasis is now being placed on the importance of communicating the benefits of exercise to patients (e.g., "Moving Medicine" – Public Health England and Faculty of Sport and Exercise Medicine). In order to standardise care for the control group across the two ExaLT trial sites (Queen Elizabeth University Hospitals Birmingham [QEUHB] and Royal Free Hospital London [RFH]) and minimise any potential variation in advice, a specifically formed 'generic' patient information exercise leaflet will be utilised for the control arm at both the QEUHB and RFH transplant centres.

Eligible participants will be individually randomised in a 1:1 ratio to receive either remotely-monitored home-based exercise and theory-based motivation support programme (intervention arm) OR a standardised patient exercise advice leaflet (control arm) whilst on the LT waiting list (max. 52 weeks + 2 weeks*) through to 24 weeks post-LT. Randomisation will be performed using minimisation method with minimisation variables age (≤55 years, >55 years), gender (male, female) and disease severity (UKELD ≤54, >54), trial site (QEUHB, RFH), as they are potential confounding factors. We will also include 'consent for the muscle sub-study' (Yes, No) as a minimisation variable in order to ensure equal representation of participants in the intervention arm (Group 1) and control arm (Group 2) .

*Participants transplanted after 52 weeks can continue on study if they are transplanted within 14 days of this date.

The efficacy of the home-based exercise and theory-based motivation support programme on QoL (primary end-point of the trial) will be assessed at 24 weeks post-LT. At this time-point, investigators will also be able to assess and report the safety and effects of the exercise/motivation intervention on clinical measures, including physical frailty/fitness and post-LT surgical complications, length of ICU/hospital stay and 30, 90 and 180 day mortality.

1.2.3. Justification for choice of intervention(s)

In 2014 the American Society for Transplantation set out a research agenda for exercise interventions in patients awaiting solid-organ transplantation.(28) Despite the higher numbers of LT, as compared to heart and lung, the application of exercise training in this population is virtually non-existent.

We carried out a literature review (29) to summarise the impact of physical exercise in patients with chronic liver disease through to LT. The majority of studies were small (1-50 patients), focused on supervised, hospital-based aerobic exercise interventions (but not resistance exercises) and largely excluded patients with significant liver failure needing LT.(30-32) Our work in this field has demonstrated that a supervised regimen of outpatient hospital-based exercise training sessions over 6 weeks is both feasible and beneficial to patients awaiting LT (n=9).(33) However, this model is neither scalable nor cost effective because each LT unit cares for patients over a large geographic area and for many patients the time and cost required to travel to their LT centre several times each week is prohibitive.(33-35)

Seven non-UK studies (4 RCTs; 3 observational studies) have demonstrated that supervised aerobic exercise after LT improves aerobic capacity, muscle mass/strength and in two studies, trends towards improved QoL.(36, 37) These small, heterogenous studies suggest that combined aerobic and

resistance-exercises yield the most promising improvements, but adherence is challenging. We carried out a proof-of-concept pilot study of a novel home-based exercise programme in patients awaiting LT.(38, 39) 18 patients underwent 12 weeks of resistance and aerobic exercises, with weekly telephone health calls. The intervention was safe and showed trends towards improved physical frailty and QoL in patients on the LT waiting list.

There are clear advantages to home-based exercise programmes (40, 41), including increased flexibility and reduced travel burdens for patients, but it is essential that we focus on patients' motivation to engage and psycho-behavioural barriers to exercise in order to optimise such interventions delivered at home. The need for behaviour change/motivational interventions has been repeatedly emphasised by our LT patient and public involvement (PPI) groups. Despite this, no studies to date have combined exercise with motivational interventions to increase intervention adherence. Understanding the social psychological processes through which motivational intervention influences patients to adopt and sustain positive changes in home-based exercise behaviour will guide larger studies of efficacy and cost effectiveness in this field. This is a key component to ensuring the long-term success of home-based tailored-made exercise interventions outside of the secure, supervised hospital environment.

1.2.4. Justification of choice of primary outcome

The SF-36v2 (which incorporates the physical component score [PCS]), is a validated, robust, reproducible patient-reported outcomes tool for assessing QoL before and after medical/surgical interventions. It is the most widely cited QoL assessment tool in the published literature for solid-organ transplantation and chronic liver disease.(9, 21, 36, 37, 42-44) The liver and transplant PPI groups (including disease support groups, National Health Service Blood and Transplant [NHSBT]) and the patient co-applicants strongly felt that the SF36v2 PCS QoL score captures the whole transplant experience from being on the transplant waiting list through to the LT and the recovery 24 weeks afterwards. The SF-36v2 PCS has been shown to strongly correlate with physical frailty, poor functional status and complications in patients undergoing LT.(9, 21) Fundamentally to the patients, their families and caregivers, QoL is the most important outcome to them in life (i.e. in their words 'there is no point prolonging life with transplantation, if your quality of life is not worth living for afterwards'). The vast majority of patients undergoing LT are of working employment age with young families. If, however, they fail to recover their functional independence and physical activity levels post-transplant (only 2 out of 5 are deemed robust 1-year post liver transplant (45)), it has deleterious effects on their self-motivation, mental/physical health, ability to work, finances and family commitments.

The SF-36 questionnaire includes 36 questions composed of 8 multi-item scales, which reflect the impact of health problems on both the physical and mental condition of the patient. A greater score reflects better QoL. Two summary sub-scores can be calculated which are weighted combinations of the eight scales, one to reflect the impact on physical function (PCS) and one to reflect the impact on psychological function mental component score (MCS).(21) A low PCS, rather than MCS, of SF-36v2 has been associated with low survival, employment and functional status in our patient population.(9, 21) Overall, we felt that the PCS was the best outcome measure in the evaluation of experimental interventions targeting physical frailty, functional status and health wellbeing in our patient

population. We also deemed an RCT powered to detect survival differences at 6-12 months post-LT as the primary end-point would not have been feasible (based on huge sample size, cost), as survival rates are consistently >90%.

2. AIMS AND OBJECTIVES

2.1. Primary Aim:

The primary aim of the study is to investigate whether a remotely monitored 'home-based exercise and theory-based motivation support programme' delivered by physiotherapists before and after LT improves the QoL of LT recipients.

2.2. Secondary Aims:

The secondary aims are to investigate whether a remotely monitored 'home-based exercise and theory-based motivation support programme' delivered by physiotherapists before and after LT improves:

- Surgical complications (comprehensive complication index [CCI])
- Mental wellbeing/health (Mental component score [MCS])
- Physical frailty and fitness (Liver Frailty Index [LFI] / Duke Activity Status Index [DASI])
- Pre-LT morbidity (United Kingdom model for End-stage Liver Disease [UKELD], Model for end-stage liver disease sodium [MELD-Na], Hospital Admission) and mortality
- Post-LT length of ICU/hospital stay, hospital re-admissions and mortality (30,90,180 and 365 days)
- Habitual physical activity levels (Daily time spent in light, moderate and vigorous intensity physical activity)
- The frequency, intensity and duration of exercise ('dose') undertaken
- Adherence to HBEP (*Group 1: intervention arm only*)
- Perceptions of the health care climate (how need supportive/empowering the physio is)
- Basic psychological need satisfaction (i.e. feelings of autonomy, relatedness, competence)
- Self-determined motivation to exercise

2.3. Study objectives:

The main objectives are to conduct a two-centre clinical trial in which 266 patients on the LT waiting list will be randomised to either a) pre- and post-LT remotely monitored 'home-based exercise and theory-based motivation support programme' delivered by physiotherapists (experimental arm, n=133) or b) a standardised patient advice leaflet (control arm, n=133) in order:

1. To determine the effect of the exercise/motivation programme on the QoL of LT recipients using the SF-36v2 health-related QoL questionnaire.
2. To determine the effect of the exercise/motivation programme on physical frailty and fitness of LT recipients using LFI and DASI.
3. To determine the effect of exercise/motivation programme on the morbidity and mortality of LT recipients by recording changes in:

   a. Pre-LT: UKELD, MELD-Na, hospital admissions, deaths.
   b. Post-LT: Post-LT length of hospital/ICU stay, re-admissions, surgical complications and deaths.
4. To measure the habitual levels of physical activity both before and after LT, using a 'blinded' electronic wrist worn accelerometer and assess the impact of the exercise/motivation programme on levels of physical activity.
5. To assess the 'dose' of exercise (frequency, intensity and duration) achieved with the exercise/motivation programme using 'blinded' electronic wrist worn accelerometer.
6. To assess adherence to the exercise programme/advice using a self-reported exercise diary and 'blinded' electronic wrist worn accelerometer.
7. To investigate how the theory-based motivation support provided by the physiotherapists, affects the patients: a) motivation to exercise; b) feelings of autonomy, relatedness, competence; and c) adherence to the home-based exercise programme using three psychological questionnaires:
   a. Health Care Climate Questionnaire (HCCQ);
   b. Basic psychological need satisfaction in exercise scale (PNSE);
   c. Behavioural Regulation in Exercise Questionaire-2 (BREQ-2)
8. Mechanistic 'Muscle' Sub-study (n= 100): To investigate the dose-dependent effect of the exercise programme on cardiopulmonary fitness (Cardiopulmonary Exercise Test [CPET]; 6-minute walk test (6MWT)), muscle biology (muscle ultrasound, biomarkers) and their association with QoL

3. TRIAL DESIGN AND SETTING

3.1. Trial design

ExaLT is a phase 2b, open-label, two-centre RCT to assess the efficacy of a home-based exercise and motivational programme in patients before and after LT.

The study will consist of 4 stages:

Stage		Time
1	Pre-screening/identification, enrolment, randomisation and baseline investigations	1-2 weeks
2	Pre-LT waiting list study intervention up to the day of LT (from visit 1 to 6 or LT)	1 –52weeks (variable)
3	Post-LT study intervention for 24 weeks (visits 7 to 9)	24 weeks (fixed) End of Intervention; primary endpoint
4	Follow-up assessment (visit 10)	24 weeks after End of intervention (i.e. 48 weeks post-LT)

Due to the unpredictable nature of the timing of LT, the duration of the study intervention ranges from a minimum of 25 weeks (1-week pre-LT; 24 weeks post-LT) to a maximum of 76 weeks (52 weeks pre-LT; 24 weeks post-LT). The maximum duration of the trial for an individual participant, including screening, intervention and the follow up visit will be approximately 2 years (100 weeks). In the event that a participant is not transplanted after 52 weeks, the study exercise regimen they were randomised to will be terminated. However, with the participant's ongoing willingness to continue in the study, their data will be collected until the trial end date (see section 7.6.3 and section 9.3.5).

Eligible participants will be randomly assigned to one of two groups:

- Group 1: Intervention group. Remotely-monitored home-based exercise and theory-based motivation support programme delivered by the physiotherapists (max. 52 weeks) through to 24 weeks post-LT.
- Group 2: Control group. Patient 'exercise' advice leaflet before and after LT.

The different levels of exercise support described above will be delivered to the participants in two phases: phase 1 pre-LT (maximum 52 weeks (+ 2 weeks)) and phase 2 post-LT (24 weeks). All patients that are transplanted within 52 weeks (+ 2 weeks) of randomisation will receive a fixed 24 weeks (~6 months) of the assigned exercise support after LT. Group 1 and 2 will contain approximately the same proportion of age groups, disease severity (UKELD), gender, trial site and 'muscle' sub-study as a result of minimisation.

3.2. Trial setting

The trial will take place across two NHS LT centres in England, namely QEUHB and RFH.

3.3. Mechanistic 'muscle' sub-study (n=100)

The main aim of the optional 'muscle' sub-study is to undertake a detailed evaluation of the biological and physiological mechanisms that may underlie any exercised-induced improvements in clinical outcomes, including QoL and physical function/frailty. A better understanding of how exercise works (i.e. on the muscular and cardiopulmonary systems) will guide future studies in terms of exercise dose-response ('frequency', 'intensity', 'duration') that are required in patients with end-stage liver disease to maximise the efficiency and longevity of LT. The sub-study will aim to recruit 100 participants (approx. 50 in each study arm) and will take place at three time-points: pre-LT visit 1 (baseline, week 0), pre-LT visit 2 (week 6), and at the post-LT visit 9 (24 weeks post-LT; end of intervention). In the event that a participant is not transplanted by visit 6 (pre-LT phase 1) of the study intervention, with the participant's ongoing willingness to continue in the study, they will be given the option of a final sub-study visit (visit 6 [+ 6 week window]; inclusive of CPET, muscle ultrasound, 6MWT) and their data will be collected until the trial end date (see section 7.6.3 and section 9.3.5). See **Section 15.0** for more information of the 'muscle' sub-study.

3.4. Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) SOPs, this trial has been risk assessed to clarify any risks relating uniquely to the ExaLT trial beyond that associated with usual care. A risk assessment has been conducted and concluded that this trial is low risk. An ongoing evaluation of risk will continue throughout the trial.

4. ELIGIBILITY

4.1. Inclusion criteria

To be eligible to participate in the ExaLT Trial, patients must meet all of the following inclusion criteria:

- Adult patients (aged 18 years or over)
- Patients listed for a cadaveric, primary LT at QEUHB or the RFH
- Being an out-patient at the time of baseline trial visit (consent)

4.2. Exclusion criteria

If any of the following apply, the patient will not be eligible to be recruited into the ExaLT Trial:

- Patients listed for LT for any of the following reasons:
    - super-urgent LT (according to the Kings College criteria)
    - multi-organ transplantation (e.g. combined liver and kidney transplant)
    - live-related donor LT
    - re-graft LT
- Patients with an inability to safely comply with the exercise intervention due to:
    - severe hepatic encephalopathy (grade 3 or 4; or as judged by the clinical investigators)
    - oxygen-dependent hepato-pulmonary syndrome
- Patients *without* liver failure, including:
    - liver cancer in the absence of cirrhosis
    - polycystic liver disease
    - rare metabolic/genetic conditions (e.g. glycogen storage disorders)
- Refusal or lacks capacity to give informed consent to participate in the trial, at the point of study visit 1 (baseline)[2]

[2] During the course of the trial, some participants may lose capacity because of complications of their liver condition(s), for example hepatic encephalopathy.

4.3. Eligibility for mechanistic 'muscle' sub-study (n=100)

To be eligible to participate in the 'muscle' sub-study, patients must meet all of the above eligibility criteria (**section 4.1/4.2**), consent for the main ExaLT trial and provide additional written consent for the sub-study.

4.4. Co-enrolment

The Trial Management Group (TMG) will consider requests for co-enrolment into other trials (e.g. donor graft machine perfusion studies) in accordance with best practice recommendations. Prior to co-enrolment being sanctioned, the following will be reviewed: study design and statistical considerations; legal and ethical considerations; biological and scientific rationale; patient considerations and logistical and organisational issues. For co-enrolment to occur, an agreement will be reached between the respective trials team prior to the patient being considered for inclusion. A log of all patients co-enrolled will be maintained by the ExaLT Trial Office.

5. RECRUITMENT AND CONSENT

It is the responsibility of the Principal Investigator [PI] (or designee as documented on the signature and delegation log) to obtain written informed consent for each participant prior to performing any trial related procedures. The PI can delegate this task to other members of the local research team if local practice allows and this responsibility has been documented in the site signature and delegation log.

Potential participants will be identified as described in section 6.1, a member of the patient's healthcare team (i.e. liver transplant coordinator) who is independent of the study/research team will inform them of the study to gauge interest in participation.

If the potential participant is interested in taking part and agree to be approached by a member of the research team, a participant information sheet (PIS) will be provided to them. The PI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the participant. They will also explain that participation is voluntary and that the participant is free to decide to take part and may withdraw from the trial at any time. The participant will be given more than 24 hours to read the PIS information and discuss potential participation with friends and family (in particular a personal consultee), prior to providing consent for the trial. The participant will be given the opportunity to ask questions before signing and dating the latest version of the informed consent form (ICF). If the participant then expresses an interest in participating in the trial, they will be asked to sign and date the latest version of the ICF.

The PI or delegate will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes and the original placed in the investigator site file (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF

maintained in the ISF. In addition, the participant understands and acknowledges that, a copy of the signed ICF will be transferred to the trial team at BCTU for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started. The same process and documentation of consent will be undertaken for participation in the mechanistic 'muscle' sub-study.

It is recognised that some participants may, during the course of the trial, lose capacity because of complications that may occur due to their pre-existing liver condition(s), for example, worsening hepatic encephalopathy. In this situation, the local research team will seek advice from a personal and/or nominated consultee (as per the Mental Capacity Act 2005) as to whether the participant would wish to continue participating in the trial.

A personal consultee can be defined as someone who is:

- Engaged in caring for the participant (not professionally or for payment) or is interested in his/her welfare, and
- Is prepared to be consulted

For the reason that family and/or social support (i.e. established friend) is a fundamental requirement during out-patient assessment for elective LT, it is extremely rare that a personal consultee cannot be found in this setting. To aid in this process, during the informed consent discussion with the participant, we will ask them to identify someone (who fulfils the above criteria), who would be willing to act as a 'personal consultee.' However, in the event a personal consultee cannot be identified, there will be the option to seek advice from a 'nominated consultee.'

A 'nominated consultee' is defined as someone who

- Has no connection with the trial
- Is willing to be consulted

This can include healthcare workers (i.e. medical consultant, paid carer).

If the personal consultee becomes unavailable during the study, or is no longer willing to undertake the role, the local research team should take steps to identify another personal consultee to take on the role. If no other appropriate person can be identified, a nominated consultee should be approached.

Where it is necessary to seek the advice of a consultee, the PI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to them. They will also explain that participation is voluntary and that they may advise that the participant be withdrawn from the trial at any time. The consultee will be given sufficient time to read the personal consultee information sheet. The consultee will be given the opportunity to ask questions before signing and dating the latest version of the consultee

declaration form. The PI or delegate will then sign and date the consultee declaration form. A copy of the consultee declaration form will be given to the consultee, a copy will be filed in the medical notes and the original placed in the ISF. In addition, the consultee understands and acknowledges that, a copy of the signed consultee declaration form will be transferred to the ExaLT Trial Office at BCTU for review.

At each visit, the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Where the participant lacks capacity, advice will be sought from a consultee as described above. Throughout the trial, the participant (or their consultee) will have the opportunity to ask questions about the trial. Should the participant regain capacity, their wishes will supersede those of the consultee.

Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants (or their consultee) will be given time to consider and if happy to continue they will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the ExaLT Trial Office. The research site is required to present the documents on headed paper of the local institution.

6. ENROLMENT, RANDOMISATION and BLINDING

Potential trial participants will be recruited from the LT services at the supra-regional LT units in QEUHB and RFH. As part of the patients consent for liver transplant (which takes place before they go on the transplant waiting list), patients are also consented to be approached for future research studies.

6.1. Participant Identification and pre-screening:

Patients who are potentially eligible for the trial (**Section 4.0 eligibility criteria**) will be identified by the multidisciplinary team (MDT): a team of healthcare professionals (e.g. Hepatologist, Transplant Coordinator, Anaesthetist, Nurses, Allied Health Professionals [AHPs]) who are directly involved in the patient's routine clinical NHS care – using the following:

- LT waiting list:
    - all patients 'active' on the UK LT waiting list are registered with NHSBT and recorded in a 'live' national database.
    - healthcare professionals (QEUHB and RFH) directly involved with the patients care on the LT waiting list have access to the NHSBT LT registry and their units LT waiting list database (on secure, password protected NHS computers).
    - in addition, both QEUHB and RFH have dedicated LT waiting MDT clinics, which are led by MJA (ExaLT CI) and CM (ExaLT PI RFH), respectively. In these weekly clinics, in which patients on the LT waiting list are under close follow-up, potential participants

will have the trial explained with oral and written information. At this stage the potential trial patient will have the opportunity to ask questions.
    - at the start of the trial, all eligible patients on the LT waiting list at QEUHB and RFH will receive an invite letter (in the post or in person) sent to them by the liver transplant coordinators who are independent of the study, which will include a brief overview of the trial and the contact details of the trials team if they would like to receive further information about the trial (i.e. PIS to be posted out).
- Out-patient LT assessment:
    - in total, QEUHB and RFLH undertake 500-600 LT assessments per year
    - during the out-patient LT assessment, patients and their next of kin [NoK]/friend (personal consultee) undergo oral, written and visual education regarding LT (i.e. waiting list, LT, risks, medications, aftercare, research opportunities etc.). An overview of the ExaLT trial will be incorporated into the assessment process.
- Trial information will also be available in the following formats and accessible to patients/public via the BCTU website:
    - ExaLT trial webpage (link to PIS, overview of study, eligibility, trial team contacts, frequently asked questions)
    - ExaLT trial leaflet (i.e. pamphlet) will be available in the LT waiting list and assessment outpatient clinics.
    - potential trial participants will then be able to approach the trial teams for further information (i.e. PIS), if they have not already received it via the above.

All identified potential trial participants who declare an interest to learn more about the trial after receiving the invite letter, will either be given the PIS:

- in person at either the liver transplant assessment or in their dedicated liver transplant waiting list clinic/specialist liver clinic (i.e. Primary sclerosing cholangitis [PSC], Hepatocellular Carcinoma [HCC])
  and/or
- via post, especially in light of the emergence of telephone/virtual video clinics (as a result of the COVID pandemic)
- after receiving the PIS the potential participant will require greater than 24 hours to read the PIS information and discuss potential participation with friends and family (in particular a personal consultee), prior to providing consent for the trial.

Details of all patients approached about the trial will be recorded on the ExaLT participant screening/enrolment log which will be kept in the ISF and should be available to be sent to the ExaLT Trial Office upon request.

If the potential trial participant provisionally agrees to enrol in the trial, after reading the PIS information and discussing their potential participation with friends and family (in particular a 'personal consultee'), **a baseline trial visit (visit 1) will be arranged**.

6.2. Enrolment (Trial Entry)

Enrolment to the ExaLT trial (+/- the 'muscle' sub-study) will take place at the baseline trial visit (**Visit 1**). The study team will aim to coincide Visit 1 with the patient's next LT waiting list clinic appointment, to avoid the additional burden of travelling to the LT unit. If this is not possible, the next available date (Monday to Friday) will be arranged.

Consent (see section 5.0)

- NO trial specific examinations, investigations or treatments, that do not involve part of the patient's routine standard healthcare, will be performed prior to obtaining written consent of the patient**.**
- A member of trials team (i.e. CI/PI or designee as documented on the signature and delegation log) will discuss with patient all the relevant information, including aims, methods, risk and benefits of the trial, prior to obtaining consent.
- At this stage the patient will also nominate a 'personal consultee(s)' in the event that they lack capacity at any stage of the trial.
- Once valid informed consent (i.e. ICF signed and dated by the patient) the eligibility checklist will be completed

Confirmation of Eligibility

The eligibility will be verified by the research nurse or another clinical member delegated by the PI via the delegation Log. See **section 4.0** for eligibility criteria.

6.3. Randomisation

Randomisation will be provided by BCTU using a secure online system, REDCap, thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the ExaLT site signature and delegation log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either system using another person's login details. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. In the event that the online system is not available, researchers should contact the ExaLT Trial Office.

6.3.1. Randomisation process

After eligibility for randomisation has been confirmed and informed consent has been given, the participant will be randomised using the online system. Randomisation forms will be provided to investigators and will be used to collate the necessary information prior to randomisation. All questions and data items on the online randomisation form must be answered prior to a potential participant being randomised into the trial and a unique trial number being issued.

Following randomisation, a confirmatory e-mail will be sent to the local PI and designated members of the trial study team (e.g. local research nurse). The local research team should add the participant

to the ExaLT participant recruitment and identification log, which links participants with their unique trial identification number. PIs must maintain this document securely and it must not be submitted to the ExaLT trial office. The ExaLT participant recruitment and identification log should be held in strict confidence.

6.3.2. Randomisation method

Randomisation will be provided by a computer-generated programme. Participants will be individually randomised in a 1:1 ratio to either:

- Group 1: Intervention group. Remotely-monitored home-based exercise and theory-based motivation support programme delivered by the physiotherapists prior LT (max. 52 weeks) through to 24 weeks post-LT.
- Group 2: Control group. Patient exercise advice leaflet before and after LT.

A minimisation algorithm will be used within the randomisation system to ensure balance in the allocation over the following variables:

- Gender (Male, Female)
- Age (≤55 years, >55 years)
- UKELD score (≤54, >54)
- Trial centre (QEBH, RFH)
- Enrolled in the 'muscle' sub-study (Yes, No)
    - this criteria will become a default "No" for all randomised patients once the target sample size of 100 patients enrolled in the sub-study is reached.

A 'random element' will be included in the minimisation algorithm, so that each participant has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received.

6.4. Blinding

The ExaLT trial is an open-label study. Due to the nature of the study intervention (i.e. exercise and motivation programme) and the fact it is delivered by the study physiotherapists it is not possible to blind the participant or the co-investigators from the allocated study intervention. Importantly, however, the participants will be 'blinded' to the electronic wrist worn accelerometers to ensure they are not getting any objective positive or negative feedback from the accelerometers on their physical exertion or activity during the trial. In addition, data analysis of the 'muscle' sub-study will be blinded, in that the individual(s) performing the analysis of the CPET, muscle ultrasound and specialist biomarkers will be blinded to the study order of the investigations and allocation of the study intervention; thereby avoiding interpretation bias.

6.5. Informing the participant's General Practitioner (GP)

If the participant has agreed, the participant's GP will be notified that they are in the ExaLT trial, using the approved ExaLT GP letter.

7. TRIAL INTERVENTION

7.1. Overview of Trial intervention (Group 1: Intervention arm)

The trial intervention will be delivered to participants in two phases:

Phase 1 - Pre-LT: From enrolment into the study (baseline) up to LT. Duration of phase 1 will range from 1 to 52 weeks (+ 2 weeks), due to the unpredictable nature of the timing of LT.

Phase 2 - Post-LT: From day 1 admission to the ward (i.e. discharge from ICU) to 24 weeks post LT. Duration of phase 2 will be fixed at 24 weeks (minus ICU length of stay, median 2-3 days [NHSBT data 2021])

The intervention for both phases will be delivered by study physiotherapists and will comprise of two core components:

1. A remotely-monitored personalised **home-based exercise programme (HBEP)** and
2. **An autonomous motivation enhancement programme, known as *Empowering Physio***, delivered to physiotherapists to support them in delivering the HBEP.

Home-based exercise programme (HBEP) - Following an initial assessment at Visit 1 (see section 7.3.1), the patients will be provided with a HBEP consisting of five sessions of aerobic and resistance exercise per week. Thereafter, in the pre-LT phase 1, participants will attend up to four face-to-face visits with the physiotherapist (visit 2 - week 6; visit 3 – week 12; visit 4 – week 24; visit 5 - week 36), during which the participant will be assessed and the HBEP revised accordingly. If the participant has not had their LT by week 52 of phase 1, the participant will be withdrawn from the physiotherapist delivered HBEP (study intervention). After LT, the participant will initially undergo physiotherapist delivered walking and basic exercise programmes (supported in concordance with *Empowering Physio* principles) until discharge from hospital. The HBEP re-commences on discharge from hospital and will be adapted according to the patient's LFI and DASI, performed within 24-72 hours of expected discharge. The PI and the consultant transplant surgeon will be consulted prior to commencing the HBEP if there are any ongoing surgical complications (i.e. biliary drain in-situ; wound dehiscence etc.). After discharge, the participant will have two face-to-face visits (visit 7 - week 6; visit 8 - week 12) with the physiotherapist. In addition, physiotherapist support to the participants will be provided in the form of virtual or telephone health calls (Telecalls) to allow revisions to their personalised HBEP and the continuing employment of *Empowering Physio* strategies techniques as required. Telecalls will take place in the pre-LT phase 1 at weeks 2, 4, 8, 10, 16 and 20 (pre-LT) and in the post-LT phase 2 at weeks 4, 8 and 16. Section 7.3 and 7.4 provide further detail of the face-to-face visits and the Telecalls.

Autonomous motivation enhancement programme - The bespoke *Empowering Physio* programme will be used to equip physiotherapists (see **section 7.2**) with the understanding and skills to support each patient's sense of autonomy, competence and relatedness in delivering the HBEP; in order to help foster more autonomous motivation for uptake and adherence to the HBEP and engagement in exercise overall.

7.2. Physiotherapy Training

To ensure consistency across sites, the physiotherapists will receive formal training from Mrs Felicity Williams (Liver/LT Specialist Physiotherapist; PI) on all aspects of the assessment (including LFI and DASI) and HBEP intervention prior to commencement of the study at sites. Furthermore, the physiotherapists will be trained in the principles and strategies of *Empowering Physio* by Professor Joan Duda (Professor of sport and exercise psychology; co-investigator). The face-to-face training will take place over a 3-day structured course (**Table 1**). The overarching aim of the bespoke *Empowering Physio* training programme is to:

1. Enhance physiotherapists' understanding of: (a) what is optimal motivation for exercise and behaviour change; (b) the importance of the motivational 'treatment' climate they create; and (c) how that created climate (the physiotherapists' behaviours) influences patients' motivation for pursuing their physical activity goals and associated well-being.

2. Provide the opportunity for the physiotherapists to: (a) learn what are the 'building blocks' of creating a more empowering motivational treatment climate when working with patients, and (b) develop strategies which facilitate the realisation of these 'building blocks.'

The three day training will involve presentation content and interactive activities to highlight how physiotherapists interact with and provide information and feedback to patients and the implications of such for patients' motivation to engage in physical activity. Physiotherapists will be asked to reflect on their own experiences in clinical practice in regard to optimal and questionable motivational stategies. The workshop will also address the importance of communication style, and 'how ' to exchange with patients so that they feel a greater sense of autonomy, competence and connection in regard to their HBEP. The persuading and directing way of communicating will be contrasted with an evoking, guiding and following manner of exchanging with patients. The physiotherapists will then have the opportunity to identify barriers to creating a more empowering treatment climate and develop potential strategies to overcome this.

Table 1: Study Physiotherapist Training Course

Training Components	Day 1	Day 2	Day 3
Study logistics	√		
Functional and nutritional assessments (LFI/6MWT/MAMC)	√		
Questionnaires (DASI/PCS-SF-36v2/MCS-SF-36v2/HCCQ/PNSE/BREQ-2)	√		
Aerobic and Resistance exercise theory	√		
Practical exercises	√		
Patient education package	√		
Muscle Ultrasound	√		
Principles and strategies of *Empowering Physio*		√	
Practical application of *Empowering Physio*			√
Principles and strategies to delivery of face-to-face consultations, patient education session and Telecalls			√
Total time (hours)	7	7	7

Health Care Climate Questionnaire(HCCQ); Basic Psychological Need Satisfaction in Exercise Scale(PNSE); Behavioural Regulation in Exercise Questionaire-2 (BREQ)

The principles and embedded strategies to more empowering physiotherapy will be revisited the following day and reviewed to ensure understanding and application. The physiotherapists will then have the opportunity to consider the face-to-face consultations they will have with their patients (with particular emphasis on the initial participant education session, exercise familiarisation, and provision of the written exercise programme) *and* Telecalls and develop/'bring to life' a planned approach (i.e. specify motivational aims, strategies) to make these exchanges more empowering. Role playing will be used to exemplify the empowering strategies that the physiotherapists will employ and address challenges that may arise.

7.2.1. Fidelity testing of physiotherapist-delivered intervention

The implementation fidelity of the physiotherapist delivered intervention will be assessed in regard to (1) expected content conveyed (e.g. explanation and demonstration of the HBEP to the patient), and (2) the degree to which the behaviours of the physiotherapist (when interacting with the patient) were motivationally empowering (and thus supportive of the patient's autonomous motivation for exercise). To test the fidelity of the behaviour therapy training throughout the entire ExaLT trial study period, at each site four patient video recordings **per physio** will take place, where recruitment numbers allow, at patient 20 (+/-3), patient 40 (+/-3) and patient 60 (+/-3). The four patient recordings include:

- The baseline visit 1 (week 0 pre-LT) session including exercise training/education
- One Telecall follow-up (either weeks 2, 4 or 8)
- One pre-LT face-to-face follow-up visit (either visit 2 or 3)
- One post-LT face-to-face follow-up visit (either visit 7 or 8)

The interactions between physiotherapist and patient will be examined using visual recordings for Telecalls and face-to-face visits. A modified (for the present exercise intervention content) of the Interpersonal Support in Physical Activity Consultations Observational Tool (ISPACOT) (46) will be employed to evaluate the degree to which the physiotherapists conveyed the expected information, as intended in the face-to-face consultations and Telecalls *and* the motivational climate manifested during these treatment sessions. In regard to the latter, the ISPACOT assesses four aspects of the treatment climate: the degree to which the physiotherapist is autonomy supportive, demonstrated social support/caring, provided structure, and exhibited interpersonal control.

7.3. Phase 1: Group 1 Pre-LT trial intervention

Pre-LT Phase 1 of the HBEP will commence the day after baseline visit 1 (maximum 3 days post visit 1) and end on either a) the day of LT, or b) 52 weeks (+ 2 weeks) if LT has not taken place. Details of the intervention timeline are summarised in **Table 2**.

7.3.1. Visit 1 (day 0) – Group 1: Design and education of personalised HBEP

After obtaining consent and completion of baseline assessments (see section 9.0), participants will meet the study physiotherapist. The baseline assessments, along with *Empowering Physio* strategies, will be used to design a personalised written HBEP for the participant. Baseline LFI and DASI will be used to guide the entry level of difficulty for the aerobic and resistance-based exercises, respectively (**Tables 3 and 4**). In addition, the entry level of difficulty for the exercises will also be influenced by discussions with the participant on ways to employ strategies to support autonomous motivation for exercise adoption and engagement. The participants will then attend an individualised physiotherapist delivered training session, which will consist of: a) patient education (1 hour), b) exercise familiarisation (1 hour) and c) issuing of devices and written information (1 hour). Details of which are provided in **Table 2**.

- *A) Patient education:* Patient education sessions on the topics of general benefits of exercise, breathless management, pacing, rate of perceived exertion and nutrition pre-and post-exercise, will be delivered in the format of power point presentation and informal discussion by the physiotherapist. In accordance with *Empowering Physio* principles, the education sessions will be delivered in a manner that makes it more likely that the information conveyed is personally meaningful and confidence enhancing. Therefore, being more likely to increase feelings of autonomy, competence and relatedness towards exercise by the participant.

- *B) Exercise familiarisation:* Participants will be taught a series of body-weight resistance exercises performed in a circuit (**Table 4**). The aim of this session is to familiarise the participant with the exercises and the use of the rate of perceived exertion tool for monitoring exercise intensity. This session will also provide an opportunity for the physiotherapist to ensure correct and safe techniques. Participants will have the opportunity to voice any concerns they have regarding the exercises and allow for these concerns to be resolved prior to completing the exercises at home. In line with *Empowering Physio* principles, the physiotherapists will also provide responsive, meaningful feedback to ensure participant's individual needs are met. For example, the physiotherapist will be guided by the participant

and adjust exercise levels as needed to ensure participants feel competent in their exercise efforts. Throughout the session, physiotherapists will acknowledge effort and progress.

- *C) Written information:* Using the results of the baseline assessments of LFI and DASI (**Figures 1 and 2**) and the discussions had with the participant, the physiotherapist will provide a personalised written aerobic and resistance HBEP. The details of which can be found below. Furthermore, the participant will be provided with a participant diary to record their completed exercise sessions.

Trial Visits	V1	THC	Devices	V2	THC	Devices	V3	THC	Devices	V4	V5	V6	LT	IP	THC	Dev
Trial Intervention	**W0**	**W2 & 4**	**W4-6**	**W6**	**W8,10**	**W10-12**	**W12**	**W16& 20**	**W22-24**	**W24**	**W36**	**W48**		**stay**	**W4**	**W**
Education																
Patient education session	**X**															
Devices and Handouts																
Accelerometer	**X**		X			X			X							
HR monitor (during structured exercise session only)	**X**		X			X			X							
Participant Diary issued	**X**													**X**		
Exercise instruction																
Pre-LT A/R exercise plan	**X**															
Review and adaptation of A/R exercises		X		**X**	X		**X**	X		**X**	**X**			**X**	X	
Review of participant diary				**X**			**X**			**X**	**X**	**X**				
Post-LT A/R exercise plan														**X**		
Empowering Physio																
Identify knowledge about benefits of exercise	**X**															
Link exercise to personally meaningful goals/events	**X**															
Decisional balance patient centred goal setting	**X**	X		**X**	X		**X**	X		**X**	**X**	**X**			X	
Supports attempts to change behaviour	**X**	X		**X**	X		**X**	X		**X**	**X**	**X**			X	
Normalise failed attempts		X		**X**	X		**X**	X		**X**	**X**	**X**			X	
Problem solving		X		**X**	X		**X**	X		**X**	**X**	**X**			X	

Table 2: Group 1 Study Intervention timelines. Key: *A/R = aerobic/resistance; HR = heart rate; LT = liver transplant; V = visit; THC*

Table 3: Aerobic exercise programme

Level of difficulty	Exercise	Intensity	Duration (mins)
1	Walking/cycling/swimming/cross-trainer/running	1x5mins @ RoPE 12-14 1x3mins recovery @ RoPE 9-11 1x5mins @ RoPE 12-14	13
2	Walking/cycling/swimming/cross-trainer/running	1x7mins @ RoPE 12-14 1x3mins recovery @ RoPE 9-11 1x7mins @ RoPE 12-14	17
3	Walking/cycling/swimming/cross-trainer/running	1x10mins @ RoPE 12-14 1x3mins recovery @ RoPE 9-11 1x10mins @ RoPE 12-14	23
4	Walking/cycling/swimming/cross-trainer/running	1x12mins @ RoPE 12-14 1x3mins recovery @ RoPE 9-11 1x12mins @ RoPE 12-14	27
5	Walking/cycling/swimming/cross-trainer/running	1x10mins @ RoPE 12-14 1x3mins recovery @ RoPE 9-11 1x10mins @ RoPE 12-14 1x3mins recovery @ RoPE 9-11 1x10mins @ RoPE 12-14	33
6	Walking/cycling/swimming/cross-trainer/running	1x15mins @ RoPE 12-14 1x3mins recovery @ RoPE 9-11 1x15mins @ RoPE 12-14	33
7	Walking/cycling/swimming/cross-trainer/running	1x20mins @ RoPE 12-14 1x3mins recovery @ RoPE 9-11 1x10mins @ RoPE 12-14	33
8	Walking/cycling/swimming/cross-trainer/running	1x30mins @ RoPE 12-14	30
9	Walking/cycling/swimming/cross-trainer/running	1x35mins @ RoPE 12-14	35
10	Walking/cycling/swimming/cross-trainer/running	1x40mins @ RoPE 12-14	40

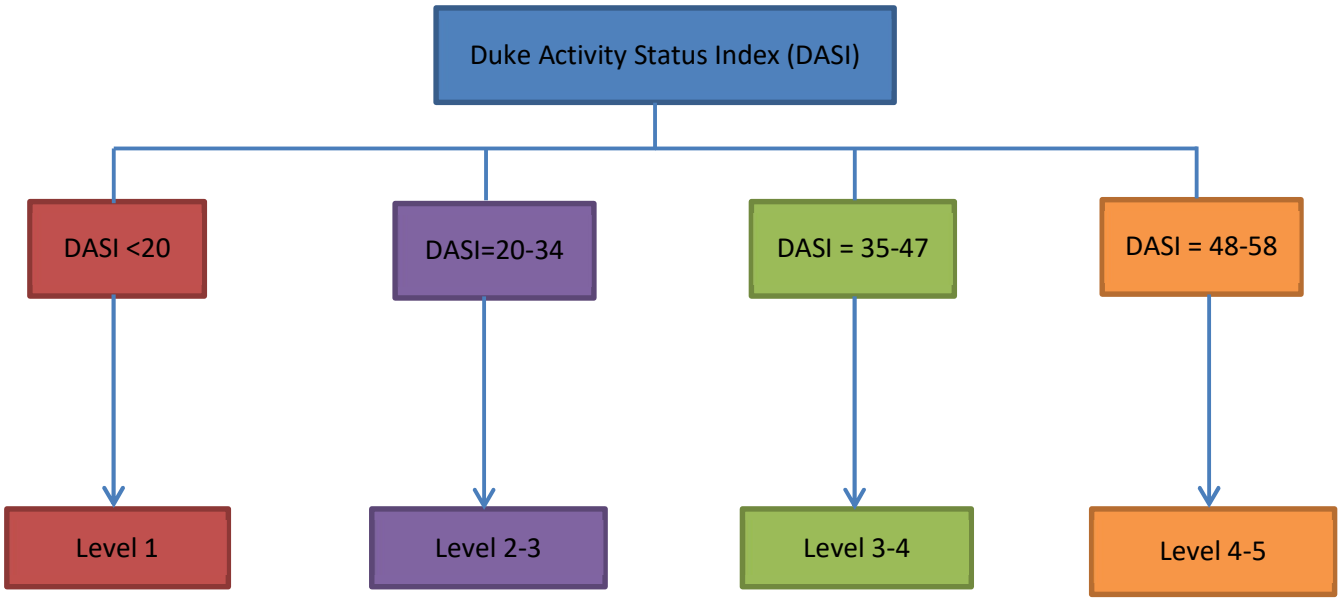
7.3.2. Aerobic exercise component of the HBEP

The initial level (duration, recovery period, intensity) of aerobic exercise sessions will be determined from the baseline DASI (**Figure 1**), while accounting for any exercise limiting comorbidities, such as ascites, peripheral oedema and/or hepatic encephalopathy. It will be recommended to the participants that they aim to complete two sessions of aerobic exercise per week. In line with *Empowering Physio* theory, a rationale for this recommendation will be provided. The participants will also be asked to select their exercise modality of choice from the following options; walking, cycling, swimming, cross-trainer, rowing ergo or running. In collaboration with the physiotherapist, the participant will be able to change their choice of modality week by week or continue with the same choice depending on their preferences. Furthermore, the physiotherapist will involve the participant in discussions about previous positive exercise experiences to facilitate personal goal setting. The level set will be appropriate to the participant's current level of function but also ensure the participant feels competent in their exercise effort. Each aerobic session will consist of alternating "work" and "active rest" periods:

- During the work periods, participants will be asked to exercise at a moderate intensity (rate of perceived exertion (RoPE) score of 12-14 (6-20 scale)).
- During their active rest periods, participants will be asked to work to a RoPE of 9-11. Details of the aerobic exercise intervention and levels of difficulty are detailed in **Table 3**.

Exercise intensity will be progressed depending on the feedback from regular Telecalls to the participant (weeks 2, 4, 8, 10, 16 and 20) pre-LT.

Figure 1 - Flow diagram for use of DASI when prescribing the 'entry level' aerobic exercise programme



7.3.3. Resistance exercise component of the HBEP

Participants will be asked to participate in a 20-minute circuit of bodyweight resistance exercises twice weekly on alternate days to the aerobic sessions. The circuit will consist of four cycles of 8-12 repetitions of five exercises, chosen by the patient (**Table 4 and 5**) with two minutes of "active rest" (walking slowly on the spot) between each exercise and each cycle. The programme and entry level will be developed according to baseline LFI (**Figure 2**), and a trial of 8-12 repetitions exercises within the designated entry level. Furthermore, the entry level will be discussed collaboratively with the participant to support feelings of competence and autonomy.

The participant will be instructed to terminate each set of an exercise when they reach a "repetitions in reserve" (RIR) of 1-2; that is, they feel they could complete 1 or 2 additional repetitions, but no more. The participant will be advised to progress to each level of difficulty once they can achieve 12 repetitions with 1-2 RIR and depending on feedback from the Telecalls at weeks 2, 4, 8, 10, 16 and 20 pre-LT. Details of the resistance exercise circuits and levels of difficulty are detailed in **Table 4 and 5**.

Figure 2 - Flow diagram for use of LFI when prescribing the 'entry level' resistance exercise programme

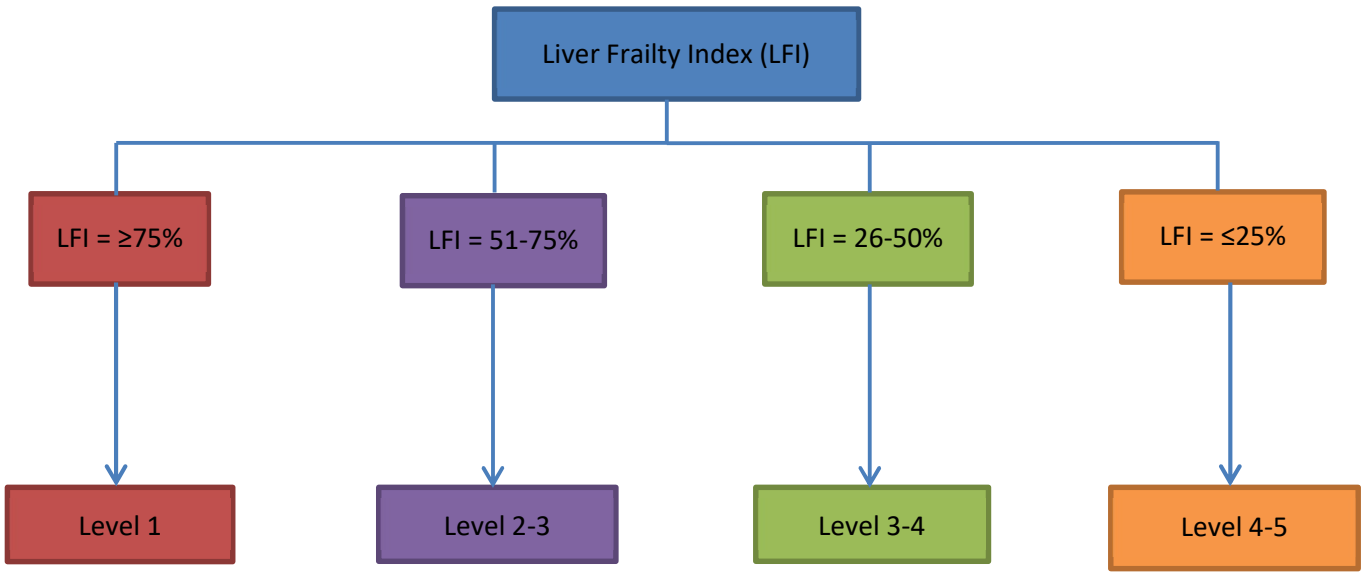


Table 4 – Resistance Exercise Programme

Muscle Group	Exercise	1	2	3	4	5
Upper Limb Press	**Horizontal press**	Wall press-up	Press-up on knees	Hands-elevated press-up	Progressively lower hands-elevated press-up	Press-
	Vertical press	Overhead press, arms only	Overhead press with light weight (e.g. soup cans)	Overhead press with heavier weight (e.g. water bottles)	Pike push-up, hands on raised surface	Pike p
Upper Limb Pull	**Horizontal pull**	Two-arm row with light weight (e.g. soup can)	One-arm row with light weight (e.g. soup cans)	Two-arm row with heavier weight (e.g. water bottles)	One-arm row with heavier weight (e.g. water bottles)	Two-a progr resist
	Lateral/Vertical pull	Lateral rotation with yellow TB	Bilateral abduction with TB	Diagonal TB pull	Vertical pull down with yellow TB	Vertic red TB
Lower Limb	**Squat**	Raised surface chair stands	Wall squat	Chair stands	Full squat	Squat (e.g. s
	Lunge	Static lunge with support	Static lunge without support	Dynamic half lunge	Dynamic full lunge	Walki
	Step ups	Low step-up (e.g. 1 stair)	Low step-up with knee raise	Low step-up with knee raise and light weight (e.g. soup cans)	High step-up with high knee	High s knee (e.g. s
Core Stability	**Anti-anterior flexion**	Four-point kneeling holds	Four-point kneeling with leg raises	Four point kneeling alternate arm and leg raises	Kneeling plank	Plank
	Glute med/anti-lateral flexion	Clams	Clams heels raised	Straight leg clam	Elbows-elevated side plank	Elevat
	Extension	Pelvic tilt in crook lying	Bridges	Bridges with yellow TB	Bridges with red TB	Bridge heel r

Table 5 – Resistance Exercise Session Template

Nº of exercises	Nº of circuits	Repetitions	Rest period between circuits (mins)	Total time (mins)
1x upper limb push 1x upper limb pull 2x lower limb 1x core/balance	4	8-12	2	26

7.3.4. Phase 1: Virtual or telephone health calls ('Telecalls') –Group 1 trial intervention

At weeks 2 (+/- 1 week), 4 (+/- 1 week), 8(+/- 1 week), 10(+/- 1 week), 16(+/- 1 week) and 20 (+/- 1 week) pre-LT, the participant will receive either a virtual or telephone health call by the physiotherapist, known as a 'Telecall'. The purpose of these calls (duration 15-30 minutes) will be to:

- Identify any adverse events or areas of concern.
- Gain feedback from the participant regarding the HBEP.
- Provide motivational support for engagement with the HBEP through the implementation of *Empowering Physio* strategies. For example, to empower patients in their attempts to be active, the physiotherapists will support attempts to change behaviour, problem solve and to develop strategies to overcome personally reported barriers and enhance self-efficacy for exercise. It is also an opportunity to revisit goals to ensure they are aligned with participant's perceptions of their exercise competencies (**Table 3**).
- Guide weekly progression of exercises and goal setting.

An interview guide underpinned by *Empowering Physio* principles and related motivation-based theories of behaviour change, will be used to provide a standardised framework of the Telecalls at both sites.

7.3.5. Phase 1: Face-to-face clinic visits (visits 2, 3, 4, 5 and 6) –Group 1 trial intervention

Participants will attend the hospital (QEUHB or RFH), in line with their routine waiting list clinic appointment (*where possible*), at weeks 6 (+/- 7 days), 12 (+/- 7 days), 24 (+/- 7 days), 36 (+/- 14 days) and 48 (+/- 14 days). At these visits, a repeat of the baseline assessment, including LFI and DASI, will be undertaken (see Procedure section 9.0). The results of these assessments, review of the participant exercise diary and discussions with the participant themselves will be used to progress exercises and revise goals of their HBEP. As per *Empowering Physio* principles strategies, the active role of the participant in the decision-making process, regarding progression and goal revision, will continue to support more autonomous reasons for engagement in the HBEP. Revisions will be based upon physical frailty/function scores (LFI, DASI) and the participant's owned perceived progress with the training HBEP. The end of the study intervention (HBEP, motivation programme) will be at 52 weeks (+ 2 weeks) if the participant has not undergone LT. At this stage, they will be asked if they wish to continue in the study (data collection only) as outlined in section 7.6.3.

7.4. Phase 2: Post-LT trial intervention

Post-LT Phase 2 of the HBEP will commence on day 1 of admission to the post-LT ward (i.e. within 24 hours of discharge from ICU) and end 24 weeks after the date of the LT surgery (visit 9). Details of the intervention timeline are summarised in **Table 2**.

7.4.6. Day 1 of ward admission (i.e. discharge from ICU) to discharge from hospital post-LT-trial intervention

The trial physiotherapists will review the participant on the post-LT ward, within 72 hours of discharge from ICU. The participants will start a supervised progressive walking programme, based upon the participant's current level of physical frailty/function, in keeping with post-surgical care. If able, the participant will be asked to complete a walk (distance determined by physiotherapist, based upon participant's current level of function) twice daily working to a RoPE of 12-14 throughout the walk. Distance walked should be increased on a daily basis provided the participant is medically safe to achieve this and feels competent in doing so. In addition, the participant will also be asked to complete twice daily a basic exercise programme consisting of upper limb, lower limb, balance, coordination and core-strengthening exercises (**Table 6**). This post-LT exercise 'inpatient' programme will also be supported in concordance with *Empowering Physio* principles. If there are concerns by the physiotherapist about the patient's safety to exercise (i.e. walk, chair stand etc.), the patient's consultant (i.e. surgeon, hepatologist) and clinical team (i.e. nurse) will be consulted, as per routine NHS care.

Within 72 hours prior discharge from hospital (or day 10 post-LT (+/- 3 days) if not discharged by this point; main exception that patient is still on ITU receiving organ support), a repeat of the baseline assessments, including LFI and DASI, will be undertaken on the ward (see Trial Procedures **section 9.0**). The results of these assessments, along with *Empowering Physio* strategies, will be used to prescribe a personalised written HBEP for the participant post-LT. The participant will also be given participant exercise diary.

Table 6: Post-Liver Transplant Basic Exercise Programme

Level	Exercise	Sets/Reps
1	Marching on the spot Pelvic tilts Wall squat Wall press	3x8-12reps
2	Step-ups Bridge holds (5 seconds) Chair stands Arm raises	3x8-12reps
3	Step-up high knees Single leg bridge holds (5 seconds) Squats Arm raise with Theraband©	3x8-12reps

7.4.7. Phase 2: Face-to-face clinic visits (visits 7, 8 and 9)- Group 1 trial intervention

Participants will attend the hospital (QEUHB or RFH), in line with their routine post-LT follow-up clinic appointment (*where possible*), at weeks 6 (visit 7; +/- 7 days) and 12 (visit 8; +/- 7 days). At these visits, a repeat of the baseline assessment, including LFI and DASI, will be undertaken (see Trial Procedures section 9.0). As per phase one, the physiotherapist will use these assessments along with *Empowering Physio* techniques and the participant's owned perceived progress to revise their personalised HBEP. Of note, visit 9 (24 weeks post-LT +/- 7 days) will mark the end of the study intervention (HBEP, motivation programme).

7.4.8. Phase 2: Virtual or telephone health calls ('Telecalls')- Group 1 trial intervention

Participants will receive a 'Telecall' (duration 15-30 minutes) by the physiotherapist at weeks 4 (+/- 1 week), 8 (+/- 1 week), and 16 (+/- 1 week) post-LT. The Telecalls will follow the same format as phase one with the purpose to highlight any participant concerns or adverse events, as well as to gain feedback on the exercise intervention. However, the *Empowering Physio* delivery will now shift to employ strategies for the participant to foster long-term autonomous motivation and maintenance of exercise behaviour.

7.5. Group 2 Control (comparator) arm

The control arm will be delivered during the pre-LT (phase 1) and post-LT (phase 2) phases of the trial. Participants will receive a standardised patient information 'exercise' leaflet, which includes standard written advice on physical activity and exercise before and after LT.

7.5.1. Phase 1 - Visit 1 (day 0) – Group 2 control arm

Following baseline assessment (see procedures 9.0) participants will receive a 20-minute face-to-face consultation with the physiotherapist, during which they will receive verbal and written (patient leaflet) advice on the generic benefits of exercise pre-LT. This will include information on how to maintain physical activity and exercise levels whilst on the LT waiting list, as well as four basic resistance exercises for participants to complete (as described in the leaflet). As part of this consultation, the physiotherapist will demonstrate these exercises and practice them with the participant to ensure they are safe to complete at home. The participants in the control group will not be required complete a participant exercise diary.

7.5.2. Phase 1 - Face-to-face clinic visits (visits 2, 3, 4, 5 and 6)- Group 2 control arm

Participants will attend the hospital (QEUHB or RFH), in line with their routine waiting list clinic appointment (*where possible*), at weeks 6 (+/- 7 days), 12 (+/- 7 days), 24 (+/- 7 days), 36 (+/- 14 days) and 48 (+/-14 days). At each visit, the participant will have an opportunity to discuss any concerns regarding physical activity or exercise they have with the physiotherapist (15 minutes). However, the physiotherapist will only provide information in line with established generic physical activity and exercise guidelines on the patient exercise leaflet. Furthermore, the participant will not receive any Telecalls during phase 1 of the study. Of note, 52 weeks (+ 2 weeks) will mark the end of control arm

(standardised patient advice leaflet) if the participant has not undergone LT. At this stage, they will be asked if they wish to continue in the study (data collection) as outlined in section 7.6.3.

7.5.3. Phase 2 – post LT Day 1 of ward admission to discharge from hospital - Group 2 control arm

As per the intervention, phase 2 of the control arm will commence on day 1 of admission to the post-LT ward (i.e. within 24 hours of discharge from ICU) and end 24 weeks after the date of the LT surgery (visit 9). The trial physiotherapists will review the participant on the post-LT ward, within 48-72 hours of discharge from ICU. The participants will start a supervised progressive walking programme, based upon the participant's current level of physical frailty/function, in keeping with routine post-surgical care. If able, the participant will be asked to complete a walk (distance determined by physiotherapist, based upon participant's current level of function) twice daily working to a RoPE of 12-14 throughout the walk. Distance walked should be increased on a daily basis provided the participant is medically safe to achieve this and feels competent in doing so. However, unlike the intervention group, no other formal exercises will be provided for the participant. If there are concerns by the physiotherapist about the patient's safety to exercise (i.e. walk etc), the patient's consultant (i.e. surgeon, hepatologist) and clinical team (i.e. nurse) will be consulted, as per routine NHS care.

Within 72 hours prior to discharge from hospital (or day 10 post-LT +/- 3 days; main exception that patient is still on ITU receiving organ support), a repeat of the baseline assessments, including LFI and DASI, will be undertaken on the ward (see Trial Procedures **section 9.0**). The participant will receive a 30-minute inpatient consultation with the physiotherapist where they will be advised to gradually increase their exercise post-LT. This information will be supported with the phase 2 post-LT patient 'exercise' advice leaflet; which will include four basic resistance exercises.

7.5.4. Phase 2 - Face-to-face clinic visits (visits 7, 8 and 9)- Group 2 control arm

Participants will attend the hospital (QEUHB or RFH), in line with their routine post-LT follow-up clinic appointment (*where possible*), at weeks 6 (visit 7; +/- 7 days) and week 12 (visit 8; +/- 7 days). As per phase 1 of the control arm, the physiotherapist will continue providing the advice highlighted in the patient 'exercise' advice leaflet. Of note, visit 9 (24 weeks post-LT +/- 7 days) will mark the end of the study of the control arm advice (standardised patient advice leaflet). Furthermore, no Telecalls will be made to the comparator group throughout phase 2 of the control arm.

7.6. Trial intervention modification or discontinuation

7.6.1. Trial intervention modification (unscheduled)

Throughout phases 1 and 2 of the trial intervention the level of HBEP will be modified (scheduled) at the face-face trial visits or via the Telecalls, based upon the participants physical frailty/function assessments (LFI, DASI) or the participant's own perceived progress with the HBEP respectively. In addition, in the event that the participant (or personal consultee), clinician (including GP, local hospital clinical team) and/or a clinical member of the study team **highlight** that there is:

- A significant deterioration in the participants liver disease severity (i.e. severe hepatic encephalopathy, new onset moderate/severe ascites, worsening anaemia, Spontaneous bacterial peritonitis [SBP]

- An acute deterioration in the participant's health status that does not require hospitalisation, but will impact on the participant's ability to comply with the HBEP.
    - musculoskeletal injury
    - systemic illness (i.e. viral illness, urinary tract infection (UTI), pneumonia)
- An acute deterioration post-LT (specifically) in the participant's health status that does not require hospitalisation, but will impact on the participant's ability to comply with the HBEP e.g.
    - post-LT surgical complication (e.g. incisional hernia)
    - complications of immunosuppression (e.g. mycophenolate induced diarrhoea/gastrointestinal upset; tacrolimus induced neuropathy/headaches)
    - opportunistic infection (e.g. cytomegalovirus [CMV])

It will be the responsibility of the PI/CI or nominated clinical co-investigator on the delegation Log to determine if the participant has had a significant deterioration in their liver disease and instruct the physiotherapist to modify the HBEP appropriately. These ad-hoc (unscheduled) modifications to the HBEP will take place via an unscheduled Telecall/face-to-face clinic visit or the next scheduled Telecall/Face-to-face trial visit.

7.6.2. Trial intervention discontinuation (unscheduled)

The trial intervention (HBEP and motivation programme) will be paused (scheduled) on the day of LT and will restart once the participant is discharged from ICU to the post-LT surgical ward. The trial intervention will be discontinued (unscheduled) if the participant is re-admitted to ICU during the post-LT period of the trial. The HBEP and motivation program will be restarted as discussed in **section 7.4**. NOTE day 1 of discharge to ICU post LT will continue to be recorded as the start of the trial intervention (irrespective of re-admissions and complications). The trial intervention (HBEP) will be discontinued immediately in the event of any of the following:

- Serious adverse events (SAE; refer to **section 10.0** for definitions). Examples include:
    - fall/musculoskeletal injury (i.e. fracture, head injury)
    - cardiac event or cerebrovascular accident [CVA] (i.e. myocardial infarction/angina, arrhythmia, stroke, transient ischaemic attack, Cerebral haemorrhage)
    - other surgical or medical emergencies (e.g. diabetic ketoacidosis, bowel obstruction, severe anaemia etc.)
    - pre-LT (on LT waiting list):
        - severe hepato-renal syndrome (HRS)/acute kidney injury (AKI)
        - severe hepatic encephalopathy
        - variceal haemorrhage requiring oesopho-gastro-duodenoscopy (OGD) +/- therapy
        - sepsis secondary to spontaneous bacterial peritonitis (SBP) or cholangitis
        - severe jaundice at the discretion of PI/CI.
    - post-LT:
        - post-LT surgical complication (e.g. bile leak, peritonitis, hepatic artery thrombosis (HAT), wound dehiscence)
        - post-LT medical complications (e.g. organ rejection, severe opportunistic infections e.g. CMV, graft dysfunction, AKI)

In the event that an SAE has resolved, the participant will *only* resume the trial intervention (HBEP) on the advice of clinical members of the trial team (including the PI/CI or nominated member of the research team as per the delegation log) after a clinical review of their health status and physical function. This clinic review will either take place via an unscheduled Telecall/face-to-face clinic visit or at the next scheduled Telecall/face-to-face trial visit. If there are concerns by the physiotherapist about the patient's safety to perform the HBEP, the patient's consultant (i.e. surgeon, hepatologist) will be consulted as per routine NHS care and the PI (or CI) for the trial site will be informed.

7.6.3. Trial exercise regimen discontinued (scheduled)

In the event a participant has not received a LT after 52 weeks, the physiotherapy-led exercise regimen the participant was randomised to will be terminated. However, with the participant's ongoing willingness to continue in the trial, routine data will be collected every 3 months for first year, and then 6-monthly until end of the study (see section 9.3.5). Note in addition to routine data (routine bloods, weight/BMI, LFI, DASI), the SP36 v2 questionnaire will be completed by the participant every 3 months for the first year.

7.7. Adherence to trial intervention (HBEP)

Adherence to the HBEP will be assessed using:

- Self-reported participant 'exercise' diary: The participants will be asked to fill in their diary every time they complete a session of structured exercise (maximum 5 sessions of HBEP per week). The study physiotherapists will be able to monitor adherence to the HBEP by reviewing the diaries at each face-to-face visit and during the scheduled telecalls with the participant.
- Wrist-worn accelerometers (Actigraph GT9X): The accelerometers will be worn 24 hours/day for set 14 day periods, ensuring they are still worn during their scheduled exercise (see **sections 8.2 and 9.0**). Accelerometers will be initialised to ensure participants will not receive any feedback on their activity levels during their participation in the trial. i.e. accelerometers are being employed as secondary outcome measures, not as part of the intervention. The devices are waterproof and do not need to be removed for bathing, showering or swimming; thereby not affecting the adherence analysis. In the event of skin irritation from the wrist watch, the participant should inform the study investigators and advice will be given accordingly. The physical activity raw data (i.e. frequency, intensity, and duration) will be collected by the physiotherapist at pre-LT visits 2-4 and post-LT visits 7-9 and safely stored for data analysis.

The patient can remain in the trial throughout the duration of the study, irrespective of the degree of adherence, but reasons for poor adherence will be documented (i.e. encephalopathy and loss of capacity).

7.8. Continuation of intervention after completion of the trial

The participant will officially complete the remotely monitored 'home-based exercise and theory-based motivation support programme' delivered by physiotherapists at visit 9 (24 weeks after LT). The hypothesis is that the participant will then have the physical functional status, knowledge,

competence, confidence and self-determined motivation to continue to engage with unsupervised exercise in the future. This hypothesis will be assessed at follow-up visit 10 (48 weeks post-LT; 24 weeks after stopping physiotherapy delivered intervention) with measures of physical and mental well-being (PCS and MCS SF-36v2 QoL questionnaire) and behaviours/motivation towards exercise (behavioural/psychological based questionnaires) (see sections 8.0 and 9.0). After the participants have completed the trial at visit 10, they will be followed up in their routine NHS post-LT clinic and will receive the standard of healthcare in place at that time. There will be no possibility of the prescribed physiotherapist delivered 'home-based exercise and theory-based motivation support programme' until the results of the trial are analysed and published.

8. OUTCOME MEASURES

All primary and secondary outcomes measures will be completed at the following time-points (*unless stated*):

- **Pre-LT (phase 1):** baseline visit 1 (0 weeks; pre-intervention), visit 2 (6 weeks; +/- 7 days), visit 3 (12 weeks; +/- 7 days), visit 4 (24 weeks; +/- 7 days), visit 5 (36 weeks; +/- 14 days) and visit 6 (48 weeks; +/- 14 days). Of note, as the timing of LT is unpredictable, the participant will enter the post-LT phase 2 of the trial on the day of LT, irrespective of how many study visits they completed in pre-LT phase 1.

- **Post-LT (phase 2):** visit 7 (6 weeks post-LT; +/- 7 days), visit 8 (12 weeks; +/- 7 days), visit 9 (24 weeks; +/- 7 days; end of intervention) and visit 10 follow-up (48 weeks; +/- 14 days).

NOTE in addition to visits listed above, on the day of admission for LT (immediately pre-LT) LFI, UKELD and MELD-Na will be completed. Post LT and within 72 hours prior discharge from hospital (**or** day 10 post-LT +/- 3 days) LFI, UKELD, MELD-Na and DASI will be completed.

8.1. Primary outcome(s)

The primary outcome measure for this trial is the **PCS from the SF-36v2 health-related QoL questionnaire at 24 weeks post LT**. The SF-36v2 questionnaire includes 36 questions composed of eight multi-item scales, which reflect the impact of health problems on both the physical and mental condition of the patient.(47, 48) A higher score reflects better quality of life. Two summary sub-scores can be calculated which are weighted combinations of the 8 scales, one to reflect the impact on physical function (PCS) and one to reflect the impact on psychological function, known as the mental component score (MCS).(21) Justification for the primary outcome measure is summarised in **Section 1.2.4**. Scoring of the SF-36v2 questionnaire will based on the instructions provided in the SF-36v2 user's manual.(49)

8.2. Secondary outcome(s)

The 'Key' secondary outcome measure to be assessed at 24 weeks post-LT is:

- **Comprehensive Complication Index (CCI)**: The CCI is a well validated, reproducible tool in surgery and LT, which provides a 0-100 index (0=no complications, 100=death) using the frequency and grade (CTCAE grade) of surgical-related complications (i.e. wound dehiscence, bile leak, abdominal collections, bleeding, hepatic artery thrombosis etc).(15, 50) The sample size will enable an accurate, representative comparison of the intervention and control arms 24 weeks post-LT to investigate if the HBEP significantly reduces surgical complications post-LT.

The other secondary outcome measure to be assessed at 24 weeks post LT are:

- **Mental component score (MCS) of SF-36v2 health-related QoL:** The SF-36v2 questionnaire is a practical, reliable, and valid measure of physical and mental health that can be completed in 5 to 10 minutes. Scoring of the (MCS) SF-36v2 questionnaire is as described above for PCS SF-36v2 questionnaire.
- **Liver frailty index (LFI):** The LFI is a composite metric of three performance-based measures: hand grip strength (HGS), time to do 5 chair stands (seconds) and time holding 3 balance positions (feet side by side, semi-tandem and tandem) to objectively assess physical frailty in ambulatory patients with end-stage liver disease.(51) The LFI score can be calculated using an on-line calculator (available at: http://liverfrailtyindex.ucsf.edu) with patient physical frailty categorised as robust, pre-frail and frail according to their index (index ≤ 3.2 (robust), 3.2-4.5 (pre-frail), >4.5 (frail)). In addition to the time-points listed above, LFI will be completed on the day admission for LT (immediately pre-LT) and prior to discharge (within 72 hours) from hospital post-LT **or** day 10 post-LT +/- 3 days.
- **Duke activity status index (DASI):** The DASI is a 12 item self-reported assessment of functional capacity that requires minimal time to complete.(52) It provides prognostic information in a variety of chronic diseases and can be used as an index of disease progression over time (53-55). In addition to the time-points listed above, DASI will be completed prior to discharge (within 72 hours) from hospital post-LT **or** day 10 post-LT +/- 3 days.
- **Pre-LT morbidity (UKELD, MELD-Na, Hospital Admissions) and mortality:**
    - **UKELD**: is a scoring system (using a patient's international normalized ratio (INR), serum bilirubin, creatinine and sodium) which is used to predict the prognosis of patients with end-stage liver disease.(56)
        - UKELD = [(5.395Xln(INR)) + (1.485Xln(creatinine)) + (3.13Xln(bilirubin)) - (81.565Xln(Na))] + 435
    - **MELD-Na Score:** is a scoring system (INR, serum bilirubin, creatinine and sodium) created in 2008, based on the original MELD score, but with the addition of serum sodium.(57) The MELD-Na, largely used for prioritisation in the United States, is a better predictor of mortality than the MELD score.
        - MELD-Na = MELD Score - Na – [0.025 x MELD x (140-Na)] + 140

      Patients on oral anti-coagulants (including warfarin and the new oral anti-coagulants; predicted to be <2%) will be excluded from the analysis, as their UKELD/MELD-Na will be artificially high. In addition to the pre-LT time-points listed above, UKELD and

MELD-Na will be completed on the day admission for LT (immediately pre-LT) and prior to discharge (within 72 hours) from hospital post-LT **or** day 10 post-LT +/- 3 days).

- **unscheduled hospital admissions:** The frequency and duration (days) of non-elective hospital admissions will be recorded between study baseline (visit 1, week 0) and LT or the 48 week visit. The reason for admission will be categorised based on the SAE recording.
- **mortality:** The date and cause (based on death certificate) of death pre-LT will be recorded.

- **Post-LT morbidity and mortality:** The post-LT morbidity will be assessed by length of ICU stay (hours), length of hospital stay (days; immediately post-LT), and frequency and duration of hospital re-admission (LT to 24 week visit 9). Of note, the post-LT complications will be captured by the CCI as described above and in addition re-listing for transplant will be recorded (date, reason).
  - **ICU length of stay (hours):** This will be calculated by a member of the site team (i.e. research nurse; research fellow) using the electronic patient records of the date/time (24hr) of admission to ICU immediately after LT to the date/time (24hr) of discharge from ICU (either through death or transfer to post-LT ward). Re-admission to ICU on the same hospital admission for LT will be included recorded and added to the total ICU length of stay (hours).
  - **Length of Hospital stay (LOS; days):** This will be calculated using the date of LT and the date of discharge from hospital to home (either through death or discharge home). In the rare event that a patient is transferred to their local non-LT hospital or an inpatient rehabilitation unit, these bed days will be included in the hospital LOS.
  - **Unscheduled Hospital re-admission (frequency, days):** The frequency and duration (days) of non-elective hospital admissions will be recorded between LT and visit 9 (24 weeks). The reason for admission will be categorised based on the SAE recording.
  - **Mortality (30 day, 90 day, 180 day and 1 year):** The date and cause of death will be documented using the death certificate for reference.
- **Habitual (daily) physical activity times:** Habitual (daily) levels of physical activity engagement (light, moderate and vigorous intensity) which may occur during the course of the trial will be measured using a 'blinded' wrist worn accelerometer (Actigraph GT9X). These will be worn for 14 days (24 hours/day):
  - Baseline (visit 1, week 0) to 14 days
  - 14 days before visit 2 (6 weeks), visit 3 (12 weeks) and visit 4 (24 weeks) pre-LT
  - 14 days before visit 7 (6 weeks post-LT), visit 8 (12 weeks post-LT) and visit 9 (24 weeks post-LT, end of intervention)

  Data captured during the 14-day periods will be analysed to quantify daily time (min/day) spent in; (1) light physical activity (1.6 – 2.9 metabolic equivalents (METS), (2) moderate physical activity (≥ 3 – 5.9 METS), (3) vigorous physical activity (≥6 METS), and sedentary time (≤1.5 METS).
- **"Dose" of exercise completed (measure of the frequency, intensity and duration of exercise):** Data will be analysed from the 'blinded' wrist worn accelerometer (Actigraph GT9X)

to understand the intensity and duration of the exercises completed during the 14 day periods.

- **Adherence to HBEP (Group 1: intervention arm only)**: As discussed in **section 7.7**, adherence to the HBEP will be measured using the 'blinded' wrist-worn accelerometer worn in the 14 day periods (described above). In addition, the participant will fill a self-reported exercise diary throughout the trial, which will be reviewed by the physiotherapist at each face-to-face trial visit until visit 9 (24 weeks post-LT, end of intervention). Using the diary, the physiotherapist will document how many structured HBEP sessions the participant has completed per week (maximum 5 per week).
- **[3]**Perceptions of the health care climate (how need supportive/empowering the physiotherapist is):** This will be measured using the Health Care Climate Questionnaire (HCCQ).(58) The HCCQ comprises 15 items/statements which represent the patient's perceptions of the degree to which they feel their interactions with their physiotherapist (health care climate) empower them to engage in exercise (e.g. "I feel that my physiotherapist has provided me choices and options"). Patients are asked to respond to each item, indicating the extent to which they agree with each statement, on a Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). For each participant, an average of the 15 items will be calculated for use in analysis. Note: Item 13 is negatively coded, and the score provided will be subtracted from a score of 8 to compute the participant's response to this item.
- **[3]**Basic psychological need satisfaction (i.e. feelings of autonomy, relatedness, competence):** This will be measured using the Basic Psychological Need Satisfaction in Exercise Scale (PNSE): The PNSE will be used to examine participants basic psychological need satisfaction, in relation to their exercise engagement.(59) The PNSE comprises 18 items, capturing the three basic psychological needs of autonomy (6 items, e.g. "I feel free to exercise in my own way"), competence (6 items, e.g. "feel that I am able to complete exercises that are personally challenging") and relatedness (6 items, e.g. I feel connected to the people who I interact with while I exercise"). Participants are asked to respond to each item, indicating the degree with which they agree with each statement, on a Likert scale from 1 (false) to 6 (true). Average scores for each of the three sub-scale will be computed (e.g. 6 items for autonomy are added and divided by 6 to give the average for autonomy need support), to determine participants degree of autonomy, competence and relatedness need support. These individual variables will be used in analysis. In addition, an overall average will also be calculated using responses to all 18 items, to provide and overall PNSE score for use in analysis.
- **[3]**Self-determined motivation to exercise:** This will be measured using the Behavioural Regulation in Exercise Questionaire-2 (BREQ-2).(60) The BREQ-2 will measure participant's degree of self-determined motivation to engage in exercise, by assessing their external, introjected, identified and intrinsic regulations, as well as motivation. Following the stem, "I take part in exercise" participants will be asked to respond to 19 items assessing intrinsic regulation (4 items; e.g., "because I enjoy doing this"), identified regulation (4 items; e.g., "because I value the benefits of doing this"), introjected regulation (3 items; e.g., "because I feel guilty when I am not doing this"), external regulation (4 items; e.g., "because my friends and family say I should") and motivation (4 items; e.g., "but I think doing this is a waste of time"). Participants were asked to rate their agreement with each statement on a 5-point Likert scale from 0 (not true for me) to 4 (very true for me). For this study, average scores for

each subscale will be computed, and used to produce composite scores for autonomous motivation (identified regulation + intrinsic regulation) and controlled motivation (external regulation + introjected regulation).

- [3]****Theory-based motivation support programme will be assessed** with (i) HCCQ, (ii) Basic PNSE and (iii) BREQ-2 Questionnaires, as discussed above. To test the theoretically-expected psychological mechanisms underlying behaviour change, a theoretical process model of behaviour change will be tested.

Specifically, we will examine whether the intervention (i.e. perceived support for patient autonomy, competence, relatedness by the physiotherapist) predicts change in the targeted psychological determinants (i.e. psychological need support, motivation for exercise), and subsequently, the targeted behaviour including physical activity and QoL. By testing the process model grounded in SDT in this way, we can begin to understand how the experiment intervention has worked. For example: which SDT constructs/determinants did the intervention successfully target/change, in order to encourage behavioural change. This will enable the home-based exercise with motivation support intervention to be subsequently refined and optimised. We will conduct this evaluation using structural equation modelling and path analysis, as previously described.(27, 61)

[3] ****** denotes where analysis will be conducted outside of the BCTU SAP by Prof Joan Duda and Dr Sally Fenton.

8.3. Mechanistic 'muscle' sub-study outcomes (n=100):

In addition to the primary/secondary outcome measures (listed above), the mechanistic 'muscle' sub-study outcomes measures will be completed at the pre-LT baseline visit 1 (0 weeks; within 3 days of visit 1), pre-LT visit 2 (6 weeks; +/- 7 days) and post-LT visit 9 (24 weeks post-LT; +/- 7 days) or visit 6 (48 weeks + 28 days) if no LT.

In the event that a participant is not transplanted by visit 6 (pre-LT phase 1), with the participant's ongoing willingness to continue in the study, they will be given the option of a final sub-study visit (visit 6, with an additional 6-week window; inclusive of CPET, muscle ultrasound, 6MWT, serology biomarkers) and their data will be collected until the trial end date (see section 7.6.3 and section 9.3.5).

The outcome measures include:

1. **6 minute walk test (6MWT):** The 6MWT is a self-paced field walking test conducted under controlled conditions and is a reliable and valid measure of exercise tolerance in various patient populations.(62) The test is inexpensive and simple to administer. It requires a 30 metre level indoor walking course and the course layout and degree of patient encouragement will be standardised, as they significantly affect the distance walked.(63) The learning effect (i.e. patient becomes more familiar with the test) will be reduced by performing two tests and recording the best result at each study time point. The 6 minute walk distance (6MWD) will be recorded in metres.
2. **Cardiopulmonary exercise testing (CPET):** Cardiopulmonary exercise testing (CPET), using a cyclo-ergometer, is the gold standard assessment tool of aerobic exercise capacity. It directly assesses gas exchange, work, heart rate and rhythm, and blood pressure during intense

exercise (64). With the exception of safety reports (i.e. new cardiac arrhythmia), the trial management group, physiotherapists and the patients clinicians will be blinded to the CPET outcome measures until the end of the trial – in order to avoid the results altering the patients clinical course (i.e. as not routine NHS care in QEUHB and RFH). All CPETs will be analysed by an independent assessor at the end of the trial, who will be blinded to the intervention and order of the CPETs. The key CPET outcomes to be measured, include:

- Oxygen consumption at anaerobic threshold (AT; ml/kg/min)
- Peak oxygen consumption (VO_2peak; ml/kg/min)
- Other measures include: ramp rate (W/min; peak power output (W); maximum heart rate (bpm); maximum oxygen pulse (ml/beat); reason for test termination (participant symptoms/request; operators request); exercised to volitional fatigue (YES/NO); ventilatory equivalents for carbo dioxide (VE/CO_2); respiratory exchange ratio at peak exercise.

It is important to acknowledge that CPET is not part of routine care for liver transplant assessment or monitoring in the two liver transplant units in the ExaLT trial. In addition, patients on the transplant waiting list have already been through a standardised cardiorespiratory risk assessment and have been deemed physically fit to proceed to liver transplant by a multi-disciplinary team. Therefore, in keeping with other CPET studies, it is deemed safe and methodologically robust to blind the clinical and research teams from the key CPET outcomes listed above. However, the research team and the local clinical liver transplant team will be immediately alerted by the trained operator of the CPET, in the event of rare, life-threatening heart arrhythmia – as this could have significant implications for the safety of the future liver transplant and their health.

3. **Right Quadricep muscle size, architecture and quality (ultrasound):** A Two-dimensional B-mode ultrasonography Esoate MyLab™ Alpha point of care ultrasound, 4.6cm probe (SL1543, 13-4Mhz scanning frequency)) will be performed by a member of the clinical trials team (research fellow, physiotherapist, or nominated co-investigator on delegation log). The following will be measured: vastus lateralis [VL) muscle thickness, fascicle pennation angle, fascicle length and total quadricep muscle anatomical cross-sectional surface area [ACSA]). All variables will be obtained offline via imageJ imaging software and will be presented as a mean. For assessment of all quadricep muscles, two extended field of view ultrasound images will be taken at 50% femur length; this will allow for the quantification of quadriceps ACSA. Echogenicity can be determined using a computer-assisted grey-scale analysis offered by ImageJ. (65)
4. **Specialist biomarkers:** Blood will be centrifuged, processed and then stored at -80^{o}C at the study sites before being transferred to the UoB (NIHR BRC Immunology and infection laboratory) for analysis of the following:
    - Common measures of oxidative stress: Total redox status, malonyldialdehyde, Myeloperoxidase, 4-Hydroxynonenal.
    - Serum antioxidant capacity: catalase, glutathione peroxidase and superoxide dismutase.
    - A profile of key myokines: IL-6, IL-10, IL-15, Irisin, leukaemia inhibitory factor, and secreted protein acidic and rich in cysteine (SPARC)

- Tumour necrosis factor alpha (not a myokine, but an inflammatory marker).
- In addition, at QEUHB site only, with participant consent, 20-30ml of urine will be stored for future research providing ethical approval for these additional studies has first been obtained (see Section 15).

A full standard operating procedure (SOP) has been produced for the 'muscle' sub-study that details the methodology of all the measures outlined above. Data from this sub-study will be combine with data collected from the main study in order to fully evaluate the effect of the exercise intervention on muscle physiology. The specialist biomarkers and muscle ultrasound will take place before the CPET/6MWT to ensure that their results are not impacted by acute/strenuous exertion of these functional tests. In addition, the CPET will take priority and precede the 6MWT (with 30 minutes rest in between tests), due to the fact that the CPET has more rigorous data outputs (i.e. VO2 peak, Anaerobic threshold, ramp gradient, maximal heart rate etc.) (see section 15).

9. TRIAL PROCEDURES

9.1. Study Timelines (estimates)

The total trial length is 55 months and comprises 6 months for trial set-up and contract execution, 24 months for recruitment (estimated 12 patients/month), maximum 76 weeks intervention (note: minimum = 1 day pre-LT + 24 weeks post-LT), and 24 weeks follow-up, primary analysis and reporting.

Prior to the study opening to recruitment, the following will take place:

- 3-day physiotherapist training days (home-based exercises; 'Empowering the Physio')
- Application and approval by REC, Sponsor (UoB), local confirmation of capacity and capability (QEUHB, RFH)

9.2. Pre-consent screening at QEUHB and RFH

Pre-consent screening will take place **before** the participant invite letters by the transplant coordinators, hepatologists (anaesthetists) and AHPs directly involved in the patients LT waiting list care (**Section 6.1.**). It is important to note that as part of the patients consent for LT (which takes place before they go on the LT waiting list), patients are also consented to be approached for future research studies. Review of the NHSBT 'active' adult liver transplant waiting list will be undertaken and all potentially eligible patients will either be given the participant invite letter and then the PIS (at a later date if they express an interest after reading the invite letter):

- In person at either their liver transplant assessment or in their dedicated liver transplant waiting list clinic/specialist liver clinic (i.e. PSC, HCC)

  OR

- Via post, especially in light of the emergence of telephone/virtual video clinics (as a result of the COVID-19 pandemic)

If a patient expresses an interest to participate in the trial after reading the PIS (either via phone, email or in person) they will be invited to attend visit 1 (baseline) of the trial. Where possible the study team will schedule visit 1 (baseline) to be on the same day as their next routine waiting list clinic appointment, during which the patient +/- relative or 'personal consultee' will be able to ask questions about the trial before providing consent.

9.3. Phase 1 Pre-LT trial visits schedule

The phase 1 Pre-LT trials visits schedule will consist of a baseline visit 1 (week 0), visit 2 (6 weeks +/- 7 days), visit 3 (12 weeks +/- 7 days), visit 4 (24 weeks +/- 7 days), visit 5 (36 weeks +/- 14 days) and visit 6 (48 weeks +/- 14 days). These are summarised in **Table 7.**

9.3.1. Pre-LT baseline Visit 1 (week 0) - maximum duration = 3-6 hours

At the beginning of the trial visit 1, **written consent** will be obtained by PI or designee as documented on the site signature and delegation log and the **eligibility criteria checklist** will be completed by a designated member of the clinical trials team (on delegation log). See section 5 and 6.2:

- NO trial specific examinations, investigations or treatments, that do not involve part of the patient's routine standard healthcare, will be performed prior to obtaining written consent of the patient.
- A member of the site research team (e.g. PI or designee as documented on the signature and delegation log) will discuss with patient, all of the relevant study information including aims, methods, risk and benefits of the trial, prior to obtaining consent.
- At this stage the patient will also be asked nominate a potential **'personal consultee(s)'** in the event that they lack capacity at any stage of the trial. A contact list of the participant's nominated personal consultee(s) will be securely stored at the trial site.
- Eligibility and confirmation of consent (including version of ICF, date, time) will be documented in the participants clinical noting.

After eligibility has been confirmed and informed consent given, the patient will be randomised in a (1:1) ratio to either the study intervention (Group 1) or control (Group 2) (**section 6.3**) and provided with a unique **Trial Identification Number** (ID). The Trial ID number will be used on all future trial documentation, alongside the patient's initials, date and visit number.

The following **data collection** will take place at Baseline visit 1 (week 0):

- **Patient demographics:** Patient's name, DOB, gender, ethnicity; post code, local hospital (non-LT centre).
- **Hospital trial site** (QEUHB, RFH)
- **Information on Covid-19**: Full course of COVID vaccination; Previous positive PCR test for COVID
- **Current medical history and clinical examination**, including: hepatic encephalopathy, ascites (defined as - mild (imaging only), moderate (on examination), severe (tense, requiring large volume paracentesis [LVP]), diuretic-resistant or diuretic-intolerant ascites, LVP (frequency), peripheral oedema, jaundice, haematemesis/melaena (< 4 weeks), pruritis, fever, right upper quadrant abdominal pain, fatigue, tiredness.

- **Past medical history:**
    - *primary chronic liver disease*
        - type (NAFLD/MAFLD, ArLD, Cryptogenic, PSC, AIH, PBC, A1AT, HBV, HCV, other)
        - HCC
            - largest Size
            - number of active lesions
            - previous treatment (TACE, RFA, SABR)
        - portal Hypertension
        - ascites
        - hepatic encephalopathy
        - spontaneous bacterial peritonitis (SBP)
        - hepatopulmonary syndrome
        - main portal vein thrombosis
    - *listing for LT (at the time)*
        - date of listing with NHSBT
        - indication (UKELD ≥ 49, HCC, Variant Syndrome i.e. recurrent cholangitis, refractory ascites)
        - UKELD score, MELD-NA
        - blood group
        - listing graft choice (DBD, DCD, or both)
- **Current/recent illnesses (<6 weeks)** specifically: SBP, variceal haemorrhage (melaena, haematemesis), hepatorenal syndrome/Acute Kidney Injury (AKI), sepsis, severe hepatic encephalopathy (admission to hospital), chest pain, shortness of breath, palpitations, dizziness/collapse, significant fall
- **Significant co-morbidities**: diabetes (Type 2 or Type 1; duration; insulin; retinopathy; neuropathy; proteinuria), hypertension; atrial fibrillation/atrial flutter, ischaemic heart disease (IHD), cerebrovascular disease (CVD), pulmonary disease (asthma, COPD, interstitial lung disease); musculoskeletal disease, mental health illness.
- **Drug History (key), including:** diuretics, beta-blockers, anti-encephalopathy medication, SBP prophylaxis, anti-depressants/anti-anxiolytic, sleeping adjuncts, analgesia, anti-diabetic drugs, long-term antibiotics, anti-pruritus, anti-coagulants.
- **Nutritional supplements** (prescribed amount):
    - oral
    - enteral
    - additional supplements
        - Creon/nutrizyme/pancrex
        - vitamin D
- **Social history**:
    - smoking status
    - alcohol intake
    - employment status
    - living situation

The following **assessments** (nurses checklists, CRFs) will take place at visit 1:

- **Full clinical examination** (including general, cardiovascular, respiratory, abdominal, neurological)
- **Clinical Observations,** including:
    - blood pressure (mm/Hg) – patient sitting 2 minutes prior.
    - resting pulse (beats/min)
    - oxygen Saturations on room air (%) – sitting
    - temperature (^oC)
- **Nutrition/Physical/functional status**:
    - wet weight (kg)
    - height (cm)
    - wet BMI (kg/m^2)
    - estimated dry weight (kg) [*using the 5/10/15% reduction rule for mild/moderate/severe ascites; 5% for peripheral oedema*]
    - estimated dry BMI (kg/m^2)
    - handgrip strength (HGS; dominant hand)
    - Mid-arm muscle circumference [MAMC] (cm)
- **LFI** (range 1.5 to 7.5; record in 2dp)
    - HGS: mean = ……. Kg (as above – autofill from above)
    - time to do 5 chair stands = …… seconds (NB if can't do record as '0')
    - balance (feet); total = …… (maximum 30 secs)
        - side = XX/10 secs
        - semi-tandem = XX/10 secs
        - tandem = XX/10 secs

The following **questionnaires** will take place at visit 1:

- DASI:
    - DASI Points =……. (range 0-58.2)
    - VO_2 peak (ml/kg) = 0.43 x DASI points + 9.6 = …….ml/kg (range 9.6-34.6 automated)
    - Metabolic equivalents (METs) = VO2 peak/3.5 = ……(range 2.74-9.89)
- SF-36v2 Health Survey (Quality of Life Questionnaire) [ ]:
    - Total score = [range 0-100]
    - PCS= [range 0-100; PRIMARY OUTCOME MEASURE]
    - MCS= [range 0-100]
    - these will be batch calculated using the Quality Metric software as described above.
- HCCQ
- Basic PNSE
- BREQ-2

The following **investigations** will be completed at visit 1:

- **Urine Albumin-to-creatinine ratio [ACR]** (*white top urine bottle to biochemistry*) – *visit 1 only*
- **12-lead ECG** (if not within previous 6 weeks) – *visit 1 only*
    - rate (beats per minute)
    - rhythm
- **Blood samples*** (*non-fasted*):

(*Bloods to be taken on day of visit. If some blood results are not available results from a NHS visit within +/-4 weeks of this visit will be accepted)

    - haematology: FBC, reticulocytes, Prothrombin Time (PT), INR
    - biochemistry: Ferritin, Trans Sats (%), B12, Folate, Vitamin D, Calcium (Adjusted Ca)
    - biochemistry: Urea & Electrolytes (including magnesium, phosphate), liver function tests (LFTs) including AST, GGT
    - biochemistry: HbA1c, TFTs (TSH, T4), lipid profile (Total cholesterol, HDL, triglyceride)
    - biochemistry: AFP, CRP, Alcohol (*if listed for ArLD*)
    - biochemistry: Ammonia (*on ice to laboratory within 15 minutes of collection*)
- The following with be calculated (study automated by eCRF):
    - UKELD** **if on oral anticoagulant – result will be void.
    - MELD-Na**
    - Childs-Pugh score** (5-15)

The following **additional <u>mechanistic 'muscle' sub-study'</u> investigations** will take place at visit 1 (*if consented for sub-study*) in the ***following order***:

1. **Specialist biomarkers:** Blood (*non-fasted*) will be collected in 2 x purple top tubes (3ml each) and 3 x red top tubes (5ml each). Blood will be centrifuged, processed, and stored at -80^{o}C at the study site (if site outside Birmingham) before being transferred in batches to our specialist laboratory at the University of Birmingham where they will be stored at 80^{o}C and then batch analysed. All plasma and serum samples will be labelled with unique Trial ID, site, date, visit number and patient initials. Batch analysis will take place for measures of oxidative stress, anti-oxidant capacity, myokines and inflammatory markers as listed in **section 8.0**. Any samples remaining at the end of the study will either be destroyed in accordance with laboratory procedures or if patient has given consent for samples to be used in future research, remaining samples will be transferred to another ethically approved study.
2. **Right Quadricep Muscle size, architecture and quality (Ultrasound):** A Two-dimensional B-mode ultrasonography Esoate MyLab^{TM} Alpha point of care ultrasound, 4.6cm probe (SL1543, 13-4Mhz scanning frequency)) will be performed by a member of the clinical trials team (research fellow, physiotherapist, or nominated co-investigator on delegation log) prior to any significant functional tests (i.e. 6MWT, CPET). The following will be measured: VL muscle thickness, fascicle pennation angle, fascicle length and total quadricep muscle ACSA. For assessment of all quadricep muscles, two extended field of view ultrasound images will be taken at 50% femur length; this will allow for the quantification of quadriceps ACSA.
3. **Cardiopulmonary exercise testing (CPET):** CPET, using a cyclo-ergometer, will be performed to directly assess gas exchange, work, heart rate and rhythm, and blood pressure during intense exercise. With the exception of safety reports (i.e. new cardiac arrhythmia), the trial

management group, physiotherapists and the patients clinicians will be blinded to the CPET outcome measures until the end of the trial. A SOP for CPET will be used at both trial sites to ensure standardised methodology for collaborating equipment, preparing the patient (mask fitting, seat height), software set-up, safety rules (i.e. contraindications, stopping rules), cycling/resting protocol and data storage. Participants will be encouraged to maintain a cycling speed of 60-65 rpm for as long as they can, whereby it will start easy and become more difficult as the resistance increases. The key CPET outcomes to be measured are summarised in **section 8.0** and will be determined by an independent, trained 'blinded' physiologist at a later date using the methods described in the POETTS guidelines.(66)

4. **6MWT (supervised by the study AHPs or Clinical Research Fellow/PIs):** 30 metre level indoor walking course and the course layout and degree of patient encouragement will be standardised. 'The learning effect' (i.e. patient becomes more familiar with the test) will be reduced by performing two tests and recording the best result. **6-minute walk distance (6MWD)** will be recorded in metres (range 50 to 2000 metres). In addition, participants will wear a pulse oximeter throughout the 6MWT and the starting SaO_2 on room air (%) and lowest SaO_2 on room air (%) will be recorded. There will be a minimum of 30 minutes rest time after the CPET.

Study Intervention:

After completion of the baseline assessments, participants will have a face-to-face consultation with the study physiotherapist. HBEP will commence a maximum of 3 days after visit 1:

- **Intervention Group 1 (see section 7.3):** A 60-minute consultation with the physiotherapist, during which the entry level of difficulty for the HBEP (aerobic and resistance) will be determined. The participant will be provided with a personalised written HBEP. The physiotherapist will record and save personalised written HBEP in the site file and patients clinical noting. The participants will then attend a physiotherapist delivered training session (group session; maximum 4 participants/day), which will consist of: a) patient education (1 hour), b) exercise familiarisation (1 hour) and c) issuing of devices and written information (1 hour).
- **Control Group 2 (see section 7.5)**: A 20-minute consultation with the physiotherapist, during which they will receive verbal and written (patient leaflet) advice on the generic benefits of exercise pre-LT.

Exercise Monitoring (**section 7.7**):

The physiotherapist will issue participants in the intervention and control groups with:

- **A participant 'exercise' diary (paper booklet), intervention group only**: for them to self-record all structured exercise undertaken during the trial.
- **A 'blinded' wrist worn accelerometer (Actigraph GT9X)**: for them to wear for the next 14 days (Days 1-14; 24 hours/day). Participants will be given a **free post envelope** and asked to return accelerometer and/or HR monitor as soon as possible after 14 days. A member of research team will then download the data from the devices, and securely store it at the trial site.

- Participant will be informed that the **devices** will be sent out again in the post and they will be asked to wear the accelerometer for 14 days prior to visit 2 (week 6). They will be asked to bring devices in with them to visit 2*.
- Participants will be asked to contact the research team should they have any queries regarding accelerometer wear.

***The blinded' wrist worn accelerometer (Actigraph GT9X)** will be sent in post to participants at least 14 days prior to visit 2 (week 6).

9.3.2. Pre-LT Visit 2 (week 6 +/- 7 days) - maximum duration = 30-60 mins*

Visit 2 will take place alongside the participant's routine LT waiting list clinic (*where possible*). At visit 2 the following will take place:

- **Record 'new' clinical events since last visit: Current/recent illnesses (<6 weeks)**, specifically: hepatic encephalopathy (I-IV), ascites (moderate to severe), number of LVP, peripheral oedema, variceal haemorrhage (requiring endoscopy), hepatorenal syndrome/AKI, sepsis/fever, significant fall.
- **Record Serious Adverse Events** (SAEs)**:** non-elective hospitalisation (Days in hospitals; if '0' = no hospitalisation); requirement for organ support/intensive care, hepatorenal syndrome/AKI, severe hepatic encephalopathy, variceal haemorrhage, serious fall/musculoskeletal injury, cardiac or cerebrovascular event, sepsis/infection requiring admission (esp. SBP, pneumonia).
- **Record 'new' medications:** diuretics, beta-blockers, anti-hepatic encephalopathy medications, SBP prophylaxis, antibiotics (not SBP prophylaxis), anti-depressants/anti-anxiolytics, sleeping adjuncts.
- **Record Nutritional supplements (prescribed amount)** – as per visit 1
- **Full examination, clinical observations and nutritional/physical/functional (including LFI)** – as per visit 1
- **Questionnaires** (DASI, SF-36v2, HCCQ, Basic PNSE, BREQ-2) – as per visit 1
- **Blood tests** (including calculation of UKELD, MELD-Na, Childs-Pugh) – as per visit 1
- **Mechanistic 'muscle' sub-study'_investigations** (if consented for 'sub-study'; biomarkers, muscle ultrasound, CPET, 6MWT *in that order*) – as per visit 1
- **Study Intervention:**
    - ***Intervention Group 1***: The study physiotherapist will progress exercises and revise the level/goals of the HBEP after review of the LFI/DASI assessments, participant 'exercise' diary and discussions with the participant themselves will be used to progress exercises and revise goals of their HBEP. As per 'Empowering Physio' principles strategies, the active role of the participant in the decision-making process, regarding progression and goal revision, will continue to support more autonomous reasons for engagement in the HBEP. The updated written HBEP will be saved in the trial site file and recorded in clinical notes.
    - ***Control Group 2***: The participant will have an opportunity to discuss any concerns regarding physical activity or exercise they have with the physiotherapist (15 minutes). However, the physiotherapist will only provide information in line with

established generic physical activity and exercise guidelines on the patient exercise leaflet.

- **Exercise monitoring**: The participant will return the wrist-worn accelerometer and the participant 'exercise' diary (intervention group only). A member of research team will then download the data from the devices, and securely store it at the trial site.
- **Preparation for next trial visit (3):**
    - at the end of the trial visit, the participant will be given a time/date for their next appointment
    - Issued with the participant 'exercise' diary (intervention group only) for them to self-record all structured exercise undertaken during the trial.
    - prior to the next trial visit the research team will post the accelerometer out to the participant for them to wear for the 14 days prior to the next trial visit (i.e. visit 3; 12 weeks).

9.3.3. Pre-LT Visits 3 (week 12 +/-7 days), 4 (week 24 +/-7 days), 5 (week 36 +/- 14 days) – max. 60min

Visits 3-5 will take place alongside the participant's routine LT waiting list clinic (*where possible*). All procedures, data collection, and study intervention will be the same as visit 2, without the mechanistic 'muscle' sub-study investigations.

Similarly to visit 2, at the end of the trial visit, the participant will be given a time/date for their next appointment and the participant 'exercise' diary (intervention group only). Prior to the trial visits 3 and 4 the research team will post the accelerometer to the participant for them to wear for the 14 days prior to the next trial visit.

Table 7: ExaLT trial visit schedule

*52-week cut-off: study intervention will stop if participant hasn't had their LT by 52 weeks (+2 weeks). (X) optional sub-study consent if haven't undergone LT within the 1-year time-frame

	BASELINE										End-of-Intervention	FOLLOW-UP
	Pre-Liver Transplant (variable time-line)						TRANSPLANT	Post-Liver Transplant (fixed time-line)				
Study visits	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6			VISIT 7	VISIT 8	VISIT 9	VISIT 10
Time points	0 weeks	6 weeks	12 weeks	24 weeks	36 weeks	48 weeks	*52 week cut-off	Inpatient stay	6-weeks post	12 weeks post	24 weeks post	48 weeks post
		(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 14 days	(+/- 14 days)		day 10 +/- 3 days	(+/- 7 days)	(+/- 7 days)	(+/- 14 days)	(+/- 14 days)
Consent	X											
Randomisation (Intervention vs. control))	X											
Clinical examination and review (routine clinic)	X	X	X	X	X	X	X	X	X	X	X	X
Standard bloods pre-LT (FBC, U+E, LFTs, AST, GGT, INR, CRP, nutrition, ammonia)	X	X	X	X	X	X	X					
Standard bloods post-LT (FBC, U+E, LFTs, AST, GGT, INR, CRP, nutrition, tacrolimus)								X	X	X	X	X
Standard clinic observations (BP, dry BMI, weight, hand grip strength, MAMC)	X	X	X	X	X	X	X	X	X	X	X	X
Frailty/Functionality assessment (LFI, DASI)	X	X	X	X	X	X	X	X	X	X	X	X
Primary outcome SF-36v2 questionnaire	X	X	X	X	X	X		X	X	X	X	X
Behavioural/psychological questionnaires (HCCQ, PNES, BREQ-2)	X	X	X	X	X	X		X	X	X	X	X
Serious adverse events (complications/morbidity)	X	X	X	X	X	X	X	X	X	X	X	X
Liver Transplant data (date, donor details, organ support, ICU stay)							X					
Exercise Adherence: review participant 'exercise' diary		X	X	X	X	X	X		X	X	X	X
Exercise Adherence: Acceleromter	week 0-2	4-6	10-12	22-24					week 4-6	10-12	22-24	
Mechanistic 'muscle' sub-study (n=100, *optional*):												
CPET, muscle USS, 6MWT, specialist biomarkers	X	X				(X)					X	
Interventions:												
Intervention: home-based exercise and theory-based motivation support programme	X	X	X	X	X	X		X	X	X	X	
Intervention: Telecall (15-30 minutes)		week 2,4	8, 10	16,20					4	8	16	
Control: standard of care patient 'exercise' advice leaflet	X							X				

9.3.4. Pre-LT Visit 6 (week 48 +/- 14 days) – max. 60 min

Visits 6 will take place alongside the participant's routine LT waiting list clinic (*where possible*). At visit 6 (week 48 +/- 14 days), the following will be undertaken:

- **Record 'new' clinical events since last visit: Current/recent illnesses (<6 weeks)** – as described for visit 2
- **Record Serious Adverse Events** (SAEs only) – as described for visit 2
- **Record 'new' medications** – as described for visit 2
- **Record Nutritional supplements (prescribed amount)** – as described for visit 1
- **Full examination, clinical observations and nutritional/physical/functional (including LFI)** – as described for visit 1
- **Questionnaires** (DASI, SF-36v2, HCCQ, Basic PNSE, BREQ-2) – as described for visit 1
- **Blood tests** (including UKELD, MELD-Na, Childs-Pugh) – as described for visit 1
- The participant will return the **participant 'exercise' diary** (intervention group only).

Participant at trial visit 6 (48 weeks +/- 14 days within randomisation) will have the option of asking questions and discussing their current HBEP with the study physiotherapist (maximum 20 minutes). They will be informed that they will be withdrawn from study intervention if they do not receive a LT by 52 weeks. However, they will be asked to continue with their study intervention up to 52 weeks post randomisation. They will have an 'optional' opportunity to consent to have the 'muscle' sub-study investigations repeated (CPET, 6MWT, muscle USS, biomarkers), as they will no longer be having the sub-study investigations 6-months post-LT (i.e. LT has not taken place).

9.3.5. Study intervention withdrawn (Scheduled)at 52 weeks

If at 52 weeks (+ 2 weeks) participant has not received a LT, they will be **withdrawn from the study intervention**. Those patients still willing to continue with routine data collection will be followed (at their routine clinic visits) up every 3 months for first year then 6-monthly until the end of the study. Data will be collected from patient notes and captured by NHSBT and existing transplant databases at participating sites. In addition, patients still willing to continue completing the SP36 v2 questionnaire will be asked to complete the questionnaire at 3 monthly intervals for the first year. Data collection (every 3 months for 1st year after study intervention termination and every 6 months until the study ends) will include:

- Routine bloods [FBC, U+E, CRP, LFTs inc AST, INR, Ammonia; including UKELD, MELD-Na, Childs-Pugh]
- LFI, DASI
- SP36 v2 questionnaire.
- Death pre-LT (including cause)
- LT data (if undergoes LT before study end date), as listed in section 9.4, 9.5.1 and severe surgical complications/SAE, re-admission to ITU, death (including cause) and re-transplantation.

This data collection will continue until the study ends/closes.

9.3.6. Pre-LT Telecalls at weeks 2, 4, 8, 10, 16 and 20 – intervention arm only

For the intervention arm only (Group 1) Telecalls will be performed by the study physiotherapist at week 2 (+/- 1 week), week 4 (+/- 1 week), week 8 (+/- 1 week), week 10(+/- 1 week), week 16(+/- 1 week) and week 20 (+/- 1 week) (**Table 7**). The purpose of these calls (duration 15-30 minutes) will be to: identify any adverse events or areas of concern; gain feedback from the participant regarding the HBEP; and provide motivational support for engagement with the HBEP through the implementation of *Empowering Physio* strategies (**Table 2**).

9.4. Day LT (unpredictable timing) – trial data collection [Inpatient stay L1]

The following (below) investigations and data collection will take place on the admission for LT (i.e. prior to the LT). This is called the L1 inpatient assessment visit. If the participant is admitted overnight, the data (where possible) will be collected in the morning prior to the LT:

- **Record 'new' clinical events since last visit: Current/recent illnesses (<6 weeks)**, specifically: hepatic encephalopathy (I-IV), ascites (moderate to severe), number of LVP, peripheral oedema, variceal haemorrhage (requiring endoscopy), hepatorenal syndrome/AKI, sepsis/fever, significant fall.
- **Record SAEs**: non-elective Hospitalisation (Days in hospitals; if '0' = no hospitalisation); requirement for organ support/intensive care [yes/no]; hepatorenal syndrome/AKI, severe hepatic encephalopathy, variceal haemorrhage, serious fall/musculoskeletal injury, cardiac or cerebrovascular event, sepsis/infection requiring admission (esp. SBP, pneumonia).
- **Record 'new' medications:** diuretics, beta-blocker, anti-hepatic encephalopathy medications, SBP prophylaxis, antibiotics (not SBP prophylaxis], anti-depressants/anti-anxiolytics, sleeping adjuncts.
- **Record Nutritional supplements (prescribed amount)** – as per visit 1-6
- **Full examination, clinical observations and nutritional/physical/functional (including LFI)** (*if possible*) ***–** as per visit 1-6
- **DASI Questionnaire (***if possible***)*** – NB no other questionnaires will be performed immediately prior to LT, as high risk of inaccuracy due to the emotional stress associated with waiting for high risk surgery (LT).
- **Blood tests** (*if possible*) ***** (including UKELD, MELD-Na, Childs-Pugh) – as per visit 1-6

*Due to the ad hoc nature of this visit it may not be possible to perform these assessments.

In cases where bloods are not performed- sites can enter bloods from a previous NHS visit if performed within **4 weeks** of this visit. Post LT bloods are not acceptable for this visit.

9.5. Phase 2 Post-LT trial schedule (inpatient stay, visits 7-9)

The phase 2 Post-LT trials schedule will consist of the inpatient stay visit (within 72 hours prior to discharge from hospital post-LT **or** 10 days (+/- 3 days) post LT), visit 7 (week 6 weeks +/- 7 days), visit 8 (12 weeks +/- 7 days), visit 9 (24 weeks +/- 14 days), visit 10 (48 weeks +/-14 days) post LT. This is called the L2 inpatient assessment visit.

9.5.1. LT data capture

The following data will be obtained by a member of the research team from the LT operation note, anaesthetic chart, ICU charts, clinical noting and the NHSBT database (*if required*) (**Table 7**):

- Date of LT
- Donor and operation details:
    - type of donor
    - type of graft
    - ABO match
    - donor age
    - cytomegalovirus (CMV) donor status
    - graft steatosis
    - normothermic machine perfusion
        - duration on the machine
    - cold ischaemic time
    - operation time
    - renal replacement therapy intra-operative; continuous veno-venous hemofiltration (CVVH)
    - recipient cardiac arrest in theatre
    - blood products in theatre
- ICU stay (time of admission to ICU to time of discharge to post-LT ward):
    - length of ICU stay (hours)* includes re-admission to ICU on the index post-LT hospital admission
    - duration of invasive ventilation (hours) = time of admission to ICU to time of extubation.
    - post-LT lactate (1st lactate on return to ICU after LT)
    - duration of inotropes
    - CVVH (including duration)
- Immunosuppression regimen (including renal-sparing regimen if required)

9.5.2. Phase 2 Post-LT inpatient surgical ward (post-ICU step-down) (Inpatient stay L2)

The following (below) investigations and data collection will take place post-LT on the inpatient surgical ward (post ICU step-down):

- **Record LT Surgical complications/SAEs (frequency, CTCAE grade)**, **including**: biliary stricture/anastomosis, bile leak, wound dehiscence, abdominal collection (requiring drainage/intravenous antibiotics), haematoma/bleeding (requiring surgical/radiological intervention), anaemia requiring blood transfusion, AKI (requiring renal replacement therapy), Ileus/bowel obstruction, re-laparotomy, portal vein thrombosis, hepatic artery (or conduit) thrombosis, bacteraemia requiring intravenous antibiotics, hyperglycaemia requiring insulin infusion, infection (pneumonia; cholangitis; urinary tract; wound; peritonitis; central nervous system; CMV), acute rejection (biopsy proven)
- **Record** any of the following:
    - re-admission to ICU
    - death (including cause)
    - re-transplantation

- **Record new medications** (specific; prior to discharge): anti-depressants/anti-anxiolytics, prescribed sleeping adjuncts, analgesics.
- **Blood (non-fasted) tests on post-LT day 1,3 and 7 (+/-1 day):**
    - FBC (full blood count; inc. neutrophils, lymphocytes, eosinophils, prothrombin time (PT) and INR
    - urea and electrolytes (inc. magnesium and phosphate). Document if on renal replacement support.
    - LFTs including AST
    - peak ALT (IU/L)
    - C-reactive protein (CRP)
    - tacrolimus trough level (if applicable)
- **Day prior to discharge or day 10 post-LT +/- 3 days record nutrition/Physical/functional status:**
    - wet weight (kg)
    - height (cm)
    - wet BMI (kg/m2)
    - estimated dry weight (kg) [*using the 5/10/15% reduction rule for mild/moderate/severe ascites; 5% for peripheral oedema*]
    - estimated dry BMI (kg/m2)
    - nutrition management:
        - route (inc. protein intake)
        - oral supplements (inc. protein intake)
        - normal diet
    - Handgrip strength (HGS; dominant hand)
        - 1st ……..2nd……..3rd……Mean =…….Kg
    - MAMC (cm; *if possible*)
    - **LFI** (range 1.5 to 7.5; record in 2dp) by member of the research team (nurse, physiotherapist, Clinical Research Fellow)
    - **DASI questionnaire**
    - **SF-36v2 Health Survey (Quality of Life Questionnaire)**
- **Record the length (days) of index hospital stay post-LT** (inc. transfer to other hospitals)
- **Record discharge destination** (home, rehabilitation unit, other hospital, care facility)

Study Intervention post-LT:

The trial physiotherapists will review all participants on the post-LT ward, within 48-72 hours of discharge from ICU and will start a supervised (basic) exercise programme, based upon the participant's current level of physical frailty/function, in keeping with post-surgical care (**see section 7.4.1**). If there are concerns by the physiotherapist about the participant's safety to exercise (i.e. walk, chair stand etc.), the participant's consultant (i.e. Transplant surgeon, hepatologist) and clinical team (i.e. nurse) will be consulted – as per routine NHS care.

The post-LT baseline assessments (LFI and DASI) undertaken 72 hours prior to discharge (or day 10 post-LT +/- 3 days), along with "Empowering Physio" strategies, will be used to prescribe a personalised written HBEP for the participant post-LT (*intervention group 1 only*). The control group

will be given the post-LT patient 'exercise' advice leaflet within 72 hours prior to discharge. Participants in the intervention group will also be given a participant 'exercise' diary to self-report exercises undertaken between discharge and visit 7.

Preparation for next trial visit 7 (6-weeks post-LT):

Prior to discharge, the participant will be given a time/date for their next trial visit appointment, which where possible will be on the same day as their routine post-LT clinic. Prior to the next trial visit (visit 7) the research team will post the accelerometer out to the participant for them to wear for the 14 days prior to the next trial post-LT visit 7.

9.5.3. Phase 2 post-LT visit 7 (6 weeks +/- 7 days) and visit 8 (12 weeks +/- 7 days) – max. 60 min

These visits will take place alongside the participant's routine post-LT clinic (*where possible*). The following investigations and data collection will take place at each visit (**Table 7)**:

- **Record 'new' clinical events** (since discharge/last visit): ascites, peripheral oedema, jaundice, confusion/delirium, fever/night sweats, severe gastrointestinal symptoms, significant fall/injury.
- **Record LT surgical complications/SAEs (frequency, CTCAE grade)**, **including**: biliary stricture/anastomosis, bile leak, wound dehiscence, new onset ascites (requiring LVP, admission), abdominal collection (requiring drainage/intravenous antibiotics), haematoma/bleeding (requiring surgical/radiological intervention), anaemia requiring blood transfusion, AKI (requiring renal replacement therapy), ileus/bowel obstruction, re-laparotomy, portal vein thrombosis, hepatic artery (or conduit) thrombosis, bacteraemia requiring intravenous antibiotics, hyperglycaemia requiring insulin infusion, infection (pneumonia; cholangitis; urinary tract; wound; peritonitis; CNS; CMV), acute rejection (biopsy proven*), other (e.g. seizure, cardiac event (i.e. MI)/CVA):
- **Record** any of the following:
    - re-admission to ICU
    - death (including cause)
    - re-transplantation
- **Record new medications** (specific; prior to discharge): anti-depressants/anti-anxiolytics, prescribed sleeping adjuncts, analgesics.
- **Immunosuppression regimen** (including renal-sparing regimen if required)

The following **assessments/investigations** (nurses checklists, CRFs) will take place at visits 7 and 8:

- **Full clinical examination** (including general, cardiovascular, respiratory, abdominal, neurological)
- **Clinical Observations** – as per visit 1-6
- **Nutrition/Physical/functional status** – as per visit 1-6
- **LFI** – as per visit 1-6
- **Questionnaires** (DASI, SF-36v2, HCCQ, Basic PNSE, BREQ-2) – as per visit 1-6
- **Blood tests (non-fasted)*:**
    - FBC (inc. neutrophils; lymphocytes; eosinophils), Prothrombin Time (PT), INR

- ferritin, trans sats (%), B12, folate, vitamin D, calcium (adjusted)
- urea and electrolytes (inc. magnesium, phosphate)
- LFTs including AST
- CRP
- HbA1c
- tacrolimus – trough level (if applicable)

(*Bloods to be taken on day of visit. If some blood results are missing, results from NHS visit within +/-4 weeks of visit will be accepted)

Study Intervention:

After completion of the assessments/investigations, participants will have a face-to-face consultation with the study physiotherapist:

- **Intervention Group 1 (see section 7):** A 30-60-minute consultation with the physiotherapist. As per phase one, the physiotherapist will use the assessments (LFI, DASI) along with "Empowering Physio" techniques and the participant's owned perceived progress to revise their personalised HBEP. The participant will be provided with a personalised written HBEP. The physiotherapist will record and save personalised written HBEP in the site file and patients clinical notes.
- **Control Group 2 (see section 7)**: As per phase 1 of the control arm, the physiotherapist will continue providing the advice highlighted in the patient 'exercise' advice leaflet.

Exercise Monitoring (**section 7.7**):

The physiotherapist will issue participants in both the intervention and control groups with:

- **A participant 'exercise' diary (paper booklet), intervention group only**: for them to self-record all structured exercise undertaken during the trial.
- **An 'blinded' wrist worn accelerometer (Actigraph GT9X)**: for them to wear for 14 days before visits 8 and 9. Participants will be asked to bring it to the next visit. Participants will be asked to contact the research team should they have any queries regarding accelerometer wear.

Preparation for next trial visit 9 (24-weeks post-LT):

The participant will be given a time/date for their next trial visit appointment, which where possible will be on the same day as their routine post-LT clinic.

9.5.4. Post-LT Telecalls at weeks 4, 8 and 16, Group 1 intervention arm only

Telecalls will be performed by the study physiotherapist at week 4 (+/- 1 week), week 8(+/- 1 week), and week 16 (+/- 1 week) post-LT (**Table 7**). The purpose of these calls (duration 15-30 minutes) will be to: identify any adverse events or areas of concern; gain feedback from the participant regarding the HBEP; and provide motivational support for engagement with the HBEP through the implementation of *Empowering Physio* strategies (**Table 2**).

9.5.5. Post-LT (End of study intervention) Visit 9 (24 weeks +/- 14 days)

The end of intervention visit (visit 9) will take place alongside the participant's routine post-LT clinic (*where possible*). The following investigations and data collection will take place at this visit:

- **Record 'new' clinical events** (since last visit): ascites [mild, moderate or severe], peripheral oedema, jaundice, confusion/delirium, fever/night sweats, severe gastrointestinal symptoms (Vomiting/diarrhoea/nausea/loss of appetite); significant Fall/injury or NONE.
- **Record LT Surgical complications/SAEs (frequency, CTCAE grade)**, **including**: biliary stricture/anastomosis, bile leak, wound dehiscence, new onset ascites (requiring LVP, admission), abdominal collection (requiring drainage/intravenous antibiotics), haematoma/bleeding (requiring surgical/radiological intervention), anaemia requiring blood transfusion, AKI (requiring renal replacement therapy), Ileus/bowel obstruction, re-laparotomy, portal vein thrombosis, hepatic artery (or conduit) thrombosis, bacteraemia requiring intravenous antibiotics, hyperglycaemia requiring insulin infusion, infection (Pneumonia; Cholangitis; Urinary tract; Wound; Peritonitis; CNS; CMV), other (record), acute rejection (biopsy proven), other (i.e. seizure, cardiac/CVA event).
- **Record** any of the following:
    - re-admission to ICU
    - death (including cause)
    - re-transplantation
- **Record new medications** (specific; since last visit: anti-depressants/anti-anxiolytics, prescribed sleeping adjuncts, analgesics.
- **Immunosuppression regimen** (including renal-sparing regimen if required)

The following **assessments/investigations** (nurses checklists, CRFs) will take place at visit 9:

- **Full clinical examination** (including general, cardiovascular, respiratory, abdominal, neurological)
- **Clinical Observations** – as per visit 1-6
- **Nutrition/Physical/functional status** – as per visit 1-6
- **LFI** – as per visit 1-6
- **Questionnaires** (DASI, SF-36v2, HCCQ, Basic PNSE, BREQ-2) – as per visit 1-6
- **Blood tests (non-fasted)** – as per visits 8 and 9
- The following **additional mechanistic 'muscle' sub-study' investigations** (nurses checklists, CRFs) will take place at visit 1 (*if consented for sub-study*) in the *following order*:
    - **specialist biomarkers** – as per visits 1 and 2
    - **right Quadricep Muscle size, architecture and quality (Ultrasound)** – as per visits 1 and 2.
    - **CPET** – as per visits 1 and 2
    - **6MWT (supervised by the study AHPs or Clinical Research Fellow/PI)** – as per visits 1 and 2.

End of study Intervention:

After completion of the assessments/investigations, participants will have a face-to-face consultation with the study physiotherapist:

- **Intervention Group 1 (see section 7):** This visit will mark the end of the study intervention delivered by the physiotherapists. No further personalised written HBEP will be provided. The participant will have a face-to-face consultation with the study physiotherapist. "Empowering Physio" techniques will be finalised and the participant will be given advice on the following domains to promote long-term motivation/engagement with exercise after the study intervention:
    - decisional balance patient-centred goal setting
    - supports attempts to change behaviour
    - normalised failed attempts
    - problem-solving
- **Control Group 2 (see section 7)**: No further patient 'exercise' advice leaflets will be provided.

Exercise Monitoring (**section 7.7**):

The physiotherapist will collect, store and download (if electronic) the participants:

- **Participant 'exercise' diary (paper booklet)** (intervention group only)
- **'Blinded' wrist worn accelerometer (Actigraph GT9X)**

Preparation for next trial visit 10 (48-weeks post-LT):

The participant will be given a time/date for their next trial visit appointment, which where possible will be on the same day as their routine post-LT clinic. The participant will be provided with a participant 'exercise' diary (intervention group only) and encouraged to continue to record any exercises undertaken between visits 9 and 10.

9.6. Post-LT (follow-up) Visit 10 (48 weeks +/- 14 days) – max. 60 mins

The end of study follow-up visit 10 (post-LT +/- 14 days) will take place alongside the participants routine post-LT clinic (*where possible*). The following investigations and data collection will take place at this visit:

- **Record LT Surgical complications/SAEs (frequency, CTCAE grade), including**: biliary stricture/anastomosis, bile leak, wound dehiscence, new onset ascites (requiring LVP, admission), abdominal collection (requiring drainage/intravenous Antibiotics), haematoma/bleeding (requiring surgical/radiological intervention), anaemia requiring blood transfusion, AKI (requiring renal replacement therapy), Ileus/bowel obstruction, re-laparotomy, portal vein thrombosis, hepatic artery (or conduit) thrombosis, bacteraemia requiring intravenous antibiotics, hyperglycaemia requiring insulin infusion, infection (Pneumonia; Cholangitis; Urinary tract; Wound; Peritonitis; CNS; CMV), other (record), acute rejection (biopsy proven*)
    - *mild [ ] moderate [ ] severe [ ]
    - pulsed steroids [ ]
    - T-cell [ ] AMR (+DSA) [ ]

  Other (i.e. Seizure, cardiac/cva event; reason for re-admission to hospital):

- **Record** any of the following:
    - re-admission to ICU
    - death: (including cause)
    - re-transplantation

The following **assessments/investigations** (nurses checklists, CRFs) will take place at visit 10:

- **Full clinical examination** (including general, cardiovascular, respiratory, abdominal, neurological)
- **Clinical Observations** – as per visit 1-6
- **Nutrition/Physical/functional status** – as per visit 1-6
- **LFI** – as per visit 1-6
- **Questionnaires** (DASI, SF-36v2, HCCQ, Basic PNSE, BREQ-2) – as per visit 1-6
- **Blood tests (non-fasted)** – as per visit 9

At the end of trial visit 10 (end of study), a member of the research team will:

- Collect/store the participant 'exercise' diary (intervention group only).
- Ensure the patient has a date for their next routine NHS post-LT clinic appointment.
- Research team will inform in writing the GP, LT units clinician and the local hospitals hepatologist that the patient has completed the trial.
- The patient will be thanked for their participation and will be informed of any future trial results, conclusions and publications in writing (or via the PPI and patient support groups).

9.7. Follow-up post visit 10.

If participants are still willing to continue with data collection after 48 weeks post LT, the following data will be collected until the end of study:

- Death (and cause)
- Re-transplantation

Data will be collected from patient notes and captured by NHSBT and existing transplant databases at participating sites.

9.8. Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants will be asked about their ongoing willingness to continue participation at all visits. Participants will be made aware from the beginning of the trial that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a *particular* aspect of the trial (i.e. study intervention, sub-study), but give consent to participate in the remaining trial visits and outcome measure data collection. The date and reason the patient withdraws consent for a *particular* aspect of the trial (state 'reason unknown' if no reason provided) will be clearly documented in the patient's medical notes.

To enable enrolment into the ExaLT trial, all patients must give consent to participate in the pre-LT and post-LT treatment period, follow-up appointments and compliance with investigations required

for treatment efficacy and safety monitoring. At any stage between randomisation and the 48-week post-LT visit, a patient may withdraw consent from being a participant in trial, without necessarily giving a reason and without any personal disadvantage. The details of withdrawal will be clearly documented and communicated to the ExaLT Trial Office. The date and reason the participant withdraws consent (state 'reason unknown' if no reason provided) will be clearly documented in the participant's medical notes. Should the participant wish to withdraw from the mechanistic 'muscle' sub-study, they will still, unless otherwise specified remain in the ExaLT trial.

Participants found to be ineligible post randomisation should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation.

The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention, but is willing to be followed up in accordance with the schedule of assessments (i.e. Participant questionnaires completed) and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis). To maintain trial participation, the participant can also reduce the frequency of their study and follow-up visits, especially if they are struggling with the trial commitment (main aim will be to ensure that visit 9 primary and secondary outcome data points are collected.

No trial related follow-up: The participant does not wish to attend trial visits in accordance with the schedule of assessments, but is willing to be followed up at standard clinic visits (i.e. collect frailty measures) and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes of levels in participation within trial (date, reason and category of status change) will be clearly documented in the source documents (patient's medical notes) and the Change of status CRF).

The investigators can withdraw a participant from the trial, after consideration of the benefit: risk ratio, at any stage of the trial. Justifiable reasons for doing so include:

- Removal from the national LT waiting list, due to:
    - poor compliance with clinic/hospital visits and/or medical therapy (i.e. alcohol relapse)
    - terminal illness/palliation (i.e. HCC out of LT criteria, irreversible 'too' unwell for LT)

- ‘too’ well for LT (i.e. liver disease has improved significantly that LT is not indicated)
- participants request

- Technical grounds (e.g. patient moves away from trial area and can no longer meet the requirements of the trial protocol)
- Pregnancy (very *unlikely in this patient population*)
- Unpredictable events (non-clinical or clinical): any event which at the discretion of the PI and/or CI makes further treatment inadvisable (i.e. incarceration)

All participants will be included in the analysis based on the intention to treat principle, either to the point of the end-point of the trial or to the point in which consent was withdrawn from participation in the trial.

10. ADVERSE EVENT REPORTING

10.1. Definitions

Table 8: Adverse event reporting definitions

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant’s usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant’s usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Consists of a congenital anomaly/ birth defect Or is otherwise considered medically significant by the Investigator**

Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

10.2. Adverse event recording – general

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of Good Clinical Practice (GCP) as set out in the UK statutory instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA). Definitions for AEs reporting are listed in **Table 8** in **Section 10.1**.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

10.3. Adverse event reporting in ExaLT

The study population have a life-threatening liver disease that requires major curative LT surgery. Therefore, due to the nature of the severity of their disease and the symptom burden that accompanies the natural history of advanced liver disease, there are expected to be a high number of Adverse Events (AEs) in these patients. For this reason, as well as the low-risk nature of the trial intervention (HBEP) to study participants, only Serious Adverse Events (SAEs) will be reported.

The reporting period for SAEs in ExaLT will be from the day of randomisation (baseline visit 1) until the end of trial follow-up (visit 10). The safety profile for this trial population and interventions are well characterised so a strategy of targeted reporting of SAEs will not affect the safety of participants.

10.4. Serious Adverse Advents (SAE) reporting in ExaLT

For all SAEs, the PI or delegate must do one of the following:

- **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the trials office on an SAE form as per **Section 10.4.1**.

- **Report SAEs to the ExaLT Trial Office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 10.4.2.

- **Report SAEs to the ExaLT Trial Office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per **Section 10.5** Expedited SAE Reporting process.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

10.4.1. SAEs not requiring reporting to the ExaLT Trial Office

At whatever time they occur during an individual's participation, from the baseline visit to end of participant follow-up (visit 10), the following are not considered to be critical to evaluations of the safety of the trial:

- Hospital admissions that last less than 24 hours (e.g. symptomatic anaemia requiring no emergency intervention)
- Pre-planned hospitalisation (e.g. elective paracentesis or post-LT elective biliary drain removal)

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

10.4.2. SAEs requiring non-expedited reporting to the ExaLT Trial Office

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition), and the SAE, may be known. That is, such events are protocol-defined as "expected" (see Section 10.5.2 Assessment of expectedness of a related SAE by the CI).

Such events should still be recorded by the trial team in the participant's notes and reported to the ExaLT Trial Office on the follow-up CRF but they do not require expedited reporting (immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined. These include:

- **Pre-LT:**
  - admission to hospital due to hepatorenal syndrome/AKI, severe hepatic encephalopathy, variceal haemorrhage requiring OGD +/- banding, serious fall/musculoskeletal injury, cardiac or cerebrovascular event (STEMI/NSTEMI/angina/arrhythmia/CVA/cerebral haemorrhage), sepsis/infection as a consequence of SBP and/or pneumonia).
- **Post-LT:**
  - jaundice
  - confusion/delirium
  - fever/night sweats

- severe gastrointestinal symptoms (vomiting/diarrhoea/nausea/loss of appetite)
- significant fall/injury due to physical frailty
- biliary stricture/anastomosis
- bile leak
- wound dehiscence
- new onset ascites (requiring LVP, admission)
- abdominal collection (requiring drainage/intravenous antibiotics),
- haematoma/bleeding (requiring surgical/radiological intervention)
- anaemia requiring blood transfusion
- AKI (requiring renal replacement therapy)
- ileus/bowel obstruction
- re-laparotomy
- portal vein thrombosis
- hepatic artery (or conduit) thrombosis
- bacteraemia requiring intravenous antibiotics
- hyperglycaemia requiring insulin infusion
- infection (pneumonia; cholangitis; urinary tract; wound; peritonitis; CNS; CMV),
- acute rejection (biopsy proven*)
    - *mild, moderate or severe
    - pulsed steroids
    - T-cell or antibody-mediated rejection

10.4.3. SAEs requiring expedited reporting to the ExaLT Trial Office

All SAEs not listed in **sections 10.4.1** and **10.4.2** must be reported to the ExaLT Trial Office on a trial specific SAE form within 24 hours of the site research team becoming aware of the event. Examples include:

- Death
- Re-transplantation
- Multi-system organ failure requiring ICU support

10.5. Expedited SAE Reporting process

On becoming aware that a participant has experienced a SAE which requires expedited reporting the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the ExaLT Trial Office.

To report an expedited SAE to the ExaLT Trial Office, the PI or delegate must complete, date and sign the trial-specific SAE form together with any other relevant, appropriately pseudoanonymised reports. Data should be submitted to the ExaLT Trial Office using the information below in accordance with the timelines given in **Section 10.4.2** and **10.4.3**.

To report a SAE

[Within 24 hours of becoming aware of event]

Complete a SAE form in REDCap online database

Email the ExaLT Trials Office: ExaLT@trials.bham.ac.uk

Sites should report the expedited SAE **within 24 hours** of becoming aware of the event. To report a SAE, complete a SAE form using the REDCap online database. In the unlikely event REDCap is not available [i.e. due to system failure], a paper SAE Form should be submitted to the ExaLT Trial Office via email. In this case, the site should enter the SAE into the REDCap as soon as it is operational.

Each SAE will be allocated a unique reference number by REDCap [or the ExaLT study Office if online system is not available]. The ExaLT study Office will notify the site via email as proof of receipt of SAE. The site and the ExaLT Trial Office should ensure that the SAE reference number is quoted on all correspondence regarding the SAE and correspondence filed in the ISF.

Where a SAE form has been completed by someone other than the PI initially [or the medically qualified delegate], the SAE form must be countersigned by the forenamed PI or the medically qualified delegate to confirm agreement with the causality and severity assessments.

If the site has not received confirmation of receipt of the SAE within 1 working day of reporting, the site should contact the ExaLT Trial Office.

10.5.1. Assessment of causality of a related SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see **Table 9**) of the event.

In defining the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per **Table 9**, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trials office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

On receipt of an SAE form, the ExaLT Trial Office will forward it, with the unique reference number, to the CI or delegate who will independently* review the causality of the SAE. A SAE judged by the PI or CI or delegate to have a reasonable causal relationship ("Related" as per Table 9**: Categories of causality**) with the intervention will be regarded as a related SAE. The severity and causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees

with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI an independent clinical causality review will be performed.

Table 9: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

10.5.2. Assessment of expectedness of a related SAE by the CI

The CI or delegate(s) will also assess all related SAEs for expectedness with reference to the criteria in **Table 10**.

Table 10: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information. For the purposes of the ExaLT Trial, **Section 10** of the approved ExaLT protocol will be used as the reference safety information.
Unexpected	An adverse event that is <u>not</u> consistent with known information about the trial related procedures.

If the event is unexpected (i.e. it is not defined in the protocol as an expected event) it will be classified as a related and unexpected SAE.

The CI will undertake review of all related SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

10.5.3. Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the ExaLT Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the Trial Office and the original kept in the ISF.

10.6. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The ExaLT Trial Office will submit a progress report to the Research Ethics Committee (REC), UoB Research Governance Team (RGT) annually starting 12 months after the date of the favourable opinion was given. An electronic copy should be emailed to the REC within 30 days of the end of the reporting period. The Trial Office will report all events categorised as Unexpected and Related SAEs to the REC and RGT within 15 days of being notified.

Details of all Unexpected and Related SAEs, and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

10.7. Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the reason why they have been taken.

10.8. Follow-up of pregnancy outcomes for potential SAEs

In the highly unlikely event that a participant was to become pregnant from date of consent until the end of the intervention period, the participant would be withdrawn from the intervention. We would however ask the participant if they were willing to continue being followed-up (data collection only).

The low risk (and general) nature of the intervention means that we would not follow-up the pregnancy or resulting offspring for SAEs.

11. DATA HANDLING AND RECORD KEEPING

11.1. Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. To allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Some data variables may be entered directly onto the CRF; these are clearly identified and detailed in **Table 11**.

Table 11: Source data in ExaLT

Data	**Source**
Participant Reported Outcomes (i.e. trial questionnaires)	The original participant-completed paper CRF is the source and will be kept with the participant's trial record at site. Sites will enter data into the REDCap online database.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be entered by Sites onto the relevant CRFs in the REDCap online database.
Imaging (i.e. muscle USS)	The source is the original imaging usually as an electronic file. Data may be supplied to the ExaLT Trial Office as a password-protected, pseudoanonymised, copy of the electronic file, or as an interpretation of the imaging provided on a CRF. Where data is interpreted, the CRF onto which it is first entered becomes the source.
Physical function/physical activity data (i.e. CPET, accelerometer)	The source is the original test out-puts which will usually be provided as an electronic file. Data may be supplied to the ExaLT Trial Office as a password-protected, pseudoanonymised copy of the electronic file, or as an interpretation of the test provided on a CRF. Where data is interpreted, the CRF onto which it is first entered becomes the source.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. telephone calls), must be documented in the source documents.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the medical notes.

11.2. Case Report Form (CRF) completion

ExaLT will use an online REDCap database. Sites will enter data directly onto the relevant form in REDCap. Paper CRFs completed prior to the REDCap database release will be stored in the investigator Site File [ISF]. The REDCap online database will include (but will NOT be limited to) the following Forms (see **Table 12**).

Table 12: Case report forms in ExaLT trial.

Form Name	Schedule for submission using online system
Randomisation form	At the point of randomisation
Baseline and follow-up CRFs including participant reported outcome measures (i.e. DASI; SF-36v2; 3 x behavioural questionnaires) and non-expedited SAEs. These include visits 1-10, in addition to Day of LT CRF and inpatient admission post-LT CRF.	As soon as possible after each follow-up assessment time point
Mechanistic 'muscle' sub-study CRF	As soon as possible after each sub-study assessment time point (visit 1, 2 and 9)
SAE form	If expedited: within 24 hours of site research team becoming aware of event.
Pregnancy notification form	As soon as possible after becoming aware of participant's pregnancy
Change of status form	As soon as possible after the point of reduced participation or death

A CRF should be completed for each individual participant.

It remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. The Site Signature & Delegation Log will identify all personnel with responsibilities for data collection. Site staff will be given individual unique usernames and will create their own private password to use the online REDCap database.

The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of data reported. This will be evidenced within the REDCap online database.

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. Missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to the ExaLT Trial Protocol.

The following guidance applies to data and partial data:

- Only CRFs provided by the Trial Office should be used.
- Time format – all times should be in accordance with the 24 hour clock.
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. E.g. 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. E.g. 3.4 rounded to the nearest whole number is 3.

- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied.
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible.
- Missing/incomplete data – should be clearly indicated/verified – all blank fields will be queried by the ExaLT Trial Office.
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the ExaLT Trial Office upon discovery.

11.3. Participant completed questionnaires

Participant completed questionnaires will be administered by a member of the research team at site and will be completed by the participant, during their visit. A member of the research team will check the questionnaires for missing data, whilst the participant is still in attendance. If missing data is identified, the participant will be asked if they intentionally didn't complete the data and if that is the case their wish will be respected.

11.4. Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific data management plan and include the processes of data entry, data queries.

Missing and ambiguous data will be queried using a data clarification system in line with the ExaLT data management plan and will focus on data required for trial outcome analysis and safety reporting. Single data entry by Site, with central monitoring by BCTU will be employed.

Site staff will enter data into the REDCap online database. The system will include in built data validation to improve data quality (e.g. to prevent nonsensical dates or numerical values).

Changes to the data, on the system will only be made by Site. BCTU staff will not have access to alter data on the online database but will be given a 'read-only view' of the trial data on the database.

Site staff will be given unique log-in usernames and will create their own private password to use the online system. These unique log-in details must not be shared with other staff. In no circumstances should staff at sites access the trial database using another person's login details. The ExaLT Trial Office will be unable to edit data in the online system.

11.5. Data security

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments).

The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, and separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office and will be implemented and maintained by the Programming Team.

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.

Operational processes: the data will be processed and stored within BCTU.

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

11.6. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g., signed ICFs, Investigator Site Files, participants' hospital notes, and paper CRFs (if used)) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 10 years in accordance with the Sponsor's policies and procedures.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Site set-up and initiation

All PIs will be asked to sign the necessary agreements including a site signature and delegation log between the PI and the ExaLT Trial Office and supply a current CV and GCP certificate. All members of the site research team are required to sign the site signature and delegation log, which details which tasks have been delegated to them by the PI. The site signature and delegation log should be kept up to date by the PI. It is the PI's responsibility to inform the ExaLT Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation, either a meeting or a tele/videoconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

12.2. Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

12.2.1. On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the ExaLT Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the ExaLT Trial Office staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

12.2.2. Central monitoring

The ExaLT Trial Office will check received ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the data management plan. Sites will be sent Data Clarification Forms (DCFs) requesting missing data or clarification of inconsistencies or discrepancies.

12.3. Audit and inspection

The PI (or delegate) will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The PI (or delegate) will comply with these visits and any required follow-up. Sites are also requested to notify the ExaLT Trial Office of any relevant inspections or local audits.

12.4. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Sites are therefore requested to notify the ExaLT Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the ExaLT Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture (i.e. Final Patients Final Visit [FPFV]) including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The ExaLT Trial Office will notify the REC and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the REC within 15 days of the end of trial. The Trial Office will provide the REC and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

Ethical approval for the mechanistic 'muscle' sub-study will be granted as part of the main ExaLT protocol. Therefore, the date of last data capture (i.e. FPFV) will include the final processing of all samples (including the sub-study specialist biomarkers), as specified in the protocol.

14. STATISTICAL CONSIDERATIONS

14.1. Sample size

The mean PCS of the SF-36v2 QoL survey for patients with advanced liver disease or on the LT waiting list is approximately 39-42, with a standard deviation [SD] ranging from 8 to 24.(21, 36, 44, 63) Previous studies have indicated that LT alone improves PCS by +4 points (≈10%) compared to pre-LT. In contrast, small studies post-LT have highlighted that basic, supervised exercise interventions improve the PCS by +8-9 points (≈20%). However, no studies to date have incorporated a pre- and post-LT exercise programme, with the addition of theory-based motivational support.

Hence for the sample size calculation we are proposing a +4 point (10%) improvement in the control arm and +12 point (30%) improvement in the experimental arm. Therefore, a meaningful clinically important difference [MCID] of 8 points with a SD of 16 will be used. The MCID is the smallest change in an outcome sufficiently important to influence management and is crucial for designing and interpreting comparative effectiveness trials. A MCID of +8 in QoL (using SF-36v2 questionnaires) has been previously reported in patients who rated their health as "excellent" or "very good" after abdominal surgery.(67) Members of the LT PPI group stated that improvement differences in PCS (SF-36v2) of up to 20% between the control and experimental treatment arms, would imply that the treatment has had a significant impact on the patients' QoL.

To detect an MCID of 8 points with SD of 16, 90% power and a type I error rate of 5%, using the standard method of difference in means (2-sided), a total of 172 participants will be required. NHS data reports that approximately 30-35% of patients on the waiting list for LT will not have their transplant within 1-year of randomisation (NHSBT database 2015 to 2020). Hence the sample size needs to be inflated to account for this and other possible dropouts. Adjusting for a 35% attrition/drop-out rate, a total of 266 participants (133 per group) will need to be recruited.

This sample size is predicted to be large enough to measure the impact of the intervention on surgical complications post LT using the CCI (i.e. key secondary outcome measure). The mean CCI post LT in

European centres is approximately 40 (range 0-100). A 25% reduction in CCI with intervention versus the control (10-points i.e. 40 vs. 30 by 6 months post transplantation) is considered a clinically meaningful improvement. With a total of 172 participants (before inflating for any attrition/drop-outs), we estimate that there will be approximately 74-87% power (alpha 5%, 2-sided test, SD 25) to detect a mean CCI difference of 10-12 points between the intervention versus control. We feel these are realistic, yet conservative estimates of power, as simulation methods (Stata 16) revealed higher power for non-parametric data – which is very possible with CCI post-LT.

14.2. Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

The primary comparison groups will be composed of those randomised to the intervention group (group 1) versus those randomised to the control group (group 2). Analyses will be based on the intention to treat (ITT) principle, i.e., participants will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised intervention or protocol deviations. In the first instance, for the primary outcome and any relevant secondary outcomes, analysis will be based on the modified ITT set, with the modified ITT set being those patients that have had a LT within 52 weeks (+ 2 weeks) from randomisation.

For all major outcomes, appropriate summary statistics and differences between groups (e.g. mean differences, relative risks, hazard ratios, etc.) will be presented with 95% confidence interval from two-sided tests. Analyses will be adjusted for the minimisation variables and baseline scores (where appropriate). There will be no adjustment for multiple testing.

14.2.1. Primary outcome(s)

The primary outcome is the PCS from the SF-36v2 QoL at 24-weeks post-LT. The SF36v2 QoL questionnaire will be administered at baseline for all randomised patients, during the pre-LT period (which will be variable between patients depending on how early they have their LT) and then at set intervals following their LT (i.e. at 6, 12, 24 and 48 weeks post LT). The data for this outcome is continuous and therefore will be summarised at each time-point (pre and post-LT) using the mean and standard deviation along with minimum and maximum values with respect to the two intervention arms and overall.

Modified ITT set analysis (Post-LT)

For the analysis of the primary outcome, initially the data collected at baseline and after LT will be considered in the first instance. The difference between group means and associated 95% confidence interval (CI) at the primary time point (i.e. 24 weeks post-LT) will be estimated through the use of a repeated measures, mixed-effects linear regression model. Data collected at assessment times for baseline and the post-LT time points up to 24 weeks will be included. Data collected at 48-weeks post LT will not be included. Parameters allowing for participant, intervention arm, baseline score, time and the randomisation minimisation variables will be included (all as fixed effects). Time will be

assumed to be a categorical (fixed) variable. To allow for a varying treatment effect over time, a time by treatment interaction parameter will be included in the model. Estimates of the least-squares mean differences between groups at the relevant time-points will be estimated from the model including this interaction parameter.

ITT set analysis (Pre-LT)

Given there is a possibility that some patients that are randomised may not end up having a LT within 52 weeks (+ 2 weeks) of being randomised, they are initially excluded from the primary outcome analysis. However, to ensure we account for all randomised patients, we will undertake a secondary analysis which will include all randomised patients regardless of having had a LT.

This analysis will only include data for the PCS of SF36v2 collected at baseline and for the pre-LT time-points only (excluding any data collected post-LT). Given patients will have a LT at different time-points (with some possibly never having a LT within 52 weeks of being randomised), we will analyse the time to LT between the groups. Patients that do not have a LT within 52 weeks (+ 2 weeks) post randomisation will be censored at 52 weeks (+ 2 weeks). A Cox proportional hazard model will be fitted on the time to LT data, and results will be expressed as the hazard ratio with 95% confidence intervals. Kaplan-Meier curves will be constructed for visual presentation of time-to-event comparisons. As a further analysis, we will explore the time to LT and pre-LT SF36v2 data using a joint model approach. This method of analysis will jointly fit the time to event (i.e. LT) data with the longitudinal PCS data collected at pre-LT time-points for all randomised patients. The results from these analyses will be interpreted alongside the findings from main primary outcome results, i.e. modified ITT set analysis.

14.2.2. Secondary outcomes

The secondary outcomes are a combination of continuous, time-to-event and categorical data.

Continuous outcomes:

The secondary outcomes that are continuous data (e.g. CCI, MCS, DASI, LFI, length of ICU and hospital stay) will be analysed using the same analysis methods as described for the primary outcome modified ITT set.

Time-to-event outcomes:

The secondary outcomes that are time-to-event data (e.g. mortality) will be analysed using survival analysis methods. Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons. A Cox proportional hazard model will be fitted, and results will be expressed as the hazard ratio with 95% confidence intervals.

Categorical outcomes:

The secondary outcome, LFI, can be summarised as continuous data (*as above*) or categorised into robust, pre-frail, or frail. The data for this outcome is summarised in 3 orderly categories; 1 = "≤3.2 (robust)", 2 = "3.2-4.5 (pre-frail)", 3 = ">4.5 (frail)". The analysis for this outcome will be conducted using a multilevel mixed-effects ordered logistic regression model and results will be expressed as odds ratio with 95% confidence intervals.

14.2.3. Planned subgroup analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see Section 6 – ENROLMENT, RANDOMISATION and BLINDING) and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.2.4. Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This however presents a risk of bias, and so sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include using multiple imputation with chained equations to impute any missing data.

Further sensitivity analysis will include a Complier Average Causal Effects (CACE) analysis for the primary outcome.

Full details will be included in the Statistical Analysis Plan.

14.2.5. Planned final analyses

The primary analysis for the trial will occur once:

- The last randomised patient has had their LT and their 24-weeks follow-up assessment post LT completed, OR
- When the last randomised patient has not had their LT within 1 year (52 weeks) of being randomised and once all corresponding outcome data has been entered onto the trial database and validated as being ready for analysis.

15. SUB-STUDY: Mechanistic 'Muscle' sub-study (n=100)

The main aim of the 'muscle' sub-study is to undertake a detailed evaluation of the biological and physiological mechanisms that may underlie any exercised-induced improvements in clinical outcomes, including QoL and physical function/frailty. A better understanding of how exercise works (i.e. on the muscular and cardiopulmonary systems) will guide future studies in terms of exercise dose-responses ('frequency', 'intensity', 'duration') that are required in patients with end-stage liver disease to maximise the efficiency and longevity of LT.

The objectives of the 'muscle' sub-study are:

1. To calculate the 'dose' of exercise (frequency, intensity, duration) completed before (after 6-weeks intervention) and after LT (after 25-72 weeks intervention, depending on the timing of LT).
2. To determine if 'dose' of exercise achieved before and after LT is associated with changes in:

   a. QoL (PCS, MCS)
   b. physical frailty (LFI and its 3 components)
   c. cardiopulmonary fitness (DASI, CPET, 6MWT)
   d. muscle mass/thickness (quadricep ultrasound)
3. To investigate if the HBEP improves the following before and after LT:
   a. muscle mass/thickness (quadricep ultrasound)
   b. cardiopulmonary fitness (CPET, 6MWT)
   c. serological markers of oxidative stress/muscle inflammation (specialist biomarkers)

   and whether these improvements are associated with clinical measures of physical frailty (LFI) and QoL (PCS, MCS).

A sub-group of 100 participants (from a total of 266 patients enrolled in the ExaLT trial) will be recruited to the mechanistic 'muscle' sub-study. Participants will be recruited continuously on a voluntary basis at both trial sites, until the target of 100 participants is achieved. Participants will have to provide written consent for the sub-study at the same time as providing consent for the main ExaLT study. The 'muscle' sub-study will contain the same proportion of participants in group 1 (n=50, exercise/motivation programme) and group 2 (n=50, control arm) as randomisation for the ExaLT trial will be minimised for participation in the 'muscle' sub-study (in addition to age, UKELD, gender and trial site). In addition, the DMC will be able to review (based on annual reports) that the baseline characteristics of the muscle sub-study population are representative of the main ExaLT trial.

At any stage between randomisation and 24 weeks post-LT (end-of-treatment [EOT]), a patient may withdraw consent from being a participant in the 'muscle' sub-group study, without necessarily giving a reason and without any personal disadvantage. The details of withdrawal will be clearly documented and communicated to the Trials Office. The date and reason the patient withdraws consent (state 'reason unknown' if no reason provided) will be clearly documented in the patient's medical notes. By withdrawing from the 'muscle' sub-study, unless specified, the patient will continue to be a participant for the remainder of the ExaLT trial, as this will not impact on the primary outcome measure (QoL).

On patient withdrawal from sub-study, blood samples already collected may have had extensive analysis performed on them, therefore we request that "withdrawal of approval for use of previously donated samples" is not permitted in the sub-study. Participants will be made aware of this in the patient information sheet prior consenting to the sub-study.

After randomisation, participants who have consented for the 'muscle' sub-study will undergo sub-study investigations at the following time points:-

- Baseline visit (visit 1), within 3 days of randomisation, **prior** to starting the study intervention (or control):
- 6 weeks of study intervention (pre-LT visit 2)
- 24 weeks after LT (post-LT visit 9; end of intervention) or sub-study visit 6 (48 weeks + 28 days) if received no LT.

The following investigation will be performed at each time point:-

- CPET to determine standard measures such as anaerobic threshold and peak oxygen consumption (i.e. integrated response to the physiological stress of maximal exercise)
- Quadricep muscle ultrasound to assess skeletal muscle thickness.
- Venous blood sampling to assess the following specialist biomarkers:
    - Common measures of oxidative stress: Total redox status, malonyldialdehyde, Myeloperoxidase, 4-Hydroxynonenal.
    - Serum antioxidant capacity: catalase, glutathione peroxidase and superoxide dismutase.
    - A profile of key myokines, including: interleukin(IL)-6, IL-10, IL-15, Irisin, leukaemia inhibitory factor, and secreted protein acidic and rich in cysteine (SPARC)
    - Tumour necrosis factor alpha (TNF-α) (not a myokine, but an inflammatory marker).

The baseline (visit 1) to 6 week (visit 2) pre-LT datasets will determine the short-term effect of the study intervention whilst on the LT waiting list. In the event that the participant undergoes LT prior to visit 2 (i.e. between weeks 0 to 6; unpredictable timing), the investigations will not be repeated until post-LT visit 9 (end of intervention). The post-LT dataset (visit 9) will determine the longer-term effect (i.e. prehabilitation and 24-weeks rehabilitation post-LT) of the study intervention on muscle, inflammation and cardiopulmonary fitness, alongside the main ExaLT trial primary and secondary outcome measures. Throughout the 'muscle' sub-study the control arm will provide the benchmark for the investigations performed on the pre-LT waiting list and 24-weeks after the LT.

In the event that a patient has not undergone a LT in the pre-LT timeframe (1 year), they will be given the *option* if they would like to consent to a muscle sub-study (CPET etc) at visit 6. As they will not be undergoing a LT within the study timeframe, the Visit 6 (+ 28 days' time window) optional sub-study visit will enable us to understand if the changes identified between weeks 0 (visit 1) and weeks 6 (visit 2) have been sustained.

A full standard operating procedure (SOP) will be produced for this sub-study.

15.3. Blood and Urine Samples for Future Research

Participants enrolled into the mechanistic sub-study will be given the option for remaining blood samples (i.e. post analysis) to be safely stored and used in future ethically approved research. At the QEUHB site only, urine samples will also be collected for future research. Urine is considered 'relevant material' under the Human Tissue Act 2004. The tracking, storage and consent for future research within the ExaLT study is in accordance with this current legislation. Participants taking part in the mechanistic sub-study will be given the option for a maximum of three 20-30ml urine samples taken as part of their routine care, to be collected and safely stored for future ethically approved research. Urine samples will be collected at similar time points as the research blood samples for the mechanistic study (i.e. visit 1, visit 2 pre LT and visit 9 (post LT) or visit 6 (+ 28 day- time window) if no

LT at 52 week. Participants will be informed that general health information accompanies these samples and that the samples may be shared with a wide range of researchers and institutions and there is a possibility of commercial or therapeutic applications.

15.4. Sample tracking

All human tissue samples should be traceable from the point of collection to the point of disposal. An individual or individuals at each site will be delegated the role of sample collection and tracking. Tracking will occur wherever samples are transported or transferred between separate physical locations.

When samples are transported for storage or for analysis, documentation detailing the date of shipment, the number of samples being shipped and the nature of the samples will be maintained and filed within the ISF or TMF as appropriate. The laboratory receiving the samples will provide a signed receipt confirming that the correct number of samples have been received in an appropriate condition. Details of all shipments and receipts will be filed in the TMF/ISF. The sponsor and the CI will be notified of any issues identified during sample shipment.

A contractual agreement must be in place between the sponsor and external body prior moving material (i.e. samples and associated general medical data) to an external body for analysis or future research. The model Non-Commercial Agreement (mNCA) agreement between sponsor and each NHS trust will cover the movement of samples from trust sites to the Institute of Biomedical research (IBR) at the University of Birmingham for storage prior analysis.

15.5. Sample storage

The analysis of the bloods samples will be undertaken as part of the data collection before the end of study declaration. If consent for future research has not been given, samples will be destroyed prior the end of study declaration. Where consent for future research has been given, samples must be transferred to a HTA licensed storage facility or ethically approved research study prior the end of study declaration. Consent forms must be retained for the duration of sample storage. Sample disposal must be documented and retained by the laboratory. All documents pertaining to sample management must be retained by the laboratory.

16. TRIAL ORGANISATIONAL STRUCTURE

16.1. Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

16.2. Coordinating centre

The trial-coordinating centre (ExaLT Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

16.3. Trial Management Group (TMG)

The Trial Management Group (TMG) comprises of individuals responsible for the day-to-day management of the trial: the CI, Co-CIs, PIs, Co-applicants, Trial Statisticians, Trial Manager and Data Manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

16.4. Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the ExaLT Trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct, and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC). The TSC will operate in accordance with a trial specific TSC Charter.

16.5. Data Monitoring Committee (DMC)

The role of the independent DMC is to monitor the trial data, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence. The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

16.6. Finance

The research costs of the ExaLT trial are funded by the National Institute of Health Research (NIHR) Efficacy and Mechanism Evaluation Programme (Ref: NIHR129318) awarded to Dr Matthew Armstrong, University of Birmingham. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess treatment costs associated with the trial, e.g., gaining consent, are estimated in the Statement of Activities. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

17. ETHICAL CONSIDERATIONS

The ExaLT trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant

subsequent amendments), which include Data Protection Act 2018; Human Tissue Act 2004; Mental Capacity Act 2005; and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments). The protocol will be submitted to and approved by the REC prior to the start of the trial. Before any participants are randomised into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

18. DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Personal data categories that will be collected and analysed include name, date of birth, NHS number and primary/secondary NHS healthcare records (including past medical history, GP practice, drug history).

Participants will only be identified by their **3 digit unique trial identification number** and **initials** on routine correspondence with the ExaLT BCTU Trial Office. The following personal identifiable data (PID) will be collected on the CRFs:

Table 13: PID captured in the ExaLT trial.

Form name	**PID**
Randomisation form	Trial number, participant's full name, date of birth, gender and NHS number
Baseline and follow-up CRFs including participant reported outcome measures (i.e. DASI; SF-36v2; 3 x behavioural questionnaires). These include visits 1-10, in addition to day of LT CRF and inpatient admission post-LT CRF Mechanistic 'muscle' sub-study CRF Change of status form	Trial number and initials
SAE form Pregnancy notification form	Trial number and partial date of birth

At site data will be securely handled and maintained in controlled access locations and follow local NHS policies and procedures for information security. The sponsor (UoB) will ensure Patient consent forms and randomisation forms are kept separately to the rest of the CRFs, in a locked filing cabinet,

in an office with controlled swipe access. Data will be entered onto a Redcap database held on secured University of Birmingham servers with restricted access and permissions.

Participants will acknowledge the transfer and storage of their informed consent form to the ExaLT Trial Office. This will be used to perform central monitoring of the consent process. Participants will acknowledge the transfer of their personal data for the purpose of medical research to BCTU at UoB. Participants will acknowledge the transfer of their personal data to BCTU at UoB, who will be processing data on behalf of the trial.

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the ExaLT Trial Office and sponsor (UoB) may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The ExaLT Trial Office will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party.

19. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

20. INSURANCE AND INDEMNITY

UoB has in place clinical trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation (QEUHB or RFH) responsible for the clinical site and is therefore indemnified through the NHS Litigation Authority.

21. POST-TRIAL CARE

In keeping with the Declaration of Helsinki 2013, all trial participants will be followed up in their routine NHS post-LT clinics and will receive the standard of healthcare in place at the time. If the participant has any ongoing additional healthcare needs at the end of the trial (i.e. disability, mental health illness) they will be referred onto the relevant specialist (i.e. physiotherapist, social care worker, psychiatrist) by the clinical/research team (i.e. PI or local clinician). There will be NHS trust funding (QEUHB, RFH) to prescribe the physiotherapist delivered 'home-based exercise and theory-based motivation support programme' in the future if the trial proves that the intervention is safe and efficacious (i.e. meets the primary end-point).

22. ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management group (TMG) and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Data will typically be available 6 months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant TMG, and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

23. PUBLICATION PLAN

Outputs from the ExaLT trial will be submitted for publication in peer reviewed journals and the findings of the trial will be made public. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review. The participants will be provided with a lay written summary of the outcome of the trial, alongside provision of the publication.

In all publications, authors should acknowledge that the trial was performed with the support of the NIHR, University of Birmingham and BCTU. Intellectual property rights will be addressed in the site agreement between Sponsor and site.

24. ADDITIONAL PLANNING

24.1 **Virtual study visits** - Protocol planning during significant UK events and/or consistent inability to visit the trial site.

A significant UK event would include:

- Viral pandemic (Local, regional, or national lockdowns) restricting hospital visits/travel and the re-introduction of social distancing.
- Industrial strike action (i.e. transport, education/university, NHS healthcare) limiting access to hospital care or trial visits.
- Terrorist or war threat to the UK.

In the event of one of the above or severe mitigating circumstances (i.e. prolonged hospital admission meaning unable to attend a series of trial visits or the 'key' primary end-point visit 9) there will be the option (approved by the local PI or CI/Co-CI) of minimal trial data capture via:

- Face-to-face trial visit on the inpatient ward (if patient hospitalised at QEUHB or RF):
    - As judged appropriate by the local PI/CI the patient will undergo trial visit investigations as per a pre-LT or post-LT visit, as described previously and with particular emphasis on:
        - SF-36v2 (primary end-point)
        - Record 'new' clinical events since last visit: Current/recent illnesses (<6 weeks)
        - Record Serious Adverse Events (SAEs)
        - Nutritional/physical/functional indices (including HGS, MAMC, LFI, DASI)
        - Study Questionnaires (HCCQ, Basic PNSE, BREQ-2)
        - Blood tests – as per visit 1 or visit 9

- Telecall and/or video call trial visit:
    - As judged appropriate by the local PI/CI the patient will undergo trial visit investigations over the phone as per a pre-LT or post-LT, as described previously and with particular emphasis on:
        - SF-36v2 (primary end-point)
        - Record 'new' clinical events since last visit: Current/recent illnesses (<6 weeks)
        - Record Serious Adverse Events (SAEs)
        - Study Questionnaires (DASI, HCCQ, Basic PNSE, BREQ-2)
        - 5 Sit-to-stand (STS) chair stands – if video call
        - 3 Balance tests (as part of LFI) – if video call
        - Wet weight (kg) – if video call
        - Blood tests – if local clinician (GP/hospital) are able to undertake and email using secure NHS approved email addresses.

In the event of a 'Virtual' trial visit the rationale will be clearly documented. A 'Virtual' trial visit will be under exceptional circumstances and will not reverted to as an easier/more convenient default trial visit.

25. REFERENCE LIST

1. Williams R, Alexander G, Aspinall R, Batterham R, Bhala N, Bosanquet N, Severi K, et al. Gathering momentum for the way ahead: fifth report of the Lancet Standing Commission on Liver Disease in the UK. Lancet 2018;392:2398-2412.
2. https://www.nsd.scot.nhs.uk/publications.
3. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant 2014;14:1870-1879.
4. Patel MS, Mohebali J, Shah JA, Markmann JF, Vagefi PA. Readmission following liver transplantation: an unwanted occurrence but an opportunity to act. HPB (Oxford) 2016;18:936-942.
5. Son YG, Lee H, Oh SY, Jung CW, Ryu HG. Risk Factors for Intensive Care Unit Readmission After Liver Transplantation: A Retrospective Cohort Study. Ann Transplant 2018;23:767-774.
6. https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/[Data from Rhiannon Taylor; NHSBT Senior Statistician; 1/3/2019].
7. Froghi F, Koti R, Gurusamy K, Mallett S, Thorburn D, Selves L, James S, et al. Cardiac output Optimisation following Liver Transplant (COLT) trial: study protocol for a feasibility randomised controlled trial. Trials 2018;19:170.
8. Onghena L, Develtere W, Poppe C, Geerts A, Troisi R, Vanlander A, Berrevoet F, et al. Quality of life after liver transplantation: State of the art. World J Hepatol 2016;8:749-756.
9. Saab S, Wiese C, Ibrahim AB, Peralta L, Durazo F, Han S, Yersiz H, et al. Employment and quality of life in liver transplant recipients. Liver Transpl 2007;13:1330-1338.
10. Phu S, Boersma D, Duque G. Exercise and Sarcopenia. J Clin Densitom 2015;18:488-492.
11. Sinclair M, Gow PJ, Grossmann M, Angus PW. Review article: sarcopenia in cirrhosis--aetiology, implications and potential therapeutic interventions. Aliment Pharmacol Ther 2016;43:765-777.
12. Dunn MA, Josbeno DA, Tevar AD, Rachakonda V, Ganesh SR, Schmotzer AR, Kallenborn EA, et al. Frailty as Tested by Gait Speed is an Independent Risk Factor for Cirrhosis Complications that Require Hospitalization. Am J Gastroenterol 2016;111:1768-1775.
13. Sinclair M, Poltavskiy E, Dodge JL, Lai JC. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. World J Gastroenterol 2017;23:899-905.
14. Tandon P, Tangri N, Thomas L, Zenith L, Shaikh T, Carbonneau M, Ma M, et al. A Rapid Bedside Screen to Predict Unplanned Hospitalization and Death in Outpatients With Cirrhosis: A Prospective Evaluation of the Clinical Frailty Scale. Am J Gastroenterol 2016;111:1759-1767.
15. Muller X, Marcon F, Sapisochin G, Marquez M, Dondero F, Rayar M, Doyle MMB, et al. Defining Benchmarks in Liver Transplantation: A Multicenter Outcome Analysis Determining Best Achievable Results. Ann Surg 2018;267:419-425.
16. Ney M, Haykowsky MJ, Vandermeer B, Shah A, Ow M, Tandon P. Systematic review: pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates. Aliment Pharmacol Ther 2016;44:796-806.
17. Orman ES, Ghabril M, Chalasani N. Poor Performance Status Is Associated With Increased Mortality in Patients With Cirrhosis. Clin Gastroenterol Hepatol 2016;14:1189-1195 e1181.
18. Painter P, Krasnoff J, Paul SM, Ascher NL. Physical activity and health-related quality of life in liver transplant recipients. Liver Transpl 2001;7:213-219.
19. Tapper EB, Baki J, Parikh ND, Lok AS. Frailty, Psychoactive Medications, and Cognitive Dysfunction Are Associated With Poor Patient-Reported Outcomes in Cirrhosis. Hepatology 2018.

20. Derck JE, Thelen AE, Cron DC, Friedman JF, Gerebics AD, Englesbe MJ, Sonnenday CJ. Quality of life in liver transplant candidates: frailty is a better indicator than severity of liver disease. Transplantation 2015;99:340-344.
21. Macdonald S, Jepsen P, Alrubaiy L, Watson H, Vilstrup H, Jalan R. Quality of life measures predict mortality in patients with cirrhosis and severe ascites. Aliment Pharmacol Ther 2019;49:321-330.
22. Bownik H, Saab S. Health-related quality of life after liver transplantation for adult recipients. Liver Transpl 2009;15 Suppl 2:S42-49.
23. Campillo B, Fouet P, Bonnet JC, Atlan G. Submaximal oxygen consumption in liver cirrhosis. Evidence of severe functional aerobic impairment. J Hepatol 1990;10:163-167.
24. Dharancy S, Lemyze M, Boleslawski E, Neviere R, Declerck N, Canva V, Wallaert B, et al. Impact of impaired aerobic capacity on liver transplant candidates. Transplantation 2008;86:1077-1083.
25. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, Feng S. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology 2017;66:564-574.
26. National Institute for Health and Care Excellence. Behaviour change: general approaches. 2013. Report No.: Public health guideline 6.
27. Duda JL, Williams GC, Ntoumanis N, Daley A, Eves FF, Mutrie N, Rouse PC, et al. Effects of a standard provision versus an autonomy supportive exercise referral programme on physical activity, quality of life and well-being indicators: a cluster randomised controlled trial. Int J Behav Nutr Phys Act 2014;11:10.
28. Mathur S, Janaudis-Ferreira T, Wickerson L, Singer LG, Patcai J, Rozenberg D, Blydt-Hansen T, et al. Meeting report: consensus recommendations for a research agenda in exercise in solid organ transplantation. Am J Transplant 2014;14:2235-2245.
29. Williams FR, Berzigotti A, Lord JM, Lai JC, Armstrong MJ. Review article: impact of exercise on physical frailty in patients with chronic liver disease. Aliment Pharmacol Ther 2019;50:988-1000.
30. Debette-Gratien M, Tabouret T, Antonini MT, Dalmay F, Carrier P, Legros R, Jacques J, et al. Personalized adapted physical activity before liver transplantation: acceptability and results. Transplantation 2015;99:145-150.
31. Roman E, Garcia-Galceran C, Torrades T, Herrera S, Marin A, Donate M, Alvarado-Tapias E, et al. Effects of an Exercise Programme on Functional Capacity, Body Composition and Risk of Falls in Patients with Cirrhosis: A Randomized Clinical Trial. PLoS One 2016;11:e0151652.
32. Zenith L, Meena N, Ramadi A, Yavari M, Harvey A, Carbonneau M, Ma M, et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. Clin Gastroenterol Hepatol 2014;12:1920-1926 e1922.
33. Morkane CM, Kearney O, Bruce D, Melikian C, Martin DS. An outpatient hospital-based exercise training programme for patients with cirrhotic liver disease awaiting transplantation: a feasibility trial. Transplantation 2019.
34. Jones M, Jolly K, Raftery J, Lip GY, Greenfield S, Committee BS. 'DNA' may not mean 'did not participate': a qualitative study of reasons for non-adherence at home- and centre-based cardiac rehabilitation. Fam Pract 2007;24:343-357.
35. Webb GJ, Hodson J, Chauhan A, O'Grady J, Neuberger JM, Hirschfield GM, Ferguson JW. Proximity to transplant center and outcome among liver transplant patients. Am J Transplant 2019;19:208-220.
36. Krasnoff JB, Vintro AQ, Ascher NL, Bass NM, Paul SM, Dodd MJ, Painter PL. A randomized trial of exercise and dietary counseling after liver transplantation. Am J Transplant 2006;6:1896-1905.
37. Moya-Najera D, Moya-Herraiz A, Compte-Torrero L, Hervas D, Borreani S, Calatayud J, Berenguer M, et al. Combined resistance and endurance training at a moderate-to-high intensity improves physical condition and quality of life in liver transplant patients. Liver Transpl 2017;23:1273-1281.

38. Williams FR, Vallance A, Faulkner T, Towey J, Durman S, Kyte D, Elsharkawy AM, et al. Home-Based Exercise in Patients Awaiting Liver Transplantation: A Feasibility Study. Liver Transpl 2019;25:995-1006.
39. Williams FR, Vallance A, Faulkner T, Towey J, Kyte D, Durman S, Johnson J, et al. Home-based exercise therapy in patients awaiting liver transplantation: protocol for an observational feasibility trial. BMJ Open 2018;8:e019298.
40. Kruger C, McNeely ML, Bailey RJ, Yavari M, Abraldes JG, Carbonneau M, Newnham K, et al. Home Exercise Training Improves Exercise Capacity in Cirrhosis Patients: Role of Exercise Adherence. Sci Rep 2018;8:99.
41. Nishida Y, Ide Y, Okada M, Otsuka T, Eguchi Y, Ozaki I, Tanaka K, et al. Effects of home-based exercise and branched-chain amino acid supplementation on aerobic capacity and glycemic control in patients with cirrhosis. Hepatol Res 2017;47:E193-E200.
42. Tanikella R, Kawut SM, Brown RS, Jr., Krowka MJ, Reinen J, Dinasarapu CR, Trotter JF, et al. Health-related quality of life and survival in liver transplant candidates. Liver Transpl 2010;16:238-245.
43. Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. BMJ 2002;324:1417.
44. Kabar I, Husing-Kabar A, Maschmeier M, Voller C, Dumke M, Schmidt HH, Heinzow H. Pictorial Representation of Illness and Self Measure (PRISM): A Novel Visual Instrument to Quantify Suffering in Liver Cirrhosis Patients and Liver Transplant Recipients. Ann Transplant 2018;23:674-680.
45. Lai JC, Segev DL, McCulloch CE, Covinsky KE, Dodge JL, Feng S. Physical frailty after liver transplantation. Am J Transplant 2018;18:1986-1994.
46. Rouse PC, Duda JL, Ntoumanis N, Jolly K, Williams GC. The development and validation of the Interpersonal Support in Physical Activity Consultations Observational Tool. Eur J Sport Sci 2016;16:106-114.
47. Ware JE, Jr. SF-36 health survey update. Spine (Phila Pa 1976) 2000;25:3130-3139.
48. 2009. SF-36v2 Health Survey.
http://www.qualitymetric.com/WhatWeDo/GenericHealthSurveys/SF36v2HealthSurvey.
49. Ware JE, Kosinski M, and Dewey J. 2001. How to Score Version 2 of the SF-36 Health Survey.
50. Schlegel A, Linecker M, Kron P, Gyori G, De Oliveira ML, Mullhaupt B, Clavien PA, et al. Risk Assessment in High- and Low-MELD Liver Transplantation. Am J Transplant 2017;17:1050-1063.
51. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, Feng S. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology (Baltimore, Md.) 2017;66:564-574.
52. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol 1989;64:651-654.
53. Carter R, Holiday DB, Grothues C, Nwasuruba C, Stocks J, Tiep B. Criterion validity of the Duke Activity Status Index for assessing functional capacity in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2002;22:298-308.
54. Tang WH, Topol EJ, Fan Y, Wu Y, Cho L, Stevenson C, Ellis SG, et al. Prognostic value of estimated functional capacity incremental to cardiac biomarkers in stable cardiac patients. J Am Heart Assoc 2014;3:e000960.
55. Wu JR, Lennie TA, Frazier SK, Moser DK. Health-Related Quality of Life, Functional Status, and Cardiac Event-Free Survival in Patients With Heart Failure. J Cardiovasc Nurs 2016;31:236-244.
56. Neuberger J, Gimson A, Davies M, Akyol M, O'Grady J, Burroughs A, Hudson M, et al. Selection of patients for liver transplantation and allocation of donated livers in the UK. Gut 2008;57:252-257.

57. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018-1026.
58. Heissel A, Pietrek A, Rapp MA, Heinzel S, Williams G. Perceived Health Care Climate of Older People Attending an Exercise Program: Validation of the German Short Version of the Health Care Climate Questionnaire. J Aging Phys Act 2020;28:276-286.
59. Leisterer S, Gramlich L. Having a Positive Relationship to Physical Activity: Basic Psychological Need Satisfaction and Age as Predictors for Students' Enjoyment in Physical Education. Sports (Basel) 2021;9.
60. Markland, D. & Tobin, V. (2004). A modification of the Behavioral Regulation in Exercise Questionnaire to include an assessment of amotivation. Journal of Sport and Exercise Psychology, 26, 191-196.
61. Fortier MS, Duda JL, Guerin E, Teixeira PJ. Promoting physical activity: development and testing of self-determination theory-based interventions. Int J Behav Nutr Phys Act 2012;9:20.
62. Hamilton DM, Haennel RG. Validity and reliability of the 6-minute walk test in a cardiac rehabilitation population. J Cardiopulm Rehabil 2000;20:156-164.
63. Sciurba F, Criner GJ, Lee SM, Mohsenifar Z, Shade D, Slivka W, Wise RA, et al. Six-minute walk distance in chronic obstructive pulmonary disease: reproducibility and effect of walking course layout and length. Am J Respir Crit Care Med 2003;167:1522-1527.
64. Ney M, Haykowsky MJ, Vandermeer B, Shah A, Ow M, Tandon P. Systematic review: pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates. Alimentary Pharmacology & Therapeutics 2016;44:796-806.
65. Akagi R, Iwanuma S, Fukuoka M, Kanehisa H, Fukunaga T, Kawakami Y. Methodological issues related to thickness-based muscle size evaluation. J Physiol Anthropol 2011;30:169-174.
66. Levett DZH, Jack S, Swart M, Carlisle J, Wilson J, Snowden C, Riley M, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. Br J Anaesth 2018;120:484-500.
67. Antonescu I, Scott S, Tran TT, Mayo NE, Feldman LS. Measuring postoperative recovery: what are clinically meaningful differences? Surgery 2014;156:319-327.