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Home-based exercise therapy in patients awaiting liver transplantation: Protocol for an observational feasibility trial

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DK, SD, JT, JJ, TP, AH - review/editing of final manuscript.

ABSTRACT

Introduction: Liver disease is the third commonest cause of premature mortality in the UK. Liver failure accelerates frailty resulting in skeletal muscle atrophy, functional decline and an associated risk of liver transplant waiting list mortality. However, there is limited research investigating the impact of exercise on patient outcomes pre-and post-liver transplantation. The waitlist period for patients listed for liver transplantation provides a unique opportunity to provide and assess interventions such as prehabilitation.

Method and Analysis: This study is a phase I observational study evaluating the feasibility of conducting a randomised control trial investigating the use of a home-based exercise program (HBEP) in the management of patients awaiting liver transplantation. Twenty eligible patients will be randomly selected from the Queen Elizabeth Hospital Birmingham Liver Transplant waiting list. Participants will be provided with an individually tailored twelve week HBEP, including step targets and resistance exercises. Activity trackers and patient diaries will be provided to support data collection. For the initial six weeks, telephone support will be given to discuss compliance with the study intervention, achievement of weekly targets, and to address any queries or concerns regarding the intervention. During weeks 6-12, participants will continue the intervention without telephone support to evaluate longer-term adherence to the study intervention. On completing the intervention, all participants will be invited to engage in a focus group to discuss their experiences and the feasibility of a RCT.

Ethics and Dissemination: The protocol is approved by the National Research Ethics Service Committee North West - Greater Manchester East and Health Research Authority (REC reference: 17/NW/0120). Recruitment into the study started in April 2017 and ended in July 2017. Follow-up of participants is ongoing and due to finish by the end of 2017. The findings of this study will be disseminated through peer-reviewed publications and international presentations.

Registration: clinicaltrials.govNCT02949505

Keywords: Prehabilitation, functional capacity, end-stage liver disease, liver transplantation.

Strengths:

1. This is the first study to investigate a home based exercise programme in patients with end-stage liver disease and listed for liver transplantation.
2. An extensive clinical evaluation of functional capacity and quality of life in a high risk group of patient in whom there is a pressing need for optimisation prior to transplantation.

Limitations:

1. A pilot study of small sample size, but with the aim and design focusing on the feasibility of a randomised control trial of prehabilitation in patients awaiting liver transplantation.

INTRODUCTION

Liver disease is the third commonest cause of premature mortality in the UK (1). Currently, a liver transplant is the only cure for end-stage liver disease (2). The existing shortage of donor organs highlights the importance of being able to accurately identify those individuals whom will benefit the most from transplantation.

Frailty is defined as the biologic syndrome of decreased reserve and resistance to stressors, which cause vulnerability to adverse outcomes (3). Liver failure accelerates this process, resulting in skeletal muscle atrophy (sarcopenia), reduced functional capacity and an associated increased risk of liver transplant waiting list mortality (4).

Evidence suggests that a subgroup of patients with end-stage liver disease who have low functional capacity, defined as a VO2max below 9mL.kg^{-1} or <60% predicted, often fail to survive to transplantation (5, 6). Furthermore, low functional capacity is associated with a number of poor post-transplantation outcomes including longer post-operative hospital stay and higher 100-day mortality (7). Despite these findings, current management of end-stage liver disease tends to focus on preventing and treating complications (i.e. variceal haemorrhage, ascites), rather than prospective strategies to improve functional capacity.

Research in non-end-stage liver disease populations has demonstrated the potential role of pre-operative exercise programmes, known as 'prehabilitation', in optimising patient's functional capacity prior to abdominal surgery and reducing post-operative complications (8, 9). Furthermore, exercise training has been shown to improve functional capacity and quality of life in a wide variety of chronic diseases (10-12). The time period for patients whilst active on the liver transplant waiting list provides a unique opportunity to provide physical interventions, such as prehabilitation. This could potentially have a significant effect on short, medium and long-term outcomes at a relatively low cost.

Recently, studies have demonstrated significant improvement in functional capacity following delivery of an exercise programme in patients with all causes of liver disease (13-16). Furthermore, significant improvements in muscle mass (14, 15) and EuroQol Group EQ-visual analogue of self-perceived health status (15) were shown. Although, all studies suggest exercise is a safe intervention in this patient population, 3 of the 4 studies excluded patients with end-stage cirrhosis (14-16). In view of this, as well as small participant numbers in each study, the safety of this intervention cannot be certain. Moreover, all studies were undertaken with weekly, directly supervised exercise sessions only. The seven UK NHS Liver Transplant centres cover a vast geographical area, therefore twice weekly visits by patients to their nearest transplant centre is unlikely to be feasible. Interventions which can be conducted local to the patient's homes or indeed in the patient's own homes need to be evaluated in a RCT.

Before a RCT can be conducted, a feasibility study is required to determine if a larger trial is possible, and if so, outline the optimal design features. Therefore, the aim of this study is to conduct a single centre feasibility trial of a novel home-based exercise programme in patients with end-stage liver disease awaiting liver transplantation.

METHODS AND ANALYSIS

Study Design Overview

The proposed feasibility trial is a single arm, single centre, study of a home-based exercise programme (HBEP) for patients listed for liver transplantation.

Patients recruited to the study at the Queen Elizabeth University Hospital Birmingham (QEUHB) UK liver transplant unit will be treated with a 12-week HBEP (Figure 1). Functional capacity, health related quality of life, anxiety and depression, anthropometry and adverse events will be assessed at baseline, 6 weeks and 12 weeks after the study intervention is commenced.

On completion of the HBEP intervention participants will be invited to attend a process evaluation focus group. The purpose of the focus group is to identify attitudes, motivators and barriers to the study intervention as well as to reflect upon the usefulness/acceptability of the study materials and equipment. Data will be collected and used to address the research questions outlined in Box 1.

Box 1 – Process Evaluation Focus Group Research Questions

1. What motivated the participants to adhere to the study intervention?
2. Did the participants identify any barriers to completing the study intervention?
3. How useful did the participants find the accelerometers?
4. How useful did the participants find the weekly telephone support?

Figure 1

Ethical and Regulatory Approval

The National Research Ethics Service (NRES) Committee and Health Research Authority North West - Greater Manchester East (REC reference: 17/NW/0120) approved version 1.1 of the study protocol. All participants will provide informed written consent.

Sample and Selection

Twenty eligible patients will be selected from the QEUHB liver transplantation waiting list using a stratified random sampling method. Subgroups will include four patients from each of the following disease types; alcoholic liver disease, non-alcoholic fatty liver disease, autoimmune liver disease, genetic liver disease and viral hepatitis. This is to ensure that various forms of liver disease will be represented in the study. Patients will be eligible to be included in the study if they meet the following criteria:

Inclusion criteria:

- Meet the UK Liver Transplant criteria for listing (17)
- Accepted on the liver transplant waiting list for a primary transplant
- Adults ≥18years

Exclusion criteria:

- Significant cardiovascular instability including a recent MI, recent CVA and/or a recent unstable cardiac arrhythmia
- Unstable encephalopathy - open to interpretation by the chief investigator
- Neither patient or next of kin non-English speaking
- Inpatient at the time of screening
- Refusal or lacks capacity to give informed consent

Once deemed eligible, patients will be sent a letter of invitation to be involved in the study along with a participant information sheet. Patients will be contacted by telephone 5-7 days after the letters are sent. If participants are willing to take part, an appointment will be arranged within 6 weeks, when patients will be able to provide informed written consent.

Method

Patients on the QEUHB liver transplant waiting list routinely attend outpatient clinics on 6-weekly basis. All study visits will be incorporated into their routine clinic follow-up. On attendance to clinic (baseline study visit), participants will complete baseline assessments of functional capacity, anthropometry and questionnaires to assess quality of life and anxiety and depression. The study intervention will be completed for 6 weeks with weekly telephone support, including a telephone questionnaire (see appendix 1). On return to clinic at week 6 (study visit 2), functional capacity, quality of life and anxiety/depression scores will be re-assessed. For the remaining 6 weeks of the study participants will continue with the HBEP, but without telephone support. This is to assess the carryover effect of information provided and assess the ability of the participants to continue the HBEP independently whilst on the waiting list. On return to clinic at 12 weeks (study visit 3) all participants will be re-assessed in terms of functional capacity, quality of life and anxiety scores. If a participant is unable to participate in exercise due to illness for a week or number of weeks then intermittent participation will be permitted. Periods of illness and intermittent participation will be recorded on the case report form (CRF) and accounted for in the data analysis.

Intervention: home based exercise programme (HBEP)

Participants will be provided with a 6 week HBEP including daily step targets and functional resistance-based exercises (Figure 2). Participants will be provided with an accelerometer (COOSA Heart Rate Monitor) to aid tracking of their daily steps and activity levels. In addition, participants will be asked to record their activity in a diary to aid self-reporting at the weekly telephone contact.

Daily step programme – During the first week, participants will be asked to monitor their daily step count via their accelerometer. Following weekly telephone contact, the participant will be advised to increase their daily step count by 200-500 steps each day every week depending on the level of function and achievement of step target of the previous week. For participants who are able, a target of 10000 steps will be set by the end of the first 6 weeks or to aim for by the end of 12 weeks. This is the recommended daily step target set by the government in order to achieve the minimum 150 minutes of moderate exercise per week and to help facilitate change in health status (Department of Health, 2011).

Functional resistance exercise sessions – During the initial assessment patients will be taught functional resistance exercises to complete at home (Figure 2). Information provided will be followed up with an exercise worksheet as well as a video to aid patient understanding and adherence. Sessions will be split into 3 levels of difficulty and participants will be advised to complete the level most suitable for them depending upon their baseline functional capacity scores. Participants will be asked to achieve a work rate of 12-13 on the BORG Rate of Perceived Exertion (RPE) score (6-20 scale) (18). An RPE of 12-13 has been shown to correlate with anaerobic threshold (19) and will therefore guide the participants to work to a training level which will elicit change in functional capacity. Participants will be advised to progress to each level depending on their RPE scores and results of the telephone health call questionnaire.

Telephone Health Call - During the first 6 weeks of the study intervention, participants will receive one 20 minute telephone call weekly from the chief investigator or a nominated member of the research team. The purpose of the telephone call is to provide support and guidance with the study intervention and address the following areas:

- Compliance to the study intervention
- Achievement of weekly pre-agreed step count and functional resistance exercise level
- Step target for the following week

- Queries or concerns regarding the intervention
- Incidence of any adverse events

After 6 weeks of the HBEP study intervention, participants will continue with the intervention without telephone support. This aims to assess longer-term adherence to the study intervention without weekly telephone support.

Process Evaluation Focus Group

Within 6 weeks of completing the 12-week study intervention all participants will be invited to attend one of two focus groups. The chief investigator, along with a member of the research team, will conduct two focus groups aiming to: (i) explore the thoughts/experiences of the participants regarding the study process, (ii) explore acceptability of the exercise programme and support provided. All participants will be invited to capture the range of participant experiences.

Figure 2

OUTCOME MEASURES

Primary Outcome

The primary outcome of the study is feasibility whereby the decision to proceed to a RCT will be made upon the following criteria:

1. No serious adverse events (defined as grade ¾) directly related to the HBEP
2. >66% of the active transplant waiting list for primary grafts must meet the eligibility criteria, to achieve timely recruitment and representation of the cohort
3. >90% recruitment to target number of participants (n=20) during the allotted study time period to achieve timely recruitment and assess willingness of patients to participate
4. >66% compliance with the step count (including ranges) whilst active on the transplant waiting list

5. >66% compliance with resistance exercises whilst active on the transplant waiting list
6. Of those who undergo initial assessment, >66% complete 6-weeks HBEP

Feedback will be documented from those participants who are approached but who refuse to consent or withdraw from the study, on the understanding that this feedback will be optional.

Candidate Primary Outcomes

The following candidate outcomes will be assessed at baseline (pre-HBEP), after 6 and 12 weeks of the HBEP. Feasibility will be determined according to the acceptability and usefulness of these outcome measures as well as time and resources needed to collect data.

Anthropometry: - At each study visit body mass index (BMI), hand grip strength, mid-arm circumference and triceps skin fold will be assessed. These assessments are currently completed as part of standard care by the QEUHB Liver Dietetic team and will be used in the study to ensure control of variables and inform the researches of any change in nutrition.

Incremental shuttle walk test (ISWT): - The ISWT is a standardised, externally paced, incremental field-walking test which evaluates maximal exercise capacity. The patient is progressively stressed to a symptom limited maximal performance by walking at different speeds around a 10m course which is dictated by an audio signal. It is a reliable (20) and valid measure which has been used in a wide range of chronic diseases (21-23) as well as a predictor of mortality post-abdominal surgery (24).

Short Performance Battery (SPB) test: - It is a physical functional tool which can identify disability and predict mortality through assessment of gait speed, balance and repeated chair stands. It is a valid tool used within the liver cirrhosis patient population. A score of less than 9 has been associated with a 45% increase in waiting list mortality in patients listed for liver transplantation, independent of the model for end stage liver disease (MELD) score (4).

EQ-5D (version 2.1): - This is a reliable and validated tool used in a wide range of health conditions and treatments. It provides information on health status which will be used to help evaluate the clinical and economic value of the study intervention (25).

Hospital Anxiety and Depression Score (HADS): - This is a reliable and valid tool for assessing anxiety and depression in medical patients (26). It will be used to identify if there is a need to include psychological support in future larger research projects. Participants will be advised in the participant information sheet that the purpose of the study is not to address any anxiety or depression concerns and if they feel this is a concern they should contact their general practitioner.

Telephone questionnaire: - This will be completed weekly throughout the first 6 weeks of the study intervention. The telephone questionnaire provides a standardised framework for assessing the participant's weekly progress and identifying any areas of concern. Furthermore, the answers will provide guided goal setting for the following week.

DATA ANALYSIS PLAN

All quantitative data will be entered into a purposefully designed secure access database and exported to SPSS for statistical analysis (Version 24). Feasibility decision rules and primary candidate outcomes will be analysed and presented using descriptive statistics.

Two focus groups will be conducted with three thematic components 1) barriers to the intervention, 2) facilitators of adherence and 3) level of support received, although, where appropriate, sufficient scope will be given to explore novel themes. Two members of the research team will conduct the focus group. Each session will be digitally recorded, transcribed verbatim and uploaded into NVivo 10 software to aid organisation and analysis of data. NVivo will be used to store data transcripts, and as a means by which codes could be highlighted and collated based upon the themes described above as well as to explore

any new emerging themes.

ADVERSE EVENTS AND ANALYSIS

An adverse event (AE) would be unlikely in this study due to the extensive investigations the patients have undergone prior to being listed for liver transplantation. However, the reporting period for AE will start at initial screening and continued until the end of the second focus group. Serious adverse events (SAE) will be reported until 30 days post each participant's liver transplant. All SAEs and adverse reactions will be evaluated and recorded using the National Cancer Institute's common terminology criteria for AEs (CTCAE, V.4.0, 2010) and reported to the Principle Investigator. All SAEs will be reported to the sponsor's Research and Development department via the SAE form in the CRF. Only those events classified as probable or definitely related will be reported to the Research Ethics Committee.

STORAGE OF DATA

All data for an individual participant will be collected by the Principal Investigator or their delegated nominees and recorded in the CRF. Participant identification on the CRF will be through their unique Participant Study Number, which will be allocated at the time of consideration for the study. Data will be collected from the time the patient is considered for entry into the study through to 30 days after they receive their liver transplant. All clinical data will be stored as per NHS regulations and held on the UK National Transplant Database.

Data from the CRF will be entered into a secure password protected database held on the University Hospitals Birmingham Trust computer. Due care will be taken to ensure data safety and integrity, and compliance with the Data Protection Act 1998. All essential documentation and trial records will be stored in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorized

personnel. Coded research data will be stored for 5 years anonymously under the property of University Hospitals Birmingham in keeping with good clinical practice.

CASE REPORT FORM

CRFs will include baseline/follow-up functional capacity, anthropometry and questionnaire scores to capture changes in outcomes. Other CRFs incorporated in the electronic database will include: medical history; eligibility screening; date of transplant; donor organ and operation data, length of ITU stay; 30-day outcome post-transplant; safety monitoring; AE reporting; study treatment adherence and attendance to focus groups.

SPONSORSHIP, INDEMNITY AND MONITORING

QEUHB will act as the sponsor through the duration of the study. As sponsor, QEUHB will be responsible for the general conduct of the study and indemnify the study centre against any claims, arising from any negligent act or omission by the hospital in fulfilling the sponsor role in respect to the study.

SOURCES OF FUNDING

The study is funded by the University Hospitals Birmingham Charities.

DISCUSSION

This is the first feasibility trial to investigate a HBEP in patients listed for liver transplantation. To-date 46 patients have been randomly screened for eligibility, of which 32 are eligible and 26 have agreed to participate in the trial.

Safety

Few small studies have investigated exercise therapy in patients with liver disease (13-16). Each study reported the safe use of exercise therapy with no adverse events described.

However, participant numbers were small (n=<24) and three of the four studies included patients with only mild liver disease, who are not as high risk as patients with end-stage liver disease. Furthermore, exercise was supervised by a health professional ensuring that participants exercised within safe training zones and were able to guide participants when to stop. To ensure safe delivery of exercise therapy in this study education will be given to the participant regarding rate of perceived exertion with clear colour coded training zones. Participants will be advised to stop exercising if reaching above 15 on the RPE score or if they feel a change in symptoms including dizziness, light headedness and chest pain. Participants will have contact numbers for the physiotherapists working on the study and will be advised to inform them if they experience any adverse event. This will also be automatically checked at the weekly telephone contact. To minimise the risk of adverse events the design of the exercise programme was based upon well documented training models delivered to other patients with chronic cardiovascular and respiratory disease.

Although this study includes participants with end stage liver disease, certain medical conditions will be excluded from the study including cardiovascular instability and unstable encephalopathy to minimise the risk of a serious adverse event. Furthermore, unstable encephalopathy may affect the participant's ability to consistently and adequately follow the exercise programme. This would affect the analysis of feasibility, as well as put unnecessary demand upon the main carer to support the patient through the process.

Challenges in study design

There are currently no validated outcome measures to assess change in functional capacity in patients with end-stage liver disease. The incremental shuttle walk test (ISWT) will be used in this study because it is a recognised measure of maximal exercise capacity and has been shown to correlate well with VO2 peak when compared to the gold standard cardiopulmonary exercise test (21). It has been previously used to measure change in functional capacity in other chronic disease types such as respiratory and cardiovascular disease (22, 23). Moreover, the ISWT has been shown to predict post-surgical morbidity in patients undergoing abdominal surgery (27).

In view of a home-based set up, it is important to promote adherence and compliance to the exercise programme. Although it is understood that patients listed for liver transplantation have a lower quality of life it is not understood what the motivational influences of this patient population are. To promote adherence to the programme a self-reported diary and an accelerometer will be given to each participant to provide daily visual feedback and empower responsibility for their daily and weekly goals. Additionally, following demonstration of the functional resistance exercises at their initial assessment, participants will be provided with written and pictorial instructions as well as a DVD of all of the exercises with front and side on views including verbal instruction from an exercise trainer. At the end of the study, each participant will be invited to attend a focus group to feedback on their experience of the study with particular reference to the level of support they receive, the clarity of the programme and motivational influences.

Due to the large geographical area, the QEUHB Liver unit covers, participants have to travel up to 300 miles per clinic appointment. It was, therefore, felt that limiting participant visits would facilitate recruitment and adherence to the study and reduce participant burden. Predominantly, patients on the liver transplant waiting list are reviewed on a 6-weekly basis. Baseline assessments will be timed with their pre-arranged clinic appointment so that 6 and 12-week follow-up will co-inside with ongoing clinic appointments.

The HBEP was designed to use movements, which would challenge the cardiorespiratory system, but also encourage movement through multiple planes of motion to improve stability, flexibility and balance. Patients with end-stage liver disease vary in age, function and exercise experience. Exercises were chosen, along with appropriate progression and regressions, in order to adapt to individual needs. Additionally, 3 levels of intensity will be available based upon increasing work time and reducing rest time. These will ensure participants exercise at a level consistent with their exercise capacity, but have room for progression over the 12 week period.

Future RCT considerations

NHS England aims to encourage and support healthier behaviours through the use of NHS accredited health apps (28). In this current study, participants will record their activity in a written diary and verbally report back at their weekly telephone support. In a larger RCT the use of accelerometers with live data collection would be considered. This would aim to empower patients to proactively monitor their activity and work towards patient centred goals. Furthermore, the physiotherapist could monitor adherence and progression of the exercise program on a daily basis. This would not only give better indication to tolerance to the exercise program but would enable specific exercise intensity advice and avoid participant reporter bias. However, it is currently unknown if all patients have access to smart phones for live data to be recorded on an app. Likewise, virtual clinics could be used instead of telephone support. This would provide a more interactive experience for the patient. The physiotherapist could review exercise techniques and demonstrate alternatives as required.

This phase 1 trial is critical in understanding potential recruitment rates, withdrawal rates, patients undergoing transplantation or death in the study period and HBEP completion rates in order to accurately power the number of participant required for the future RCT.

SUMMARY

To the best of our knowledge this is the first study to investigate a HBEP in patients listed for liver transplantation. The enrolment of participants to the study was completed in July 2017 and the final results are expected by May 2018.

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Appendices

Appendix 1

Telephone Questionnaire

1. How many days per week did you achieve your daily step target?

   0 1-2 3-4 5-7

If 5-7 please proceed to question 3

2. What prevented you from achieving your daily step target more frequently?

3. How many times did you complete the functional resistance exercise session this week?

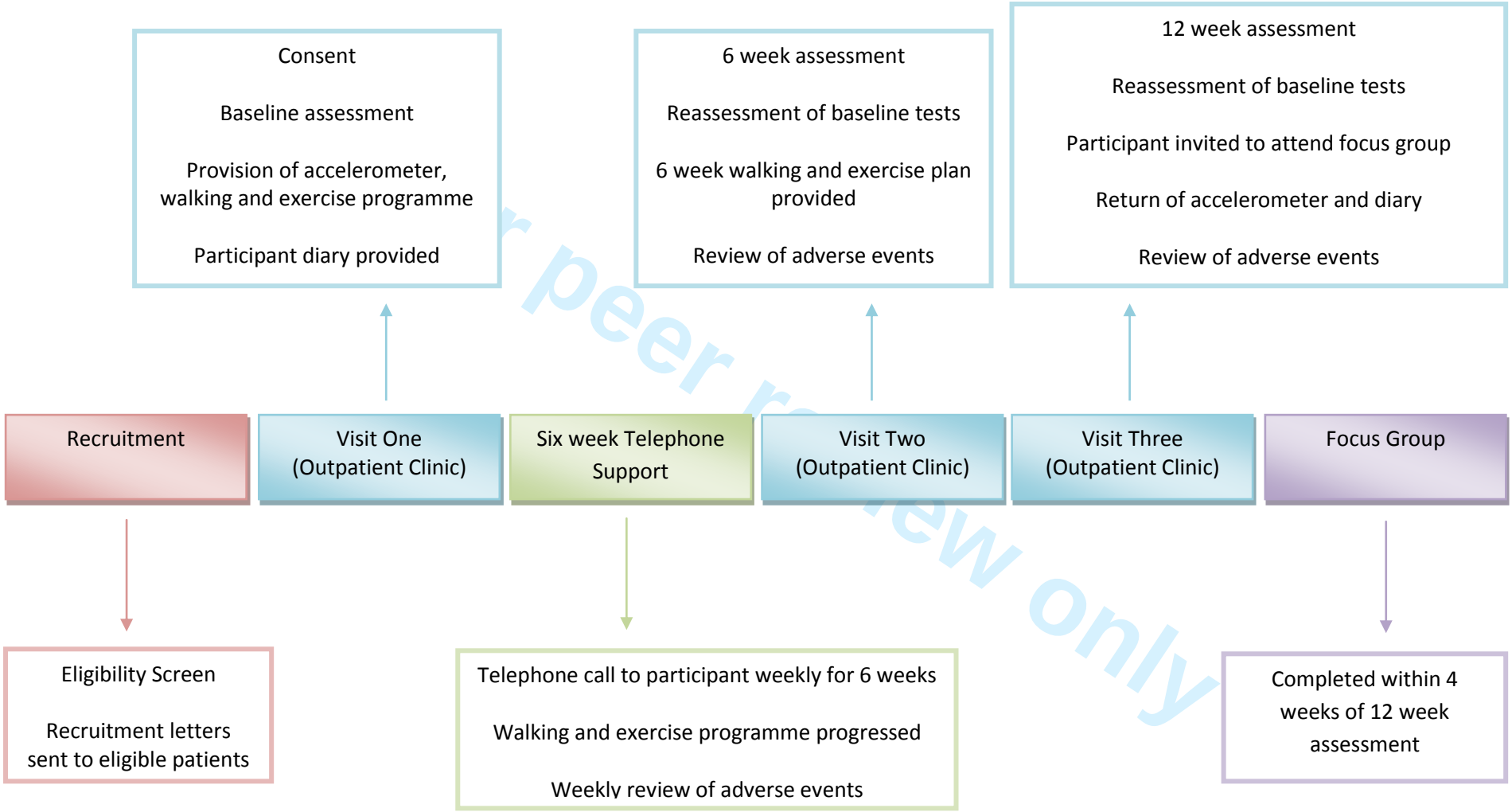
   None 1 2 3 >3

If >1 please go to question 5

4. What prevented you from completing the functional resistance exercise sessions?

5. Did you experience any of the following symptoms during or after your exercise?

   a. **Muscular pain**
   b. **Wheeziness**
   c. **Shortness of breath**
   d. **Light headedness**
   e. **Dizziness**
   f. **Headache**
   g. **Chest pain/discomfort**



a)

b)

c)

Appendix 1

Telephone Questionnaire

1. How many days per week did you achieve your daily step target?

   0 1-2 3-4 5-7

If 5-7 please proceed to question 3

2. What prevented you from achieving your daily step target more frequently?

3. How many times did you complete the functional resistance exercise session this week?

   None 1 2 3 >3

If >1 please go to question 5

4. What prevented you from completing the functional resistance exercise sessions?

5. Did you experience any of the following symptoms during or after your exercise?

   a. **Muscular pain**
   b. **Wheeziness**
   c. **Shortness of breath**
   d. **Light headedness**
   e. **Dizziness**
   f. **Headache**
   g. **Chest pain/discomfort**

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Home-based exercise therapy in patients awaiting liver transplantation: Protocol for an observational feasibility trial

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Home-based exercise therapy in patients awaiting liver transplantation: Protocol for an observational feasibility trial

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ABSTRACT

Introduction: Liver disease is the third commonest cause of premature mortality in the UK. Liver failure accelerates frailty resulting in skeletal muscle atrophy, functional decline and an associated risk of liver transplant waiting list mortality. However, there is limited research investigating the impact of exercise on patient outcomes pre-and post-liver transplantation. The waitlist period for patients listed for liver transplantation provides a unique opportunity to provide and assess interventions such as prehabilitation.

Method and Analysis: This study is a phase I observational study evaluating the feasibility of conducting a randomised control trial (RCT) investigating the use of a home-based exercise program (HBEP) in the management of patients awaiting liver transplantation. Twenty eligible patients will be randomly selected from the Queen Elizabeth Hospital Birmingham Liver Transplant waiting list. Participants will be provided with an individually tailored twelve week HBEP, including step targets and resistance exercises. Activity trackers and patient diaries will be provided to support data collection. For the initial six weeks, telephone support will be given to discuss compliance with the study intervention, achievement of weekly targets, and to address any queries or concerns regarding the intervention. During weeks 6-12, participants will continue the intervention without telephone support to evaluate longer-term adherence to the study intervention. On completing the intervention, all participants will be invited to engage in a focus group to discuss their experiences and the feasibility of a RCT.

Ethics and Dissemination: The protocol is approved by the National Research Ethics Service Committee North West - Greater Manchester East and Health Research Authority (REC reference: 17/NW/0120). Recruitment into the study started in April 2017 and ended in July 2017. Follow-up of participants is ongoing and due to finish by the end of 2017. The findings of this study will be disseminated through peer-reviewed publications and international presentations. In addition, the protocol will be placed on the British Liver Trust website for public access.

Registration: clinicaltrials.govNCT02949505

Keywords: Prehabilitation, functional capacity, end-stage liver disease, liver transplantation.

Financial and other competing interests: None to declare.

Strengths:

1. This is the first study to investigate a home based exercise programme in patients with end-stage liver disease and listed for liver transplantation.
2. An extensive clinical evaluation of functional capacity and quality of life in a high risk group of patient in whom there is a pressing need for optimisation prior to transplantation.

Limitations:

1. A pilot study of small sample size, but with the aim and design focusing on the feasibility of a RCT of prehabilitation in patients awaiting liver transplantation.

INTRODUCTION

Liver disease is the third commonest cause of premature mortality in the UK (1). Currently, a liver transplant is the only cure for end-stage liver disease (2). The existing shortage of donor organs highlights the importance of being able to accurately identify those individuals whom will benefit the most from transplantation.

Frailty is defined as the biologic syndrome of decreased reserve and resistance to stressors, which cause vulnerability to adverse outcomes (3). Liver failure accelerates this process, resulting in skeletal muscle atrophy (sarcopenia), reduced functional capacity and an associated increased risk of liver transplant waiting list mortality (4).

Evidence suggests that a subgroup of patients with end-stage liver disease who have low functional capacity, defined as an anaerobic threshold of less than 9mL.kg^{-1}min^{-1} , have lower survival rates post-transplantation(5) and predict a longer hospital stay (6). Despite these findings, current management of end-stage liver disease tends to focus on preventing

and treating complications (i.e. variceal haemorrhage, ascites), rather than prospective strategies to improve functional capacity.

Research in non-end-stage liver disease populations has demonstrated the potential role of pre-operative exercise programmes, 'known as prehabilitation', in optimising patient's functional capacity prior to abdominal surgery and reducing post-operative complications (7, 8). Furthermore, exercise training has been shown to improve functional capacity and quality of life in a wide variety of chronic diseases (9-11). The time period for patients whilst active on the liver transplant waiting list provides a unique opportunity to provide physical interventions, such as prehabilitation. This could potentially have a significant effect on short, medium and long-term outcomes at a relatively low cost (12).

Recently, studies have demonstrated significant improvement in functional capacity following delivery of an exercise programme in patients with all causes of liver disease (13-17). Furthermore, significant improvements in muscle mass (14, 15) and EuroQol Group EQ-visual analogue of self-perceived health status (15) were shown. Although, all studies suggest exercise is a safe intervention in this patient population, 3 of the 5 studies excluded patients with end-stage cirrhosis (14-16). In view of this, as well as small participant numbers in each study, the safety of this intervention cannot be certain. Moreover, all studies were undertaken with weekly, directly supervised exercise sessions only. The seven UK NHS Liver Transplant centres cover a vast geographical area, therefore twice weekly visits by patients to their nearest transplant centre is unlikely to be feasible. Interventions which can be conducted local to the patient's homes or indeed in the patient's own homes need to be evaluated in a RCT.

Before a RCT can be conducted, a feasibility study is required to determine if a larger trial is possible, and if so, outline the optimal design features. Therefore, the aim of this study is to conduct a single centre feasibility trial of a novel home-based exercise programme in patients with end-stage liver disease awaiting liver transplantation.

METHODS AND ANALYSIS

Study Design Overview

The proposed feasibility trial is a single arm, single centre, study of a home-based exercise programme (HBEP) for patients listed for liver transplantation.

Patients recruited to the study at the Queen Elizabeth University Hospital Birmingham (QEUHB) UK liver transplant unit will be treated with a 12-week HBEP (Figure 1). Functional capacity, health related quality of life, anxiety and depression, anthropometry and adverse events will be assessed at baseline, 6 weeks and 12 weeks after the study intervention is commenced.

On completion of the HBEP intervention participants will be invited to attend a process evaluation focus group. The purpose of the focus group is to identify attitudes, motivators and barriers to the study intervention as well as to reflect upon the usefulness/acceptability of the study materials and equipment. Data will be collected and used to address the research questions outlined in Box 1.

Box 1 – Process Evaluation Focus Group Research Questions

1. What motivated the participants to adhere to the study intervention?
2. Did the participants identify any barriers to completing the study intervention?
3. How useful did the participants find the accelerometers?
4. How useful did the participants find the weekly telephone support?

Figure 1

Ethical and Regulatory Approval

The National Research Ethics Service (NRES) Committee and Health Research Authority North West - Greater Manchester East (REC reference: 17/NW/0120) approved version 1.1 of the study protocol. The NRES, HRA and UHB Research and Dissemination group will be informed of any protocol modifications within 7 days. All participants will provide informed written consent.

Sample and Selection

Twenty eligible patients will be selected from the QEUHB liver transplantation waiting list using a stratified random sampling method, completed by MJA. Subgroups will include four patients from each of the following disease types; alcoholic liver disease, non-alcoholic fatty liver disease, autoimmune liver disease, genetic liver disease and viral hepatitis. This is to ensure that various forms of liver disease will be represented in the study. Patients will be eligible to be included in the study if they meet the following criteria:

Inclusion criteria:

- Meet the UK Liver Transplant criteria for listing (18)
- Accepted on the liver transplant waiting list for a primary transplant
- Adults ≥18years

Exclusion criteria:

- Significant cardiovascular instability including a recent MI, recent CVA and/or a recent unstable cardiac arrhythmia
- Unstable encephalopathy - open to interpretation by the chief investigator
- Neither patient or next of kin non-English speaking
- Inpatient at the time of screening
- Refusal or lacks capacity to give informed consent

Once deemed eligible, patients will be sent a letter of invitation to be involved in the study along with a participant information sheet. Patients will be contacted by telephone 5-7 days after the letters are sent by the chief investigator or a nominated member of the research team. If participants are willing to take part, an appointment will be arranged within 6 weeks, when patients will be able to provide informed written consent.

Method

Patients on the QEUHB liver transplant waiting list routinely attend outpatient clinics on 6-weekly basis. All study visits will be incorporated into their routine clinic follow-up. On attendance to clinic (baseline study visit), participants will complete baseline assessments of functional capacity, anthropometry and questionnaires to assess quality of life and anxiety and depression. The study intervention will be completed for 6 weeks with weekly telephone support, including a telephone questionnaire (see appendix 1). On return to clinic at week 6 (study visit 2), functional capacity, quality of life and anxiety/depression scores will be re-assessed. For the remaining 6 weeks of the study participants will continue with the HBEP, but without telephone support. This is to assess the carryover effect of information provided and assess the ability of the participants to continue the HBEP independently whilst on the waiting list. On return to clinic at 12 weeks (study visit 3) all participants will be re-assessed in terms of functional capacity, quality of life and anxiety scores. If a participant is unable to participate in exercise due to illness for a week or number of weeks then intermittent participation will be permitted. Periods of illness and intermittent participation will be recorded on the case report form (CRF) and accounted for in the data analysis.

Intervention: home based exercise programme (HBEP)

Participants will be provided with a 6 week HBEP including daily step targets and functional resistance-based exercises (Figure 2). Participants will be provided with an accelerometer (COOSA Heart Rate Monitor) to aid tracking of their daily steps and activity levels. In

addition, participants will be asked to record their activity in a diary to aid self-reporting at the weekly telephone contact.

Daily step programme – During the first week, participants will be asked to monitor their daily step count via their accelerometer. Following weekly telephone contact, the participant will be advised to increase their daily step count by 200-500 steps each day every week depending on the level of function and achievement of step target of the previous week.

Functional resistance exercise sessions – During the initial assessment patients will be taught functional resistance exercises to complete at home (Figure 2). Information provided will be followed up with an exercise worksheet as well as a video to aid patient understanding and adherence. Exercises will be regressed if the participant is unable to complete any of the techniques demonstrated in figure 2. For example, a step or bed will be used for hand positioning in the rock press and bear crawl exercises. The public and patient involvement (PPI)_group advised to keep exercise sessions short to aid compliance. Therefore, sessions will be 20-25 minutes for each individual but the difficulty of the session will be split into 5 levels as described in table 1. Participants will be advised to complete the level most suitable for them depending upon their baseline functional capacity scores. Participants will be asked to achieve a work rate of 12-13 on the BORG Rate of Perceived Exertion (RPE) score (6-20 scale) (19). An RPE of 12-13 has been shown to correlate with anaerobic threshold in healthy individuals (20) and will therefore guide the participants to work to a training level which will elicit change in functional capacity. Participants will be advised to stop exercising if reaching above 15 on the RPE score or if they feel a change in symptoms including dizziness, light headedness and chest pain. Participants will be advised to progress to each level depending on their RPE scores and results of the telephone health call questionnaire. At the 6 week assessment, participants will be advised to progress to a different level of exercise and to continue to increase their step count by 200-500 steps per day, per week depending upon the results of their functional capacity scores. Additional exercises, as shown in level 4 and 5 in table 1, will be taught if needed.

Table 1 – Levels of Difficulty for each Exercise Session

Level	Exercises	Work to rest timings	Number of circuits	Total Session Time (mins)
1	Frog Squat Rock Press Lunge Bear Crawl	20 secs of each exercise 40 secs rest	5	20
2	Frog Squat Rock Press Lunge Bear Crawl	30 secs of each exercise 30 secs rest	5	20
3	Frog Squat Rock Press Lunge Bear Crawl	40 secs of each exercise 20 secs rest	5	20
4	Frog Squat Rock Press Lunge Bear Crawl Side Bear Crawl	40 secs of each exercise 20 secs rest	4	20
5	Frog Squat Rock Press Lunge Bear Crawl Side Bear Crawl Kicksit	40 secs of each exercise 20 secs rest	4	24

Telephone Health Call - During the first 6 weeks of the study intervention, participants will receive one 20 minute telephone call weekly from the chief investigator or a nominated member of the research team. The purpose of the telephone call is to provide support and guidance with the study intervention and address the following areas:

- Compliance to the study intervention
- Achievement of weekly pre-agreed step count and functional resistance exercise level
- Step target for the following week
- Queries or concerns regarding the intervention
- Incidence of any adverse events

After 6 weeks of the HBEP study intervention, participants will continue with the intervention without telephone support. This aims to assess longer-term adherence to the study intervention without weekly telephone support.

Process Evaluation Focus Group

Within 6 weeks of completing the 12-week study intervention all participants will be invited to attend one of two focus groups. The chief investigator, along with a member of the research team, will conduct two focus groups aiming to: (i) explore the thoughts/experiences of the participants regarding the study process, (ii) explore acceptability of the exercise programme and support provided. All participants will be invited to capture the range of participant experiences.

Figure 2

OUTCOME MEASURES

Primary Outcome

The primary outcome of the study is feasibility whereby the decision to proceed to a RCT will be made upon the following criteria:

1. No serious adverse events (defined as grade ¾) directly related to the HBEP
2. >66% of the active transplant waiting list for primary grafts must meet the eligibility criteria, to achieve timely recruitment and representation of the cohort
3. >90% recruitment to target number of participants (n=20) during the allotted study time period to achieve timely recruitment and assess willingness of patients to participate
4. >66% compliance with the step count (including ranges) whilst active on the transplant waiting list
5. >66% compliance with resistance exercises whilst active on the transplant waiting list
6. Of those who undergo initial assessment, >66% complete 6-weeks HBEP

Feedback will be documented from those participants who are approached but who refuse to consent or withdraw from the study, on the understanding that this feedback will be optional.

Candidate Primary Outcomes

The following candidate outcomes will be assessed at baseline (pre-HBEP), after 6 and 12 weeks of the HBEP. Feasibility will be determined according to the acceptability and usefulness of these outcome measures as well as time and resources needed to collect data.

Anthropometry: - At each study visit body mass index (BMI), hand grip strength (kg) (Cranlea Human Performance Digital Hand Grip Dynamometer) , mid-arm circumference (cm) and triceps skin fold (mm) (Holtain Tanner/Whitehouse Skinfold Caliper) will be assessed. These assessments are currently completed as part of standard care by the QEUHB Liver Dietetic team and will be used in the study to ensure control of variables and inform the researches of any change in nutrition.

Incremental shuttle walk test (ISWT): - The ISWT is a standardised, externally paced, incremental field-walking test which evaluates maximal exercise capacity. The patient is progressively stressed to a symptom limited maximal performance by walking at different speeds around a 10m course which is dictated by an audio signal. It is a reliable (21) and valid measure which has been used in a wide range of chronic diseases (22-24) as well as a predictor of mortality post-abdominal surgery (25).

Short Performance Battery (SPB) test: - It is a physical functional tool which can identify disability and predict mortality through assessment of gait speed, balance and repeated chair stands. It is a valid tool used within the liver cirrhosis patient population. A score of less than 9 has been associated with a 45% increase in waiting list mortality in patients listed for liver transplantation, independent of the model for end stage liver disease (MELD) score (4).

EQ-5D (version 2.1): - This is a reliable and validated tool used in a wide range of health conditions and treatments. It provides information on health status which will be used to help evaluate the clinical and economic value of the study intervention (26).

Hospital Anxiety and Depression Score (HADS): - This is a reliable and valid tool for assessing anxiety and depression in medical patients (27). It will be used to identify if there is a need to include psychological support in future larger research projects. Participants will be advised in the participant information sheet that the purpose of the study is not to address any anxiety or depression concerns and if they feel this is a concern they should contact their general practitioner.

Telephone questionnaire: - This will be completed weekly throughout the first 6 weeks of the study intervention. The telephone questionnaire provides a standardised framework for assessing the participant's weekly progress and identifying any areas of concern. Furthermore, the answers will provide guided goal setting for the following week.

Other Outcomes

Disease severity: - To understand the relationship between the severity of liver disease and functional capacity at baseline, and possibly inform the need for stratification in the future RCT, the Child-Turcotte-Pugh (CP), Model for End Stage Liver Disease (MELD) and the United Kingdom Model for End Stage Liver Disease (UKELD) will be reported. These scores will be used to compare the study sample selected with the entire waiting list to ensure there is a representative balance of disease severity in the study. In addition, these scores will be calculated at 6 and 12 weeks to inform future hypothesis development for the future RCT.

Number and reason for dropouts: - All registered dropouts will be recorded according to their reason including; (1) withdrawal of consent, (2) liver transplantation, (3) acute decompensation leading to incapacity to follow the study intervention, or (4) death. This will provide valuable information when planning recruitment for the RCT.

DATA ANALYSIS PLAN

All quantitative data will be entered into a purposefully designed secure access database and exported to SPSS for statistical analysis (Version 24). Feasibility decision rules and primary candidate outcomes will be analysed and presented using descriptive statistics.

Adverse events reported by telephone or in person will be descriptively reported in terms of frequency (%). To determine compliance with the intervention, the number of days when participants achieved their step count and completed the functional resistance exercises will be reported as categorical variables on a week by week basis (week 1-5).

Two focus groups will be conducted with three thematic components 1) barriers to the intervention, 2) facilitators of adherence and 3) level of support received, although, where appropriate, sufficient scope will be given to explore novel themes. Two members of the research team will conduct the focus group. Each session will be digitally recorded, transcribed verbatim and uploaded into NVivo 10 software to aid organisation and analysis of data. NVivo will be used to store data transcripts, and as a means by which codes could be highlighted and collated based upon the themes described above as well as to explore any new emerging themes.

ADVERSE EVENTS AND ANALYSIS

An adverse event (AE) would be unlikely in this study due to the extensive investigations the patients have undergone prior to being listed for liver transplantation. However, the reporting period for AE will start at initial screening and continued until the end of the second focus group. Serious adverse events (SAE) will be reported until 30 days post each participant's liver transplant. All SAEs and adverse reactions will be evaluated and recorded using the National Cancer Institute's common terminology criteria for AEs (CTCAE, V.4.0, 2010) and reported to the Principle Investigator. All SAEs will be reported to the sponsor's Research and Development department via the SAE form in the CRF. Only those events classified as probable or definitely related will be reported to the Research Ethics Committee.

STORAGE OF DATA

All data for an individual participant will be collected by the Principal Investigator or their delegated nominees and recorded in the CRF. Participant identification on the CRF will be through their unique Participant Study Number, which will be allocated at the time of consideration for the study. Data will be collected from the time the patient is considered for entry into the study through to 30 days after they receive their liver transplant. All clinical data will be stored as per NHS regulations and held on the UK National Transplant Database.

Data from the CRF will be entered into a secure password protected database held on the University Hospitals Birmingham Trust computer. Due care will be taken to ensure data safety and integrity, and compliance with the Data Protection Act 1998. All essential documentation and trial records will be stored in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorized personnel. Coded research data will be stored for 5 years anonymously under the property of University Hospitals Birmingham in keeping with good clinical practice.

CASE REPORT FORM

CRFs will include baseline/follow-up functional capacity, anthropometry and questionnaire scores to capture changes in outcomes. Other CRFs incorporated in the electronic database will include: medical history; eligibility screening; date of transplant; donor organ and operation data, length of ITU stay; 30-day outcome post-transplant; safety monitoring; AE reporting; study treatment adherence and attendance to focus groups.

SPONSORSHIP, INDEMNITY AND MONITORING

QEUHB will act as the sponsor through the duration of the study. As sponsor, QEUHB will be responsible for the general conduct of the study and indemnify the study centre against any

claims, arising from any negligent act or omission by the hospital in fulfilling the sponsor role in respect to the study.

Contact name of trial sponsor: Dr. Chris Counsell

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SOURCES OF FUNDING

The study is funded by the University Hospitals Birmingham Charities.

DISCUSSION

This is the first feasibility trial to investigate a HBEP in patients listed for liver transplantation. To-date 46 patients have been randomly screened for eligibility, of which 32 are eligible and 26 have agreed to participate in the trial.

Safety

Few small studies have investigated exercise therapy in patients with chronic liver disease (13-16). Each study reported the safe use of exercise therapy with no adverse events described. However, participant numbers were small (n=<24) and three of the four studies included patients with only mild liver disease, who are not as high risk as patients with end-stage liver disease. Furthermore, exercise was supervised by a health professional ensuring that participants exercised within safe training zones and were able to guide participants when to stop. To ensure safe delivery of exercise therapy in this study education will be given to the participant regarding rate of perceived exertion with clear colour coded training zones. Furthermore, participants will have contact numbers for the physiotherapists working on the study and will be advised to inform them if they experience any adverse event. This will also be automatically checked at the weekly telephone contact. To minimise the risk of adverse events the design of the exercise programme was based upon well documented training models delivered to other patients with chronic cardiovascular and

respiratory disease in terms of number of sessions per week, length of exercise programme (6-12 weeks), and intensity (28, 29).

Although this study includes participants with end stage liver disease, certain medical conditions will be excluded from the study including cardiovascular instability and unstable encephalopathy to minimise the risk of a serious adverse event. Furthermore, unstable encephalopathy may affect the participant's ability to consistently and adequately follow the exercise programme. This would affect the analysis of feasibility, as well as put unnecessary demand upon the main carer to support the patient through the process.

Challenges in study design

There are currently no validated outcome measures to assess change in functional capacity in patients with end-stage liver disease. The incremental shuttle walk test (ISWT) will be used in this study because it is a recognised measure of maximal exercise capacity and has been shown to correlate well with VO2 peak when compared to the gold standard cardiopulmonary exercise test (22). It has been previously used to measure change in functional capacity in other chronic disease types such as respiratory and cardiovascular disease (23, 24). Moreover, the ISWT has been shown to predict post-surgical morbidity in patients undergoing abdominal surgery (30).

In view of a home-based set up, it is important to promote adherence and compliance to the exercise programme. Although it is understood that patients listed for liver transplantation have a lower quality of life, compared to healthy individuals, it is not understood what the motivational influences of this patient population are. To promote adherence to the programme a self-reported diary and an accelerometer will be given to each participant to provide daily visual feedback and empower responsibility for their daily and weekly goals. Additionally, following demonstration of the functional resistance exercises at their initial assessment, participants will be provided with written and pictorial instructions as well as a DVD of all of the exercises with front and side on views including verbal instruction from an exercise trainer. At the end of the study, each participant will be

invited to attend a focus group to feedback on their experience of the study with particular reference to the level of support they receive, the clarity of the programme and motivational influences.

Due to the large geographical area, the QEUHB Liver unit covers, participants have to travel up to 300 miles per clinic appointment. It was, therefore, felt that limiting participant visits would facilitate recruitment and adherence to the study and reduce participant burden. Predominantly, patients on the liver transplant waiting list are reviewed on a 6-weekly basis. Baseline assessments will be timed with their pre-arranged clinic appointment so that 6 and 12-week follow-up will co-inside with ongoing clinic appointments.

The HBEP was designed to use movements, which would challenge the cardiorespiratory system, but also encourage movement through multiple planes of motion to improve stability, flexibility and balance. Patients with end-stage liver disease vary in age, function and exercise experience. Exercises were chosen, along with appropriate progression and regressions, in order to adapt to individual needs. Additionally, 5levels of intensity will be available based upon increasing work time and reducing rest time. These will ensure participants exercise at a level consistent with their exercise capacity, but have room for progression over the 12 week period.

Future RCT considerations

NHS England aims to encourage and support healthier behaviours through the use of NHS accredited health apps (31). In this current study, participants will record their activity in a written diary and verbally report back at their weekly telephone support. In a larger RCT the use of accelerometers with live data collection would be considered. This would aim to empower patients to proactively monitor their activity and work towards patient centred goals. Furthermore, the physiotherapist could monitor adherence and progression of the exercise program on a daily basis. This would not only give better indication to tolerance to the exercise program but would enable specific exercise intensity advice and avoid participant reporter bias. However, it is currently unknown if all patients have access to smart phones for live data to be recorded on an app. Likewise, virtual clinics could be used

instead of telephone support. This would provide a more interactive experience for the patient. The physiotherapist could review exercise techniques and demonstrate alternatives as required.

This phase 1 trial is critical in understanding potential recruitment rates, withdrawal rates, patients undergoing transplantation or death in the study period and HBEP completion rates in order to accurately power the number of participant required for the future RCT.

SUMMARY

To the best of our knowledge this is the first study to investigate a HBEP in patients listed for liver transplantation. The enrolment of participants to the study was completed in July 2017 and the final results are expected by May 2018.

Contributor statement:
FRW - concept, design, recruitment and 1st draft and review/editing of final manuscript.
AV, TF, JF and MJA - concept, design, recruitment and review/editing of final manuscript.
DK, SD, JT, JJ, TP, AH - review/editing of final manuscript.
SD - provided consent for use of photographs in Figure 2

Acknowledgements:
Mr Brendan Turner[5] – contribution and provided consent for use of photographs in Figure 2

Figure Legends

Figure 1 – Study Design Overview

Figure 2 - Functional resistance exercises; a) Lunge, b) Rock Press, c) Frog Squat, d) Bear Crawl, e) Side Bear Crawl, f) Kick Sit

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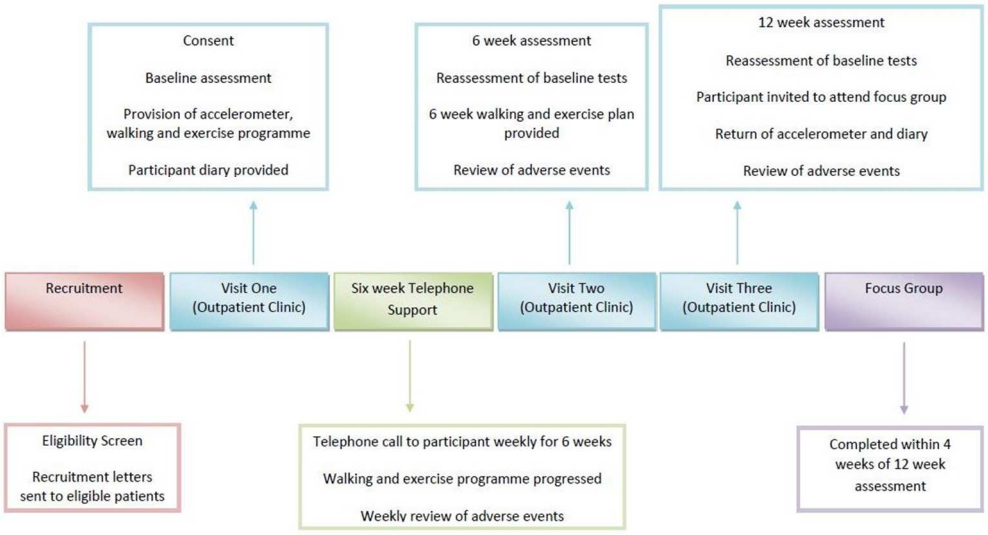

Figure 1 - Study Design Overview

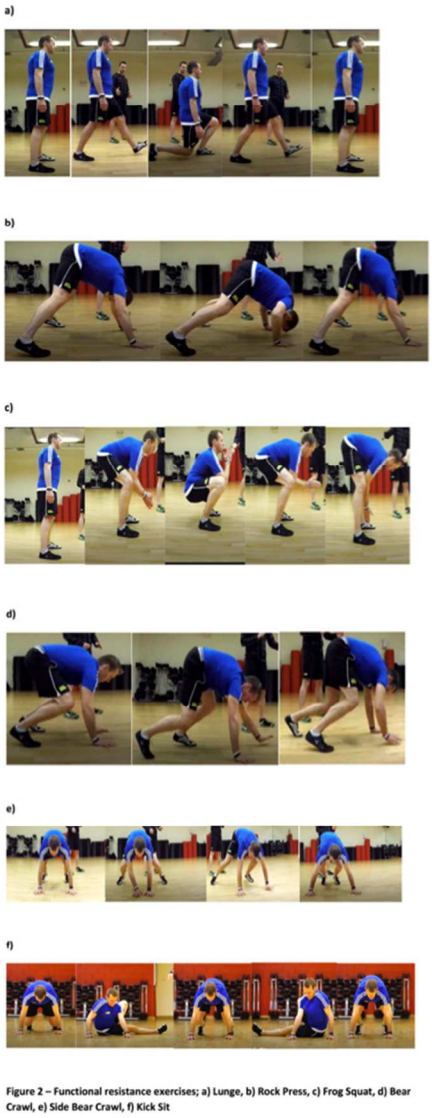

Figure 2 – Functional resistance exercises; a) Lunge, b) Rock Press, c) Frog Squat, d) Bear Crawl, e) Side Bear Crawl, f) Kick Sit

Figure 2 - Functional resistance exercises; a) Lunge, b) Rock Press, c) Frog Squat, d) Bear Crawl, e) Side Bear Crawl, f) Kick Sit

190x275mm (96 x 96 DPI)

Appendix 1

Telephone Questionnaire

1. How many days per week did you achieve your daily step target?

   0 1-2 3-4 5-7

If 5-7 please proceed to question 3

2. What prevented you from achieving your daily step target more frequently?

3. How many times did you complete the functional resistance exercise session this week?

   None 1 2 3 >3

If >1 please go to question 5

4. What prevented you from completing the functional resistance exercise sessions?

5. Did you experience any of the following symptoms during or after your exercise?

   a. **Muscular pain**
   b. **Wheeziness**
   c. **Shortness of breath**
   d. **Light headedness**
   e. **Dizziness**
   f. **Headache**
   g. **Chest pain/discomfort**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Version: 2.0 Date: 06.10.17
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2 and 6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	6

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	1
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2 and 8
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	6
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	N/A
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2 and 3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3 and 4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6-7
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5-7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6 - 9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10 - 12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	N/A
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6 - 7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	15
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.