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'Effects of a home-based bimodal lifestyle intervention in frail patients with end-stage liver disease awaiting orthotopic liver transplantation': study protocol of a non-randomised clinical trial

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ABSTRACT

Introduction Patients with end-stage liver disease awaiting orthotopic liver transplantation (OLT) are generally classified as frail due to disease-related malnutrition and a progressive decline in musculoskeletal and aerobic fitness, which is associated with poor pre-OLT, peri-OLT and post-OLT outcomes. However, frailty in these patients may be reversable with adequate exercise and nutritional interventions.

Methods and analysis Non-randomised clinical trial evaluating the effect of a home-based bimodal lifestyle programme in unfit patients with a preoperative oxygen uptake (VO_2) at the ventilatory anaerobic threshold ≤13 mL/kg/min and/or VO_2 at peak exercise ≤18 mL/kg/min listed for OLT at the University Medical Center Groningen (UMCG). The programme is patient tailored and comprises high-intensity interval and endurance training, and functional exercises three times per week, combined with nutritional support. Patients will go through two training periods, each lasting 6 weeks.

The primary outcome of this study is the impact of the programme on patients' aerobic fitness after the first study period. Secondary outcomes include aerobic capacity after the second study period, changes in sarcopenia, anthropometry, functional mobility, perceived quality of life and fatigue, incidence of hepatic encephalopathy and microbiome composition. Moreover, number and reasons of intercurrent hospitalisations during the study and postoperative outcomes up to 12 months post OLT will be recorded. Finally, feasibility of the programme will be assessed by monitoring the participation rate and reasons for non-participation, number and severity of adverse events, and dropout rate and reasons for dropout.

Ethics and dissemination This study was approved by the Medical Research Ethics Committee of the UMCG (registration number NL83612.042.23, August 2023) and is registered in the Clinicaltrials.gov register (NCT05853484). Good Clinical Practice guidelines and the principles of the Declaration of Helsinki will be applied. Results of this study will be submitted for presentation at (inter)national congresses and publication in peer-reviewed journals.

Trial registration number NCT05853484.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The previously established concept of home-based prehabilitation for patients undergoing major abdominal surgery is adapted to frail patients with end-stage liver disease awaiting orthotopic liver transplantation (OLT).
⇒ Comprehensive evaluation of predetermined study outcomes, coupled with regular assessments, facilitates the examination of both effectiveness and feasibility.
⇒ The programme is semisupervised, and the adherence of patients to the protocol throughout the study period is still to be determined.
⇒ Due to the possibility of patients undergoing OLT during the study period, it is anticipated that not all patients will be able to complete the entire study.

INTRODUCTION

Patients with end-stage liver disease (ESLD) awaiting orthotopic liver transplantation (OLT) are generally classified as frail, which is defined as a clinical syndrome characterised by unintentional weight loss, self-reported exhaustion, muscle weakness and low physical activity.[1] Disease-related malnutrition and deterioration in musculoskeletal and aerobic fitness contributes to frailty in patients with ESLD, and is strongly correlated with poor pre-OLT, peri-OLT and post-OLT outcomes.[2–10] However, adequate physical exercise training and nutritional support, a concept better known as 'prehabilitation', can

help improve frailty in these patients, and is progressively implemented in non-transplant surgical fields.[4 11] Noteworthy, the average time patients spent on the waiting list for OLT provides a suitable opportunity to execute a prehabilitation programme.

Emerging evidence suggests that prehabilitation is safe, feasible and effective in patients with ESLD.[12–20] However, previous studies contain several limitations that hamper definitive conclusions. First, the small sample size and selection of relatively fit patients limit the generalisability of the reported results. Second, most programmes were hospital or community based, which can influence participation rate and patient's adherence to the protocol. Especially unfit patients might experience physical difficulty in persevering an intense exercise programme outside their homes for prolonged periods.[21] Third, a variety of physical exercise training regimens and training intensities were reported, ranging from high-intensity interval training (HIIT) to low-intensity walking programmes. Franssen *et al* suggested that personalised HIIT in combination with adequate supervision to ensure sufficient training exposure is the most effective exercise regimen to improve aerobic fitness.[22] Lastly, previous studies merely used inaccurate assessment modalities (eg, the 6-min walk test) to detect improvement in aerobic fitness. Instead, the cardiopulmonary exercise test (CPET) is regarded as the gold standard in aerobic fitness assessment.[23]

Malnutrition is associated with the progression of liver failure and a higher rate of disease-related complications.[5] Yet, previous studies often forgot to include nutritional support in their programme. Adequate nutritional intake is a key component to enhance the anabolic effect of exercise programmes.[24] Protein intake stimulates the transport of amino acids into muscle fibres, thereby contributing to the synthesis of myofibrillar proteins.[24] Moreover, transport of amino acids into muscle fibres is also essential for the synthesis of mitochondrial proteins required for aerobic metabolism and thus aerobic fitness.[24–26] Hence, as previously pointed out by Gillis *et al*, interventions to improve physical fitness should be designed to draw on this synergetic effect between physical exercise training and nutrition.[24]

Taken together, in the current study, frail patients with ESLD awaiting OLT will be invited to partake in a semisupervised home-based bimodal prehabilitation programme, comprising a physical exercise programme and nutritional intervention. The primary objective is to assess the impact of the programme on improving patients' aerobic fitness.

METHODS AND ANALYSIS

Study design

This is a single-centre, single-arm, non-randomised clinical trial investigating the effect and feasibility of a semisupervised home-based bimodal lifestyle programme (FIT4Cirrhotics@Home) in patients with ESLD awaiting OLT. The study takes place at the University Medical Center Groningen (UMCG), Groningen, the Netherlands, expected start in late 2023 and will run until patient inclusion is completed (anticipated in early 2025). In this article, the latest version of the study protocol (version 3, August 2023) will be discussed. For this study protocol, Standard Protocol Items: Recommendations for Interventional Trials guidelines were adhered to.[27 28]

Patient and public involvement

This study's methodology and objectives were formulated solely by the researchers, without active patient involvement. However, the researchers have previously conducted a similar home-based bimodal lifestyle programme with high patient-reported satisfaction scores.[29]

Eligibility criteria

All patients must meet the following inclusion criteria: (1) aged at least 18 years, (2) diagnosed with ESLD and listed for OLT, (3) oxygen uptake (VO_2) at the ventilatory anaerobic threshold (VAT) ≤13 mL/kg/min and/or VO_2 at peak exercise (VO_{2peak}) ≤18 mL/kg/min, (4) understands spoken and written Dutch language and (5) understands the purpose of the study and has given informed consent to participate. Patients meeting any of the following exclusion criteria will be excluded: (1) experienced a major adverse cardiac event (eg, myocardial infarction) or cerebrovascular accident in the past 6 months, (2) medical history of an uncontrolled heart rhythm disorder, (3) hepatic encephalopathy grade 3–4, (4) acute (on chronic) liver failure, (5) non-treated oesophageal varices, (6) model for end-stage liver disease score ≥30 or (7) incapable of cycling.

Recruitment

Prior to being listed for transplantation, patients with ESLD will be screened for contraindications for OLT by the consulting hepatologist. During this screening, patients will be informed about the current study. Next, as part of standard care, patients being listed for OLT are rereferred for CPET to determine baseline aerobic fitness. Based on CPET results, eligible patients will be contacted by the trial coordinator to provide extensive information about the study, and plan the first study visit if patients are interested in participating in the study. During the first study visit, written informed consent will be obtained from patients, after which baseline assessments will be performed. Importantly, patients will be informed that if they are called for OLT during the study period, the programme will stop immediately.

Home-based bimodal prehabilitation programme

The study comprises an exercise programme combined with nutritional support during two periods of 6-week home-based training each (12 weeks in total), followed

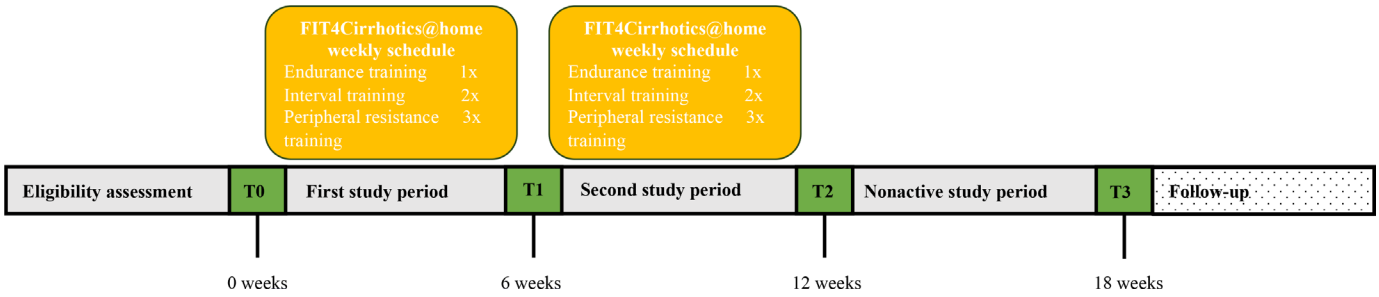

Figure 1 Timeline of the study.

by a non-active study period (figure 1). During the non-active period, patients are actively followed up, with the aim to evaluate whether a relapse in frailty of patients occurs, or if patients are able to maintain their fitness (eg, by pursuing exercise initiatives).

High-intensity interval and endurance training

Each week, patients will perform two HIIT and one endurance training session on an advanced cycle ergometer in an upright position (Lode Corival Home+, Lode BV, Groningen, the Netherlands) delivered to the patients' home (figure 2). A community physical therapist in the living area of the patient will be asked to supervise the patient, after receiving verbal and written instructions on the use of the cycle ergometer and goals and content of the programme. During the first week, all training sessions are supervised, and during the remaining weeks solely the first training session. The physical therapist supervision plan is the same for both study periods (online supplemental figure 1).

Furthermore, in order to individually set up, monitor progression and optimise the exercise intensity accordingly, in the first week and thereafter every other week, patients will perform a steep ramp test (SRT) under supervision of the physical therapist.[30] Based on SRT performance, training intensity for the subsequent training sessions will be determined. The HIIT sessions consist of a 3-min warmup at 20 W, 14 high-intensity intervals of 30 s at 60% of the peak work rate achieved at the SRT interspersed with 14 low-intensity intervals of 60 s at 20 W, and a cool-down recovery of 1 min, thereby taking 25 min to execute (table 1). Next, the endurance training sessions consist of a 3-min warmup at 20 W, followed by two endurance intervals of 15 min each at 40% of the peak work rate achieved at the SRT interspersed with a 5-min low-intensity interval at 20 W, and a cool-down recovery of 3 min, thereby taking 40 min to execute (table 2).

Directly after each training session, patients will be asked to fill out the 6–20 Borg-scale for rating of perceived exertion.[31] Moreover, data about training duration and intensity (work rate), heart rate (variability) and pedalling frequency will be uploaded to an online platform. Both the physical therapist and the trial coordinator are able to access this online platform, and are as such able to remotely monitor training progression and adherence. The physical therapist will discuss the training results on a regular basis with the patient, and can, in case of unexpected problems, consult the trial coordinator.

Peripheral resistance training

The patient will be instructed to perform different types of functional exercises (a total of nine exercises of about 30 s, with 1 min rest interspersed) three times a week:

Figure 2 The cycle ergometer used in the home-based physical exercise training programme.

Table 1 High-intensity interval training structure

Training phase	Duration	Training intensity	Pedalling frequency
Warm-up	3 min	20 W	40–80 rpm
Interval training	21 min intervals (n=14)	**Work interval intensity** 30 s at 60% of the WR_{peak} achieved at the steep ramp test **Low recovery intensity** 60 s at 20 W	60–100 rpm 40–60 rpm
Recovery	1 min	20 W	40–80 rpm

rpm, revolutions per minute; W, watt; WR_{peak}, work rate at peak exercise.

Table 2 Moderate-intensity endurance training structure

Training phase	Duration	Training intensity	Pedalling frequency
Warmup	3 min	20 W	40–80 rpm
Endurance interval training	35 min intervals (n=2)	**Endurance training intensity** 15 min at 40% of the WR_{peak} achieved at the steep ramp test **Recovery intensity** 5 min at 20 W	60–100 rpm 40–60 rpm
Recovery	2 min	20 W	40–80 rpm

rpm, revolution per minute; W, watt; WR_{peak}, work rate at peak exercise.

- Three different exercises of 8–15 repetitions of elastic band exercises of the upper extremities with a Thera-Band to improve muscle strength and endurance (with resistance varying by colour from light to heavy).
- Three repetitions of the 30-s chair stand test for the lower extremities.
- Three repetitions of 30-s stepping up and down on the first tread of the stairs for the lower extremities.

Patients will be provided with a set of Thera-Band resistance bands. The resistance band training will be executed with a maximum of 8–15 repetitions, consistent with 60%–80% of the one-repetition maximum (1-RM).[32] The 1-RM for each of the three exercises of the patient will be individually determined using the indirect 1-RM determination via the Oddvar-Holten diagram.[33] In short, this calculation is done as follows: the physical therapist makes an estimation of the weight that can be lifted (with a Thera-Band) for 10–20 times; the number of repetitions that can be maximally performed is registered; the percentage of intensity can then be found in the Oddvar-Holten diagram at the number of repetitions and 1-RM can be computed by the formula: ((lifted weight (kg) × 100%)/percentage of corresponding intensity). During the first week, the physical therapist will explain and supervise the patient during the resistance training. In this way, the patient will become familiar with the exercises to execute them unsupervised. In weeks 2–6, progression is monitored on a weekly basis.

Nutritional support

As part of standard care, all patients listed for OLT are referred to a specialised dietician for a nutritional assessment. The consulting dietician evaluates the current nutritional intake of patients, informs patients about the increased risk of malnutrition as a serious complication of ESLD and gives dietary advice to achieve and maintain a sufficient and balanced nutritional intake. Furthermore, individual patients' protein requirements are calculated based on their fat free mass.[34] Patients with inadequate protein intake are given dietary advice to increase their protein intake, and a prescription for additional protein supplementation if necessary. Additionally, to potentiate the muscle protein response and enhance the anabolic effect of the exercise programme, patients of this study will be provided with protein supplementation (ProSource-Nocarb, GLNP B.V., Naarden, the Netherlands). The protein supplementation comes in sachets and provides a standard dosage of 15 g of a high quality (whey and casein) protein and 60 kcal. Patients are instructed to dissolve the sachets in 250 mL of a dairy product to come to a total of approximately 20 g protein. The protein supplementation is sugar free, which makes it also suitable for use in patients with diabetes. Patients are instructed to take the protein supplementation immediately following each training sessions. During each study visit, the trial coordinator will evaluate the intake of the protein supplementation.

Study assessments

During four study visits (T0, T1 T2, T3), with an interval of 6 weeks in-between, all study assessments will be performed. A detailed events schedule is depicted in table 3.

Aerobic fitness

Under supervision of a sports physician, patients perform a CPET on an electronically braked cycle ergometer in an upright position (Lode Excalibur Sport, Lode BV, Groningen, the Netherlands). During the test, patients will be fitted with a 12-lead ECG to measure heart rate response, as well as with a face mask (7450 V2, Hans Rudolph, Kansas City, Missouri, USA) that is connected to a calibrated respiratory gas analysis system to determine breath-by-breath VO_2, carbon dioxide production, and minute ventilation (Quark CPET, Cosmed Benelux BV, Nieuwegein, the Netherlands). Patients will be instructed to maintain a pedalling frequency between 60 and 80 rpm throughout the test. The test begins with 2 min of resting measurements, followed by a 3-min warmup phase of unloaded cycling. Subsequently, work rate increases by constant work rate increments of 5, 10, 15, or 20 W/min, depending on the patient's self-reported fitness and intended to ensure a test duration between 8 and 12 min. During the study, the patient will be reassessed at the CPET using the same protocol of work rate increments chosen at the screening CPET. The test continues until the patient is physically unable to maintain at least 60 rpm, despite strong verbal encouragement.

The test effort will be considered maximal when the heart rate at peak exercise is ≥85% of predicted and/or a respiratory exchange ratio at peak exercise ≥1.10 is achieved. The VAT will be determined using the ventilatory equivalents and V-slope method.[35 36] VO_{2peak} will be

Table 3 Events schedule

Events schedule							
Procedure	**Screening**	**T0**	**First study period**	**T1**	**Second study period**	**T2**	**T3**
Week	0	0	0–6	6	12-Jun	12	18
Eligibility assessment							
Informed consent	X						
Inclusion/exclusion criteria	X						
Study assessments							
Aerobic fitness							
CPET	X	X*	X	X	X	X	X
Steep ramp test		X		X			
Sarcopenia							
Muscle thickness		X		X		X	X
SARC-F questionnaire		X		X		X	X
Liver disease specific frailty							
Liver Frailty Index		X		X		X	X
Anthropometry							
BMI		X		X		X	X
Quality of life							
SF-36		X		X		X	X
LDSI		X		X		X	X
Perceived fatigue							
MFI		X		X		X	X
Anxiety and depression							
STAI-6		X		X X		X X	X X
PHQ-9		X					
Hepatic encephalopathy							
West Haven		X		X		X	X
ANT		X		X		X	X
Microbiome composition							
Stool sample		X		X		X	X

*Results of the screening CPET are used for the T0 assessment.
ANT, animal naming test; BMI, body mass index; CPET, cardiopulmonary exercise test; LDSI, liver disease symptom index; MFI, multidimensional fatigue index; PHQ-9, 9-item Patient Health Questionnaire; SARC-F, Strength, Assistance with walking, Rising from a chair, Climbing stairs and Falls; SF-36, 36 item short form; STAI-6, 6 item Spielberger State-Trait Anxiety Inventory.

determined by calculating the average VO_2 over the last 30 s of the test.

Aerobic capacity is also estimated by performing a SRT on a biweekly basis on the cycle ergometer at the patients' home. A modified version of the SRT will be used to increase feasibility in an unfit patient population with low physical resilience.[30] Patients will be instructed to maintain a pedalling frequency between 60 and 80 rpm throughout the test. The test starts with a 2-min warmup phase of unloaded cycling, followed by an incremental phase with constant increments of 10 W per 10 s (1 W/s) until a sustained drop in pedalling frequency below 60 revolutions occurs, despite strong verbal encouragement. The test is ended with a 2-min cooling-down phase with unloaded cycling. The main outcome, the achieved work rate at peak exercise (WR_{peak}), is used to determine the training intensity in the subsequent training sessions (see tables 1 and 2) and has been found to correlate strongly with VO_{2peak} attained at the CPET.[30]

Sarcopenia

To assess skeletal muscle status, the cross-section (anterior–posterior diameter) of the musculus biceps brachii, rectus femoris and vastus intermedius will be measured bilaterally with a handheld ultrasound system (Philips FUS6882 Lumify L12-4, Philips, Eindhoven, the Netherlands).[37] Patients will be positioned in a supine position to acquire full muscle relaxation. Subsequently,

the transducer will be placed perpendicular to the long axis of the muscles. The musculus biceps brachii will be measured at two-thirds of its length, between the tip of the acromion and elbow fold with the elbow extended and the forearm in supine position. The musculus rectus femoris and vastus intermedius will be measured halfway between the spina iliaca anterior superior and the cranial border of the patella. A ruler will be used to measure the distance between anatomical landmarks and ensure fixed measuring points for each study visit.

Moreover, patients will be asked to fill out the Strength, Assistance with walking, Rising from a chair, Climbing stairs and Falls questionnaire to reflect health status changes associated with the consequences of sarcopenia.[38]

Liver disease specific frailty

The Liver Frailty Index (LFI) will be determined using the Liver Frailty calculator (available at: https://liver-frailtyindex.ucsf.edu).[39] Besides sex, the LFI comprises three performance-based metrics. First, the isometric muscle force from grip strength of the hand will be measured using a hand-held dynamometer (HHD) (Jamar FAB12-0604+, JLW Instruments, Chicago, USA). The patient will be seated and asked to hold the HHD vertically with one hand while executing the maximal voluntary grip-force contraction test. To prevent muscle fatigue, both hands will be tested in counterbalanced order, and a 30-s break between tests will be maintained. Next, the time it takes to rise from and sit down on a chair five times (Timed Chair-Stand test) is measured. The patients' arms should be folded across the chest, and the timer is started when they first rise from the chair and stopped when they are standing after the fifth chair rise. If the patient cannot complete all five times of rising and sitting again in 60 s, 0 will be entered for the time. Finally, a balance test is performed by testing three feet positions (side-by-side, semitandem and tandem) for 10 s each. For each position, the timer is started when the patients' feet are in the correct position and they have let go of any support. If they are losing position the timer is stopped, and the patient will be reminded that they need to hold the position for the entire 10 s for it to count. The patient may try again, but if they do not complete the test, the time recorded will be used in the calculation. Additionally, the time it takes patients to cover a distance of 4 m is measured, enabling the determination of the short-physical performance battery as well.[40]

Anthropometry

Body mass and body height will be measured with a calibrated electronic scale (Inventum PW415ZW, Bilthoven, the Netherlands) and a metric measuring tape with a wall stop, respectively. The body mass index (kg/m^2) will be calculated as the body mass divided by the body height squared.

Quality of life

To assess generic physical and mental health related quality of life, the Short Form-36 health questionnaire will be used.[41] Next, the Liver Disease Symptom Index 2.0 will be used to assess how patients experience liver disease specific symptoms during daily activities.[42] The questionnaire evaluates symptom severity and symptom hindrance in the past week.

Perceived fatigue

Patients are asked to fill out the multidimensional fatigue inventory to assess the perceived level of fatigue.[43]

Anxiety and depression

The waiting-list period is for many patients a period of uncertainty and unpredictability, and consequently anxiety and depression are common among patients awaiting OLT.[44] During the study period, anxiety and depression symptoms will be evaluated using, respectively, the short-form of the Spielberger State-Trait Anxiety Inventory and the 9-item Patient Health Questionnaire.[45 46]

Hepatic encephalopathy

Clinically overt hepatic encephalopathy will be assessed by the West Haven criteria.[47] Additionally, minimal hepatic encephalopathy will be test for by conducting the animal naming test in patients.[48]

Microbiome compositions

ESLD is associated with alterations in microbiome composition, and an important consequence of these alterations is the development of pathological translocation of bacteria and bacterial products from the intestinal tract to the lymph nodes.[49] It is thought that this translocation triggers systemic inflammation that is characteristic of advanced ESLD, resulting in bacterial infections, a major cause of morbidity and mortality.[49] Physical activity might modulate the microbiome composition.[50] To investigate this association, patients will be asked to collect a faeces sample 1 day prior to each study visit. A FecesCatcher (TAG Hemi, Zeijen, the Netherlands) will be sent to the patients' home. Patients are provided with means (either ice cubes or a cooler) for cold storage to the study visit the following day. Subsequently, the faeces sample will be immediately stored at −80°C. Composition analysis will take place after completion of the study to avoid potential variation of a 'between-batch' effect.

It is pivotal to note that the goal of the microbiome measurements is to determine whether intraindividual changes are occurring in the microbiome of participating patients, regardless of the underlying cause. Within our hospital, we have a significant amount of reference data concerning the microbiome: ranging from ESLD (within Transplantlines[51]) to healthy individuals (within Lifelines[52]). If we observe that the participants' microbiome shifts during the course of the study from the unhealthy (Transplantlines) spectrum to the healthy spectrum (Lifelines), this provides additional context regarding the

multiple levels at which individuals are improving their condition in the study.

Study outcomes

Primary outcome

Primary outcome is to measure the effect of the bimodal lifestyle programme on the aerobic fitness of patients, defined as the absolute/relative change in VO_2 at the VAT and VO_{2peak} between study visit T1 and T0.

Secondary outcomes

Secondary outcomes are individual changes in aerobic fitness after the second and non-active study period. Furthermore, changes in sarcopenia, liver disease-specific frailty, anthropometry, perceived quality of life, fatigue and anxiety and depression symptoms, incidence of hepatic encephalopathy, microbiome composition and laboratory results will be compared. Also, number and reasons of intercurrent hospitalisations during the study, and postoperative outcomes up to 12 months post OLT are recorded.

Finally, feasibility of the programme will be determined by recording participation rate and reasons for non-participation, number and severity of adverse events, and dropout rate and reasons for dropout. Patients' adherence to the protocol will be determined based on data about training frequency, training intensity and training duration, which are uploaded to the online training platform.

Data analysis

Sample size calculation

A determinant of the primary outcome of this study, the VO_2 at the VAT, was used for the sample size calculation. Patients with ESLD are particularly frail and therefore we hypothesise that the expected mean increase in VO_2 at the VAT after the first 6-week study period will be approximately 1.5 mL/kg/min with an SD of 2.5 mL/kg/min, based on the study of Dunne *et al*.[53] If the true difference in the mean response of matched pairs is 1.5 mL/kg/min, 24 patients need to be included to be able to reject the null hypothesis that this response difference is zero with a probability (power) of 0.80. The type I error probability associated with this test of this null hypothesis is 0.05.

Statistical analysis

The R software package (R Foundation for Statistical Computing, Vienna, Austria) will be used for statistical analysis and a p-value of <0.05 will be considered statistically significant. Descriptive statistics, including mean±SD, median and IQR, and frequency distributions, will be used to display the baseline characteristics of the study cohort. A repeated measurements analysis will be used to analyse changes over time in the primary and secondary outcomes. The primary and secondary endpoints will be presented as a percentage (proportion), mean and actual numbers. For each outcome, a 95% CI for the mean based on the t-distribution will be presented. Furthermore, individual response profiles will be graphically depicted and presented in tables.

In case of missing data (eg, dropouts due to OLT during the study), the so far collected data of the home-based bimodal lifestyle programme, and postoperative outcomes will be used for the data analysis. Since individual differences in outcomes over time are compared, no multiple imputation approach will be applied in case of missing data. For the primary outcome, a predetermined subgroup analyses (stratification) will be performed for patients who completely adhered to the study protocol during the entire first 6 weeks of the study versus those who did not.

SAFETY CONSIDERATIONS

All (serious) adverse events ((S)AE) reported by the participant, or observed by the investigator or staff will be recorded in the case report form (CRF). The investigator will report all SAEs to the primary investigator without undue delay after obtaining knowledge of the event. An SAE will be reported through the web portal 'ToetsingOnline' to the accredited medical ethics committee within 7 days of first knowledge for SAE resulting in death or are life-threatening followed by a period of maximum 8 days to complete the initial preliminary report. All other SAE will be reported within a period of maximum 15 days after first knowledge of the event.

DATA ACCESS

Each participant will be assigned a unique number and their data will be captured in an electronic CRF. Participants will be informed that data will be pseudonymised. Encoded data will only be provided on request to authorised parties. Study data and human material will be stored up to 15 years after collection. Research data will be handled with due observance of the Dutch Law for Protection of personal data and the privacy statement of the centre.

ETHICS AND DISSEMINATION

Consent

Informed consent will be acquired by the trial coordinator or hepatologist, as appropriate. Both the patient and one of the aforementioned contributors have to sign the informed consent form with a wet signature, named and dated.

Ethical considerations

The study is approved by the Medical Ethics Committee Groningen, the Netherlands (registration number NL83612.042.23, August 2023). Any protocol amendments need to be reviewed and approved by the Medical Ethics Committee Groningen. This study will be conducted in accordance with Good Clinical Practice guidelines and

the principles of the Declaration of Helsinki. This study is registered in ClinicalTrials.gov (NCT05853484).

Dissemination

Results of this study will be submitted for presentation at (inter)national congresses and publication in a peer-reviewed journal. The trial coordinator will prepare the manuscript and authorship is determined by the publication policy as stated in the study protocol. A summary of the study findings will also be made available to the website of the funder, UMCG Transplantatiefonds, Groningen Transplant Center Foundation, Groningen, the Netherlands. This summary is intended to provide information about the most important study outcomes to the general public.

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