## 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

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| **TITLE (PROVISIONAL)** | Patient-centred rehabilitation for non-communicable disease in a low-resource setting: study protocol for a feasibility and proof-of-concept randomized clinical trial |
| **AUTHORS** | Heine, Martin; Fell, Brittany; Robinson, Ashleigh; Abbas, Mumtaz; Derman, Wayne; Hanekom, Susan |

## VERSION 1 - REVIEW

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| **REVIEWER** | Carl J Lavie<br>Ochsner,USA |
| **REVIEW RETURNED** | 14-Sep-2018 |

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| **GENERAL COMMENTS** | This looks like a good study.My only comment would be to include other papers from low resource centers( Pesah E et al. Prog Cardiovasc Dis 2017; 60: 267-280 and Grace SL et al. PCVD 2016;59: 303-322) and making cardiac rehabilitation more available and affordable ( Maddison R et al. Heart 2018; Lavie CJ et al. Heart 2018; Kachur S et al. PCVD 2017;60: 103-114; Ghisi GLM et al. Can J Cardiol 2018; on-line |

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| **REVIEWER** | Elias Mpofu<br>University of Sydney, Australia University of North Texas, USA |
| **REVIEW RETURNED** | 25-Sep-2018 |

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| **GENERAL COMMENTS** | The goal to develop a protocol for life style rehabilitation support in low resource settings has much to be commended. The authors propose a courageously conceived postponed information randomization model for subsequent field trailing. The treatment protocol aimed at addressing function with disability, and prioritizing function rather than the specific disability is also admirable and in line with current rehabilitative supports framed on the World Health Organization's International Classification of Functioning, Disability and Health. The major limitation with the proposal is that it is overly ambitious and aimed to do so many things and with way to many outcomes as to be inoperable in real world settings. Moreover, the recruitment protocol is overly inclusive, even by health and function standards. A case is not made as to the imperative to prioritize lifestyle as mainstay intervention. The proposal could be more persuasive with some scaling down or uncluttering. |

| REVIEWER | Loheetha Ragupathi<br>Thomas Jefferson University Hospital, United States |
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| REVIEW RETURNED | 29-Sep-2018 |

| GENERAL COMMENTS | The study protocol submitted is detailed and thorough in describing the proposed study. The study addresses an important area of investigation, which may influence future policy decisions on rehabilitative care in low-resource settings. There are only a few outstanding questions regarding the study.<br><br>1. The proposed dates of patient enrollment<br>2. The resources required for the rehabilitation program could be explained in more detail. What type of "medical professional" is supervising and conducting the rehabilitation?<br>3. In analyzing the cost/benefit of the rehabilitation program, I would think it is also important to report provider level costs in order to make an assessment of the feasibility of scaling up a program such as what is proposed.<br>4. Regarding the postponed information model, it is not mentioned as to when the full extent of the study is disclosed to all the participants |
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| REVIEWER | Heidi Lempp<br>King's College London, UK |
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| REVIEW RETURNED | 28-Nov-2018 |

| GENERAL COMMENTS | This is a very well written and clear study protocol, each step is easy to follow and the Background section provides detailed information about the feasibility to conduct the study in a LMIC.<br>I have a few minor comments:<br>p.1/line 43: Keywords 'developing countries', however in the paper the authors state correctly in my view LMIC, ther seems to be a mismatch of words?<br>p.17/line20: who or what is a rehabilitation specialist, can authers provide an example, pl, I was unclear about the role.<br>p.21/line23: I assume the authors need to remove the comma after the word 'key' so it reads 'key exercises?<br>p.22/line16: pl provide (a) relevant reference(s) for 'vicarious learning'.<br>p.23/line19: can the authors pl specify with whom the focus groups will be conducted, e.g. study particpants and/or research team, not clear to me.<br>SPIRIT Checklist:<br>p.35/line2-3; point 19: did not read any infomration about data management on p.9 of the manuscript<br>p.35/line12; point 20c: did not see any information about missing data handling on p.23-24. |
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. This looks like a good study. My only comment would be to include other papers from low resource centers ( Pesah E et al. Prog Cardiovasc Dis 2017; 60: 267-280 and Grace SL et al. PCVD 2016;59:

303-322) and making cardiac rehabilitation more available and affordable ( Maddison R et al. Heart 2018; Lavie CJ et al. Heart 2018; Kachur S et al. PCVD 2017;60: 103-114; Ghisi GLM et al. Can J Cardiol 2018; on-line

Response:

- The respective recommended citations were included where applicable (Pesah et al. 2017; Lavie et al 2018; Kachur 2017) and highlighted in yellow. [11, 13, 19]

- The following recommendations were considered, but not included: Maddison et al. (Telemedicine may be a cost-effective alternative delivery model in some low-resource settings, but is less applicable to the respective context study still will take place); Ghisi et al 2018.

- The following studies were already part of the study protocol / rationale: Grace et al 2016 [57]

Reviewer: 2

1. The major limitation with the proposal is that it is overly ambitious and aimed to do so many things and with way too many outcomes as to be inoperable in real world settings. Moreover, the recruitment protocol is overly inclusive, even by health and function standards. A case is not made as to the imperative to prioritize lifestyle as mainstay intervention. The proposal could be more persuasive with some scaling down or uncluttering.

Response: We agree with the reviewer that our protocol is ambitious; we disagree it is too ambitious.

We agree that the number of outcomes we've selected are unlikely to be implemented as a collective; however, we'd like to stress out that this study is not designed to show effectiveness, and that these outcomes are part of the feasibility objectives of this study. In particular the three functional capacity tests are included to determine their respective feasibility and clinical relevance in a low-resource setting.

The quadruple burden of disease including high incidences of communicable disease, non-communicable disease, maternity-related disorders, and trauma warrant an inclusive recruitment protocol in order to retain a close to the real-world setting as possible. For example, a study by Derman et al (BJSM, 2014) showed that 84%!! of patients with NCD had two or more comorbidities; and that was in a South African high-resource setting with excellent primary and secondary care services. It can be anticipated that these statistics are worse in a low-resource setting, with the addition of communicable disease and trauma specifically. Hence, we believe that a less inclusive recruitment protocol would compromise the external validity of our results to a real-world setting. The four non-communicable diseases are all four related to lifestyle behavior (e.g. physical inactivity, poor diet and lifestyle behaviors), and their gold-standard, evidence-based, rehabilitative treatment includes exercise and education to combat these behaviors

We've attempted to unclutter the protocol a bit by changing some of the headings, and moving some sections to obtain a better flow. We believe that these minor updates improve the readability of the manuscript, and will increase the confidence of the reviewer in the feasibility and value of the study as an entirety.

Reviewer: 3

1. The proposed dates of patient enrollment

Response: This study will run for the duration of one year… with recruitment starting Jan 2019 and final assessment late December 2019. The following was added under the “participants” section: “… for the study duration of one year between January 2019 and December 2019.”

2. The resources required for the rehabilitation program could be explained in more detail. What type of "medical professional" is supervising and conducting the rehabilitation?

Response: in the participants section, the term “medical professional” was changed to family physician; this specific post at the day clinic still had to be filled at the time of initial submission but more clarity has been provided now.

3. In analyzing the cost/benefit of the rehabilitation program, I would think it is also important to report provider level costs in order to make an assessment of the feasibility of scaling up a program such as what is proposed.

Response: We agree with the reviewer that this is valuable. In fact, though the focus is on cost to the patient, we’re already collecting vital information from a provider perspective, including state delivered medication, inpatient services utilized, and outpatients’ services utilized. Together with the cost of providing this specific intervention in a real-world setting, should give us a good indication on the cost-benefits from a provider perspective. However, in the context of a low-resource setting and the impact out-of-pocket expenses may have in such a setting we initially focus on the less-studied patient-perspective.

4. Regarding the postponed information model, it is not mentioned as to when the full extent of the study is disclosed to all the participants

Response: Due to the low-resource setting, informing patients in writing about the study results and full extent of randomization model is challenging (physical mail does not arrive, email is not available to most participants, phone numbers change quickly. Alternatively, the full extent could be disclosed at the final follow-up assessment; yet, one would also not want to disclose the full extent before the last patient’ last visit. Hence, we opt to disclose the full extent of the model (and study findings) at a patient-information day to be scheduled early 2020. The following was added to the manuscript: “Participants will be informed about the full extent of this model during a patient-information day upon completion of the study.”

Reviewer: 4

1. p.1/line 43: Keywords 'developing countries', however in the paper the authors state correctly in my view LMIC, there seems to be a mismatch of words?

Response: We agree that developing countries is not a 100% matching keyword. In our opinion, neither is LMIC. Ideally, one would use low-resource setting as a keyword, yet this is not a MeSH term (nor is LMIC). We’ve therefore chosen to use developing countries, as this is a MeSH term.

2. p.17/line20: who or what is a rehabilitation specialist, can authors provide an example, pl, I was unclear about the role.

Response: We understand the unclarity; this has been changed to read now that “an independent physiotherapist” will review 10% of the therapy sessions to monitor treatment fidelity.

3. p.21/line23: I assume the authors need to remove the comma after the word 'key' so it reads 'key exercises?

Response: we thank the reviewer for pointing out this small error; the comma has been removed.

4. p.22/line16: pl provide (a) relevant reference(s) for 'vicarious learning'.

Response: a reference was added[60] that reviews the concept of vicarious learning (i.e. learning from the experiences of others). We believe that particularly in low-resource settings; people find innovative ways to for instance exercise or eat health, that they can share with others.

5. p.23/line19: can the authors pl specify with whom the focus groups will be conducted, e.g. study participants and/or research team, not clear to me.

Response: We agree that this could be specified. This item now reads: “Acceptance of the program is evaluated using group-based focus interviews with both participants of the intervention, and participants that declined the intervention.”

SPIRIT Checklist:

6. p.35/line2-3; point 19: did not read any information about data management on p.9 of the manuscript

Response: we apologize for an errors in the reporting checklist. The following section was added / changed to provide a more clear description of our data management solution, and was moved to the first paragraph under the heading “Baseline assessment and randomization logistics”:

“Data collection and randomization are facilitated through www.castoredc.com. Castor EDC is an intuitive and secure cloud-based electronic data capture platform that facilitates defined user roles, advanced monitoring, participant management, and powerful calculations. Data storage is compliant with data storage is compliant with all relevant regulations including good clinical practice.”

7. p.35/line12; point 20c: did not see any information about missing data handling on p.23-24.

Response: I’d like to highlight here, that this is a feasibility study, and our primary objective is not to analyze effectiveness of the intervention. If anything, the origin of missing data will be part of answering the feasibility objective. However, we do intend to conduct preliminary longitudinal analysis. This specific objective and how we aim to handle missing data (by using mixed-model analysis) has been outlined in more detail in the manuscript: “. It has been shown that both these longitudinal data techniques are robust to missing data in the analysis of continuous outcomes. [62,63]”. These two references refer to papers (Prof. Twisk his group) that highlight the ability of these mixed-models to handle missing data.

A new and updated spirit checklist is uploaded with this submission.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Elias Mpofu<br>University of North Texas |
| **REVIEW RETURNED** | 29-Jan-2019 |

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| **GENERAL COMMENTS** | This is a very worthwhile study. However, in stating you rationale for the study you could explicitly state the fact that the qualities of rehabilitation support interventions that work in developing country settings are incompletely understood. It should not seen like you are primarily seeking to investigate the cross-cultural trans-portability of western models to a non-western setting, which |

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| | others would consider to be a neo-colonial, paternalistic approach. You need to do further proof editing of the manuscript for minor types. |

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| **REVIEWER** | Heidi Lempp<br>King's College London |
| **REVIEW RETURNED** | 11-Jan-2019 |

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| **GENERAL COMMENTS** | The comments I have highlighted have been all addressed.<br>I was unsure about to add two more co-authors to the paper, is that in line with the journal guidelines? |

## VERSION 2 – AUTHOR RESPONSE

Reviewer 2

1. This is a very worthwhile study. However, in stating you rationale for the study you could explicitly state the fact that the qualities of rehabilitation support interventions that work in developing country settings are incompletely understood. It should not seen like you are primarily seeking to investigate the cross-cultural trans-portability of western models to a non-western setting, which others would consider to be a neo-colonial, paternalistic approach.

Response: We thank the reviewer for pointing this out, and couldn't agree more that transporting western models to a non-western setting is neither a primary or secondary aim of this study. We have made subtle changes to the manuscript in two places where we feel that idea may have come across; steering away from "knowledge transfer" to a message of creating new knowledge that is applicable to the context:

Abstract: Despite the disproportionate disease burden in low-resourced settings, and due to the complex context and constraints in these settings, the delivery and study of evidence-based rehabilitation treatment in a low-resource setting is poorly understood.

Page 4-5: While there is substantial evidence for the benefits of exercise-based rehabilitation in high-resource settings,[16–19] the study, delivery, and implementation of evidence-based rehabilitation in low-resourced settings is poorly understood.

2. You need to do further proof editing of the manuscript for minor types.

Response: We apologize for any typos etc. The manuscript was further proof-read by a native speaker not directly involved in the study. Based on her feedback, numerous small changes were made throughout the manuscript. Track changes has been used to highlight all of these.