PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Home-based exercise therapy in patients awaiting liver transplantation: Protocol for an observational feasibility trial
AUTHORS	Williams, Felicity; Vallance, Alice; Faulkner, Thomas; Towey, Jennifer; Kyte, Derek; Durman, Simon; Johnson, Jill; Holt, Andrew; Perera, T; Ferguson, James; Armstrong, Matthew

VERSION 1 – REVIEW

REVIEWER	Moritz Tobiasch LKH Universitätskliniken Innsbruck I. Medizinische Klinik Innsbruck, Austria
REVIEW RETURNED	14-Sep-2017

GENERAL COMMENTS	The manuscript focuses on a relevant and under-investigated issue in end stage liver disease and liver transplantation. The research question is by no doubt novel and interesting, and the suggested study design is clear, feasible and straightforward for its purpose as a phase I trial. I feel that the protocol can be accepted with a few minor addenda - please accept my sincere apologies to increase the study team's workload by my remarks: Patients on liver transplant waiting lists cover a broad range of physical impairment. For clarification and a possible post-hoc stratification (hypothesis generating for the upcoming RCT), I would suggest to add common laboratory values and liver disease staging scores in the baseline data, as well as in the outcome measurements (e.g., Child-Turcotte-Pugh and MELD scores), and state this explicitly in the study description. Furthermore, as secondary endpoints, I would suggest to register dropouts: in this study, the most likely would likely be (1) withdrawal of consent, (2) liver transplantation, (3) acute decompensation leading to incapacity to follow the study protocol, or (4) death. These data might be useful in planning the subsequent RCT. As stated in the manuscript, several candidate primary outcomes for subsequent studies will be assessed. I would like to encourage the study team to explicitly state their policy as to the handling of incomplete or missing data (as the study cohort is pretty small), and how primary data should be edited, especially concerning outlier analysis: if performed (something I would not suggest to do, seen the small study size and the pre-planned stratification), by which method (Mahalanobis distance, Cook's distance, leverage). I assume that the usual statistical tests for normality, linearity, homoscedasticity, and internal and external validity checks are planned and will be conducted.

	If these analyses could be integrated in the manuscript, this would enhance reproducibility to a great extent. Thank you for submitting this manuscript and make it open for discussion.

REVIEWER	Dr Matthew Wallen Federation University Australia
REVIEW RETURNED	18-Sep-2017

GENERAL COMMENTS	The primary aim of this study protocol by Williams and colleagues (2017) is to determine the feasibility of a home-based exercise program in patients with end-stage liver disease awaiting liver transplantation. As the authors highlight, patients with end-stage liver disease frequently present as deconditioned, demonstrating significant reductions in cardiopulmonary function, functional capacity, and muscle mass, compared to healthy age-matched controls. Importantly, impairments in these physiological parameters prior to liver transplantation has also been associated with poor clinical outcomes across the liver transplant continuum. Given that exercise training is a well-established method of evoking positive changes in these prognostically relevant markers of deconditioning, the inclusion of pre-operative exercise training, or 'prehabilitation', prior to liver transplantation, is logical. The study protocol describes a prospective 12-week phase 1 observational investigation of home-based exercise training at a single study site. Participants will be asked to achieve a prescribed number of steps per day, as well as perform body weight resistance exercises. All prescribed exercises will be progressively increased over the 12-weeks. Participants will receive weekly telephone calls during the first six weeks to identify if any adverse events had occurred, identify the participants compliance to the prehabilitation program, and to progress the exercise prescription. Testing of participants will occur before (Week 0), during (Week 6) and after (Week 12) the study period. Following the 12-week intervention phase, participants will also be invited to attend a focus group aiming to explore the feasibility and acceptability of the project. The manuscript is well-written and adequately describes the study methodology. The registration for the trial has been provided and institutional ethical clearance has been approved. I do, however, have some comments for the authors to consider: • Page 3, Line 40: please spell randomised control trial in full, or alternatively, abbreviate in the first instance on page 3, Line 21. • Page 4, Line 47: can the authors please define VO2max in the first instance. VO2max (or more commonly VO2peak in this population) is also commonly expressed as mL.kg-1.min-1. Furthermore, is this '9 mL.kg-1.min-1' the anaerobic threshold opposed to VO2peak? • Page 4, Line 47-48: The sentence is elaborating on how patients with poor aerobic capacity may not survive to transplantation. However, the article by Moran and colleagues (2016) is primarily reviewing the literature in regards to preoperative CPET predicting post-operative outcomes. Perhaps the paper by Ow and Colleagues (2014) may be more appropriate.

	• Page 5, Line 5: the sentence should read “known as ‘prehabilitation’, in optimising a patient’s…” • Page 5, Line 16: A reference highlighting the cost-benefit of exercise interventions should be included. • Page 5, Line 21: The study by Debette-Gratien (2015) should be included here as they also performed a pilot feasibility study of exercise training in liver transplant candidates. • Page 9, Line 18-19: the in-text reference should be numbered. • Page 9, Line 35: the sentence should read “correlated with the anaerobic threshold in healthy individuals (19)…” • Can the authors please provide more details in regards to the ‘functional resistance exercise sessions’? I cannot see where the authors have defined the frequency, sets, repetitions and duration for this. Furthermore, can the authors please clarify what differentiates the ‘three levels of difficulty’? • On a similar note to the point above, can the authors please justify why only three exercises (I am assuming with technique modifications depending on the level of difficulty) were included in the program? This is based on the Figure 2 that the authors refer to in the text. The American College of Sports Medicine recommends the inclusion of 8-10 exercises. • Although the patients will be educated about gradual progression during the initial 6 weeks, will they be encouraged in the final phone consultation to continue progressing both step count (although the goal is to achieve 10,000 steps by Week 12) and resistance exercises during the remaining 6 weeks? If so, this needs to be specified. • Page 11, Lines 19-23: can the authors please provide details of the equipment used and references for the measures of hand-grip strength, MAC and triceps skin fold. Will these measurements • Please refer to the telephone questionnaire appendix on Page 12, Lines 25-30. • Can the authors please provide further details in regards to the data analysis plan, particularly for the quantitative data collected pre, during and post intervention. • Page 14, Line 56: Should this read “exercise therapy in patients with chronic liver disease”? • Page 15, Line 14-15: These details would be better placed in the methods section, as it is describing an intensity not to exceed. • Page 15, Line 24: A reference supporting the well documented training models needs to be included here. • Page 16, Line 8: This should read “transplantation have a lower quality of life compared to healthy individuals…”

REVIEWER	Professor William Bernal Liver Intensive Therapy Unit Kings College Hospital London UK
REVIEW RETURNED	18-Sep-2017

GENERAL COMMENTS	The MS is clear and well written and the study begins to address an area now recognised as of considerable clinical importance, but where there is little data to inform and support practice. It is my understanding that there are now several such trials underway internationally.

	Although this is badged as a pilot / feasibility study, My concerns relate to the small sample size. The authors proposal to sub-stratify by aetiology will reduce numbers further and complicate analysis. Are the authors to also ensure that the population has a representative balance of functional compromise? I'm also unsure how the proposed 12-week follow-up time will address the fact that at least a proportion will undergo transplant and the patient cohort will be smaller still.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment 1: Patients on liver transplant waiting lists cover a broad range of physical impairment. For clarification and a possible post-hoc stratification (hypothesis generating for the upcoming RCT), I would suggest to add common laboratory values and liver disease staging scores in the baseline data, as well as in the outcome measurements (e.g., Child-Turcotte-Pugh and MELD scores), and state this explicitly in the study description.

Response 1: Thank you for your valid comments. Please see last paragraph page 12:
'To understand the severity of liver disease in parallel to functional capacity at baseline, and possibly inform the need for stratification in the future RCT, the Child-Turcotte-Pugh (CP) score, Model for End Stage Liver Disease (MELD) and the United Kingdom Model for End Stage Liver Disease (UKELD) will be reported. In addition, these scores will be calculated at 6 and 12 weeks to inform future hypothesis development for the future RCT.'

Comment 2: As secondary endpoints, I would suggest to register dropouts: in this study, the most likely would likely be (1) withdrawal of consent, (2) liver transplantation, (3) acute decompensation leading to incapacity to follow the study protocol, or (4) death. These data might be useful in planning the subsequent RCT.

Response 2: Thank you for your comments. Please see 1st paragraph page 13:
'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 on the waiting list. This will provide valuable information when planning recruitment for the RCT.'

Comment 3: As stated in the manuscript, several candidate primary outcomes for subsequent studies will be assessed. I would like to encourage the study team to explicitly state their policy as to the handling of incomplete or missing data (as the study cohort is pretty small), and how primary data should be edited, especially concerning outlier analysis: if performed (something I would not suggest to do, seen the small study size and the pre-planned stratification), by which method (Mahalanobis distance, Cook's distance, leverage). I assume that the usual statistical tests for normality, linearity, homoscedasticity, and internal and external validity checks are planned and will be conducted. If these analyses could be integrated in the manuscript, this would enhance reproducibility to a great extent.

Response 3: Thank you for this interesting comment. The primary outcome of the current study is feasibility, whereby decisions to proceed to designing an RCT will be based on achieving the following criteria (as stated in the manuscript):
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
If the feasibility study highlights poor recruitment and/or poor compliance and completion of the HBEP, then a larger RCT of HBEP in patients on the waiting list will not be undertaken. Although we fully agree with the reviewer that outlier analysis and sample distribution analysis would be key components in the methodology of a large RCT to enable reproducibility, we feel it is too premature to document details to this extent in the current feasibility study.

Reviewer: 2
Response 1: We thank the reviewer for their positive comments and have made the following changes to the manuscript:

Comment 2. Page 3, Line 40: please spell randomised control trial in full, or alternatively, abbreviate in the first instance on page 3, Line 21.

Response 2: Changed. Abbreviation added to page 3, line 21.

Comment 3. Page 4, Line 47: can the authors please define VO2max in the first instance. VO2max (or more commonly VO2peak in this population) is also commonly expressed as mL.kg-1.min-1. Furthermore, is this '9 mL.kg-1.min-1' the anaerobic threshold opposed to VO2peak?

Response 3: Thank you for highlighting this error. Please see amended details on page 4:
'defined as an anaerobic threshold of less than 9mL.kg-1min-1 , have lower survival rates post-transplantation (5) and predict a longer hospital stay (6).'

Comment 4. Page 4, Line 47-48: The sentence is elaborating on how patients with poor aerobic capacity may not survive to transplantation. However, the article by Moran and colleagues (2016) is primarily reviewing the literature in regards to preoperative CPET predicting post-operative outcomes. Perhaps the paper by Ow and Colleagues (2014) may be more appropriate.

Response 4: Thank you for your comments. This has been reworded (as described above):
'defined as an anaerobic threshold of less than 9mL.kg-1min-1 , have lower survival rates post-transplantation (5) and predict a longer hospital stay (6).'

Comment 5. Page 5, Line 5: the sentence should read "known as 'prehabilitation', in optimising a patient's…"

Response 5: Thank you for your comment, this has been amended.

Comment 6. Page 5, Line 16: A reference highlighting the cost-benefit of exercise interventions should be included.

Response 6: Thank you for your comment. Reference 12 has been added, which highlights cost-benefit of exercise interventions in respiratory disorders:
(12) DoH. An Outcome Strategy for COPD and Asthma: NHS Companion Document. [Best Practice Guideline] 2012 [cited 2017 4th October]

Comment 7. Page 5, Line 21: The study by Debette-Gratien (2015) should be included here as they also performed a pilot feasibility study of exercise training in liver transplant candidates.

Response 7: Thank you for bringing this paper to our attention. This study has been added to the manuscript, as reference (17)

Comment 8: Page 9, Line 18-19: the in-text reference should be numbered.

Response 8: Thank you for highlighting this reference. The information was written in error as it was decided prior to commencing the study that due to unknown levels of activity in this patient sub group, step targets would be made on a week by week and individual basis depending upon achievement of targets from the previous week. This has been clarified in the manuscript:
'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).'

Comment 9: Page 9, Line 35: the sentence should read "correlated with the anaerobic threshold in healthy individuals (19)…"

Response 9: Thank you for your comment. This has been updated.

Comment 10: Can the authors please provide more details in regards to the 'functional resistance exercise sessions'? I cannot see where the authors have defined the frequency, sets, repetitions and duration for this. Furthermore, can the authors please clarify what differentiates the 'three levels of difficulty'?

Response 10: This is a very valid point and we thank you for bringing this to our attention. The details of the exercise programme including clarification of levels of difficulty have been included in the manuscript, as well as the inclusion of table 1 (on page 10).
'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.'

Comment 11: On a similar note to the point above, can the authors please justify why only three exercises (I am assuming with technique modifications depending on the level of difficulty) were included in the program? This is based on the Figure 2 that the authors refer to in the text. The American College of Sports Medicine recommends the inclusion of 8-10 exercises.

Response 11: Thank you for highlighting this. Figure 2 was based on an example sample only. We have now updated Figure 2 to include all of the exercises provided. We acknowledge the recommendations from The American College of Sports Medicine, however these guidelines are written for healthy individuals and do not acknowledge the complications that accompanies end-stage liver disease. Due to the variation in participant ability, the frailty of this patient population and feedback received from the PPI group we started the participants on 4 exercises but repeated them in a circuit format (5 circuits of 4 exercises). Due to the home-based nature and lack of participant contact, the authors felt it important to ensure good technique of a smaller number of exercises which could be repeated. This was agreed with the PPI group. Participants also had the opportunity to discuss any concerns they had with the exercises during the weekly telephone health call. On review of the exercises at 6 weeks, if it was felt that the participant had progressed enough, a further 1-2 exercises were added (please see table 1).

Comment 12: Although the patients will be educated about gradual progression during the initial 6 weeks, will they be encouraged in the final phone consultation to continue progressing both step count (although the goal is to achieve 10,000 steps by Week 12) and resistance exercises during the remaining 6 weeks? If so, this needs to be specified.

Response 12: Thank you for your comments. This information has been added to the functional resistance exercise paragraph on page 8 and 9:
'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.'

Comment 13: Page 11, Lines 19-23: can the authors please provide details of the equipment used and references for the measures of hand-grip strength, MAC and triceps skin fold.

Response 13: Thank you for bringing this to our attention. This has now been updated in the manuscript on page 10.
'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.'

Comment 14: Please refer to the telephone questionnaire appendix on Page 12, Lines 25-30. Can the authors please provide further details in regards to the data analysis plan, particularly for the quantitative data collected pre, during and post intervention.

Response 14: The main quantitative data with regards to the study, which will include Short performance battery tests, incremental shuttle work test and depression/anxiety scores will be assessed and recorded at baseline (pre), 6 (during) and 12 weeks (post); after face-to-face assessment at these 3 study visits. The main purpose of the telephone questionnaire was to review adverse events, provide advice regarding weekly progression and to give the participant the opportunity to discuss any concerns. The data analysis plan for these details has been updated on page 12, line 21-24, of the manuscript.
'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).'

Comment 15: Page 14, Line 56: Should this read “exercise therapy in patients with chronic liver disease”?

Response 15: Thank you for your comment. This has been updated.

Comment 16: Page 15, Line 14-15: These details would be better placed in the methods section, as it is describing an intensity not to exceed.

Response 16: Thank you for your comments. This has been moved to the methods section on page 7.

Comment 17: Page 15, Line 24: A reference supporting the well documented training models needs to be included here.

Response 17: Thank you for your comment. References 28 and 29 have been added, which highlight the similarities in training programmes in terms of frequency, intensity and length of exercise programme.
(28) Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE. Thorax. 2013;68(Suppl 2):ii1-ii30.
(29) Rehabilitation AoCPiC. Standards for Physical Activity and Exercise in the Cardiovascular Population. 2015 [cited 2017 04.10].

Comment 18: Page 16, Line 8: This should read “transplantation have a lower quality of life compared to healthy individuals…”

Response 18: Thank you for your comment. This has been updated in the manuscript.

Reviewer 3
Comment 1: The MS is clear and well written and the study begins to address an area now recognised as of considerable clinical importance, but where there is little data to inform and support practice. It is my understanding that there are now several such trials underway internationally.

Response 1: Thank you for the positive comments. We agree that there is an increasing interest in this field with regards to trials investigating exercise in patients with liver disease, but to the best of our knowledge no ongoing trial is investigating a novel home-based exercise program in this high risk cohort (liver transplant waiting list).

Comment 2: Although this is badged as a pilot / feasibility study, My concerns relate to the small sample size. The author’s proposal to sub-stratify by aetiology will reduce numbers further and complicate analysis. Are the authors to also ensure that the population has a representative balance of functional compromise?

Response 2: The main purpose of the pilot study was to assess the feasibility in terms of recruitment, consent, adverse events, patient compliance and completion of the HBEP. We felt that a randomly selected cohort from the waiting list, stratified for disease type, would provide an adequate representation of the list to assess the feasibility of a HBEP. It is not our intention in the current feasibility study to perform sub-group analysis of the disease types, as eluded to by the reviewer the sample size is too small. This, however, will certainly be taken into account when performing a sample size calculation for a future RCT.

Even though we do not currently have baseline objective functional read-outs on all of the non-study patients on our waiting list (i.e. SPBT, ISWT), we will look to compare MELD, CPS and UKELD of the study sample selected compared to the entire waiting list to ensure that there is a representative balance of disease severity in the study. Please see updated paragraph on page 12, line 1-7 of the manuscript.

'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.'

Comment 3: I'm also unsure how the proposed 12-week follow-up time will address the fact that at least a proportion will undergo transplant and the patient cohort will be smaller still.

Response 3: Thank you for your comment. As part of the feasibility assessment of the study, we wanted to analyse how many were lost to transplant during the 12 week period. This has now been addressed in the manuscript and discussed within the "number and reason for dropout" section within "other outcomes" of Methods and Analysis. The number of drop outs and the timing of transplantation will aid with calculating a sample size for a future RCT.

VERSION 2 – REVIEW

REVIEWER	Moritz Tobiasch University Hospital Innsbruck, Innsbruck, Austria
REVIEW RETURNED	12-Oct-2017

GENERAL COMMENTS	thank you very much for revising your manuscripts and accepting the reviewers' input. In my opinion, the present manuscript is ready for publication. Please allow one small comment (I admit to succumb to my personal vanity, and I clearly do not intend to provoke another round of reviewing): In an investigator-initiated, phase I feasibility trial, brevity is a virtue - but specifying the statistical workup of this pretty interesting and well-thought study as "descriptive statistics" (p13 of 53, sentence 2) might not catch all of its elaboration. Again, I thank your for sharing the study setup with the community, and I hope that I haven't complicated the work too much.

REVIEWER	Matthew Wallen Federation University Australia
REVIEW RETURNED	05-Nov-2017

GENERAL COMMENTS	Thank you for satisfactorily addressing my initial feedback. I have no further comments.