SUPPLEMENTARY METHODS

Physiotherapy Training

To ensure consistency across sites, the physiotherapists receive formal training from FW (Senior Liver 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 JD (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.

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, an additional four patient video recordings **per physio** will take place at patient 40 (+/-3) and

patient 60 (+/-3) (total 8 additional recordings per physio). Visit recordings will be identical to those completed at patient 20 (+/-3) and 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 audio for Telecalls and visual recordings for 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.

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

The main aim of the 'muscle' sub-study was 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 were:

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) were recruited to the sub-study. Participants were recruited continuously on a voluntary basis, until the target of 100 participants is achieved. Participants had to provide written consent for the sub-study at the same time as providing consent for the main EXALT study. The sub-study aimed to contain the same proportion of participants in group 1 (n=50, HBEP) and group 2 (n=50, control arm), as randomisation for the EXALT trial was minimised for participation in the sub-study (in addition to age, UKELD, gender and trial site). In addition, throughout the duration of the trial the DMC are able to review (based on annual reports) whether the baseline characteristics of the sub-study population are representative of the main EXALT trial.

At any stage between randomisation and 24 weeks post-LT (end-of-treatment), a patient may withdraw consent from being a participant in the sub-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 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 (SF-36v2 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 sub-study will undergo the following baseline investigations (in addition to the EXALT trial baseline investigations at visit 1; within 3 days) prior to starting the study intervention (or control):

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 patient's 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 LT assessment or monitoring in the two LT units in the EXALT trial. In addition, patients on the LT waiting list have already been through a standardised cardiorespiratory risk assessment and have been deemed physically fit to proceed to LT 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 LT 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 LT and their health.

3. **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). 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 and urine):** Blood will be centrifuged, processed and then stored at -80^{o}C at the study sites before being transferred to the University of Birmingham (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, 20-30ml of urine will be stored for future research providing ethical approval for these additional studies has first been obtained.

These investigations will then be repeated after 6 weeks of study intervention (pre-LT visit 2) and 24 weeks after LT (post-LT visit 9; end of intervention). 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 sub-study the control

arm will provide the bench mark for the investigations performed on the pre-LT waiting list and 24-weeks after the LT.

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 affected 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).

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.