

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prehabilitation in patients with cirrhosis awaiting liver transplantation: protocol of a feasibility study
AUTHORS	Benmassaoud, Amine; Gillis, Chelsia; Geraci, Olivia; Martel, Myriam; Awasthi, Rashami; Barkun, Jeffrey; Chen, Tianyan; Edgar, Linda; Sebastiani, Giada; Carli, Francesco; Bessissow, Amal

VERSION 1 – REVIEW

REVIEWER	Koen Reyntjens University Medical Centre Groningen, Anaesthesiology
REVIEW RETURNED	10-Dec-2023

GENERAL COMMENTS	nice protocol, my only remark is that you also should take into account what the patient does in between contacts, as this is a guarantee for the success of the intervention and even more important than the intervention itself.
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REVIEWER	Wayel Jassem King's College London, Institute of Liver Studies
REVIEW RETURNED	19-Dec-2023

GENERAL COMMENTS	Well-written manuscript Exclusion criteria are very stringent, and the authors may only reach patients who may not need pre-conditioning before transplantation. Additionally, for the above reason, the authors may require significantly more patients to prove their hypothesis. Why are the maintenance sessions only once / 2 weeks? I expect them to be more frequent.
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REVIEWER	Oliver Tavabie King's College Hospital NHS Foundation Trust
REVIEW RETURNED	30-Jan-2024

GENERAL COMMENTS	In the introduction - it states that this is the first study to assess feasibility of a home based prehab program - williams et al 2019 reported the first feasibility study of a home based exercise program which is a critical component of prehab - I think a more balanced statement is that this is the first feasibility study of a multimodal prehab program The exclusion criteria are quite restrictive and will exclude patients who would likely most benefit from intervention - what is the justification for excluding patients with refractory ascites? Other points - point II - presumably this is acute hepatic decompensation -
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	<p>this probably needs to be clearer - v - could you define what you mean by persistent HE - is this persistent overt HE?</p> <p>I am unclear as to how some of the clinical exploratory outcomes will be assessed (particularly post-transplant outcomes) without a control group - I am also not sure it is necessary for this feasibility study to show this - it may be more appropriate to look at the feasibility of collecting different surrogates for 'good' clinical outcomes</p> <p>I can't find details of funding or a proposed start date - please provide</p> <p>There are typos across the manuscript - please address</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Koen Reyntjens, University Medical Centre Groningen

Comments to the Author: nice protocol, my only remark is that you also should take into account what the patient does in between contacts, as this is a guarantee for the success of the intervention and even more important than the intervention itself.

Response to reviewer: Dear Dr. Reyntjens, thank you for your input. We agree with your comment. As part of the protocol, participants are provided a booklet where they document the physical activities they do outside of the program, as additional information. This was written in the submitted protocol:

Patients will also be asked to complete a diary describing physical activity outside of the programmed session that will be reviewed by the kinesiologist. This diary will be included in a patient booklet.

Reviewer: 2

Dr. Wayel Jassem, King's College London

Comments to the Author: Well-written manuscript. Exclusion criteria are very stringent, and the authors may only reach patients who may not need pre-conditioning before transplantation. Additionally, for the above reason, the authors may require significantly more patients to prove their hypothesis.

Why are the maintenance sessions only once / 2 weeks? I expect them to be more frequent.

Response to reviewer: Dear Dr. Jassem, thank you for your comments. We agree that the list of exclusion criteria is quite exhaustive. It follows a recently published consensus statement for the safe exercise of patients with cirrhosis (PMID 29964066). As participants will be performing high-intensity interval training, we preferred to maximize their safety. Furthermore, as this is a feasibility study, our primary aim will be to assess whether this intervention is feasible. We are therefore less concerned with sample size. As there is no data on maintenance phase, the chosen frequency of exercise training (once every 2 weeks) was meant to balance participant involvement and expected benefits.

Reviewer: 3

Dr. Oliver Tavabie, King's College Hospital NHS Foundation Trust

Comments to the Author: In the introduction - it states that this is the first study to assess feasibility of a home based prehab program - williams et al 2019 reported the first feasibility study of a home based exercise program which is a critical component of prehab - I think a more balanced statement is that this is the first feasibility study of a multimodal prehab program.

Response to reviewer: Dear Dr. Tavabie, we wish to apologize for the confusion. We clarified that we are talking about multimodal prehabilitation. Furthermore, our study will be hospital-based, and more akin to the study by Morkane et al, as opposed to the study by Williams which was home-based.

The exclusion criteria are quite restrictive and will exclude patients who would likely most benefit from intervention - what is the justification for excluding patients with refractory ascites? Other points - point II - presumably this is acute hepatic decompensation - this probably needs to be clearer - v - could you define what you mean by persistent HE - is this persistent overt HE?

Response to reviewer: Thank you for these comments. As stated above, we agree that the list of exclusion criteria is quite exhaustive. It follows a recently published consensus statement for the safe exercise of patients with cirrhosis (PMID 29964066). As participants will be performing high-intensity interval training, we preferred to maximize their safety. This is why we preferred to exclude patients with refractory ascites. We clarified the other exclusion criteria to reflect “acute hepatic decompensation” and “overt HE”. Thank you.

I am unclear as to how some of the clinical exploratory outcomes will be assessed (particularly post-transplant outcomes) without a control group - I am also not sure it is necessary for this feasibility study to show this - it may be more appropriate to look at the feasibility of collecting different surrogates for 'good' clinical outcomes

Response to reviewer: Thank you for the comment. The post-transplant outcomes are meant to be descriptive and exploratory. Indeed, without a control group, there cannot be a comparison.

I can't find details of funding or a proposed start date - please provide

Response to reviewer: The funding information is presented after the references. The proposed study start date has been added to the manuscript right after the abstract.

Registration: [clinicaltrials.gov \(NCT05237583\)](https://clinicaltrials.gov/ct2/show/study/NCT05237583)

First posted on [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05237583): February 14, 2022

Actual study start (first participant recruited): February 23, 2022

Expected date of study completion: October, 2024

There are typos across the manuscript - please address

Response to reviewer: Thank you. This has been addressed.

VERSION 2 – REVIEW

REVIEWER	Wayel Jassem King's College London, Institute of Liver Studies
REVIEW RETURNED	18-Apr-2024

GENERAL COMMENTS	Thank you for the revision
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REVIEWER	Oliver Tavabie King's College Hospital NHS Foundation Trust
REVIEW RETURNED	02-Apr-2024

GENERAL COMMENTS	Many thanks for addressing my comments. Good luck with this important piece of work
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