## 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)** | Rehabilitation Enablement in Chronic Heart Failure-a facilitated self-care rehabilitation intervention in patients with heart failure with preserved ejection fraction (REACH-HFpEF) and their caregivers: Rationale and protocol for a single centre pilot randomised controlled trial |
| **AUTHORS** | Eyre, Victoria; Lang, Chim C.; Smith, Karen; Jolly, Kate; Davis, Russell; Hayward, Christopher; Wingham, Jennifer; Abraham, Charles; Green, Colin; Warren, Fiona; Britten, Nicky; Greaves, Colin; Doherty, Prof Patrick; Austin, Jackie; Van Lingen, Robin; Singh, Sally; Buckingham, Sarah; Paul, Kevin; Taylor, Rod; Dalal, Hayes |

## VERSION 1 - REVIEW

| | |
|---|---|
| **REVIEWER** | Donal, Erwan<br>Rennes University Hospital<br>Rennes, France |
| **REVIEW RETURNED** | 12-Jun-2016 |

| | |
|---|---|
| **GENERAL COMMENTS** | This is a nice protocol. The design paper is OK. But the presentaiton or may be the protocol is rather complex and difficult to conduct.<br>It seems that the authors are ready to start and have succeeded in gettinggrant and ethical approval so it is difficult to criticize the protocol. Nevertheless, the presentation is a bit confusing.<br>the endpoint could be more precisely defined and the duration of the study? 4 or 6 months<br>what is the primary endopoint, what is the seondary endpoints, only clinical data: no biomarker, no echo data? It might be something to consider<br>the authors could discussed (there is no real discussion) more the background of the study and the findings in the existing literature.<br>what about the treatment, the optimzation of the treatment?<br>the flow chart could be simpler. |

| | |
|---|---|
| **REVIEWER** | William Man<br>Respiratory Biomedical Research Unit,<br>Royal Brompton & Harefield NHS Foundation Trust and Imperial College, UK<br><br>I have co-authored review articles and national/international guidelines with Sally Singh, and a recent paper with Sally Singh, Patrick Doherty and Rod Taylor reviewing the basis for generic breathlessness rehabilitation. |
| **REVIEW RETURNED** | 23-Jun-2016 |

| | |
|---|---|
| **GENERAL COMMENTS** | This is an excellent manuscript detailing the rationale and protocol |

| | |
|---|---|
| | for a pilot RCT of a self-management manual intervention (REACH-HF) in patients with heart failure with preserved LV ejection fraction. The description of the methodology is detailed and transparent. There are some very nice touches particularly around assessment of caregivers and the fidelity assessment.<br><br>Just a few minor points:<br>1) There appeared to be a lot of questionnaires - some appeared to be measuring similar constructs - is there a degree of redundancy? This also puts additional time pressure on patients and risks questionnaire fatigue.<br>2) What was the rationale for the 4 month and 6 month timepoints?<br>3) Is there a rationale for EF>45 rather than say >50? |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1 (Name: DONAL)
Institution and Country: Rennes University Hospital, Rennes, France
Please state any competing interests or state 'None declared': no competing interest

1. This is a nice protocol. The design paper is OK. But the presentation or may be the protocol is rather complex and difficult to conduct. It seems that the authors are ready to start and have succeeded in getting grant and ethical approval so it is difficult to criticize the protocol. Nevertheless, the presentation is a bit confusing.

We acknowledge that the protocol for this funded pilot study is quite complex with a mixed research methods approach and the inclusion of a mechanistic sub study. However, we based the presentation of the design of this study on the published protocol for our sister full trial in HFrEF (Taylor RS, Hayward C, Eyre V, et al. Clinical effectiveness and cost-effectiveness of the Rehabilitation Enablement in Chronic Heart Failure (REACH-HF) facilitated self-care rehabilitation intervention in heart failure patients and caregivers: rationale and protocol for a multicentre randomised controlled trial. BMJ open 2015;5(12):e009994.)

2. The endpoint could be more precisely defined and the duration of the study? 4 or 6 months? What is the primary endpoint, what are the secondary endpoints? Only clinical data: no biomarker, no echo data? It might be something to consider.

Since this study is a pilot study, we are assessing the feasibility of a definitive trial by collecting and analysing the pilot study outcome measures as detailed in the paper. One of the pilot study outcomes is an assessment of the completion and completeness of main trial outcome measures at 4 months and 6 months follow up; all main trial outcome measures are also listed in the paper. Because this is a pilot study, we have not specified primary or secondary patient endpoints.

3. The authors could discuss (there is no real discussion) more the background of the study and the findings in the existing literature.

As this is a protocol and accord with the protocol publication of our sister full trial, we have intentionally kept the introduction and conclusion sections brief. We believe we have clearly presented the rationale for this pilot trial and by summarising the results of previous systematic reviews/meta-analysis, we have also summarised the findings of the previous literature.

4. What about the treatment, the optimisation of the treatment?

Currently there is no fully evidence-based drug therapy that significantly improves survival or prevents

hospitalisations in patients with HFpEF. The optimisation of treatment is more relevant to patients with HFrEF (ejection fraction <45%), where there are prognostic benefits in titrating patients up to optimal doses of beta blockers and drugs counteracting the renin-angiotensin system. Given the current evidence base, the optimisation of drug treatment is not recommended in national clinical guidelines for patients with HFpEF. Usual care will therefore be determined by local clinical protocols.

5. The flow chart could be simpler.

Our flowchart follows CONSORT guidelines and follows the format of the flow diagram in our published protocol for sister trial in HFrEF.

Reviewer: 2 (Name: William Man)
Institution and Country: Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust and Imperial College, UK
Please state any competing interests or state 'None declared': I have co-authored review articles and national/international guidelines with Sally Singh, and a recent paper with Sally Singh, Patrick Doherty and Rod Taylor reviewing the basis for generic breathlessness rehabilitation.

1. This is an excellent manuscript detailing the rationale and protocol for a pilot RCT of a self-management manual intervention (REACH-HF) in patients with heart failure with preserved LV ejection fraction. The description of the methodology is detailed and transparent. There are some very nice touches particularly around assessment of caregivers and the fidelity assessment.

Thank you for your review of our paper and for your positive feedback.

2. There appeared to be a lot of questionnaires - some appeared to be measuring similar constructs - is there a degree of redundancy? This also puts additional time pressure on patients and risks questionnaire fatigue.

We acknowledge that there are a number of questionnaires that we are asking study participants to complete. However, since this is a pilot study, we are assessing the completion and completeness of main trial outcome measures as one of our study outcome measures. In addition the outcome measures are those we have successfully applied in our sister full HFrEF trial
In advance of our HFpEF and HFrEF trials, we tested this outcome during a feasibility study with the finding that there were generally excellent levels of outcome completion and patients/caregivers perceived relatively low outcome burden (http://www.rcht.nhs.uk/RoyalCornwallHospitalsTrust/WorkingWithUs/TeachingAndResearch/ReachHF/FeasibilityStudyResults.aspx).
As part of this pilot study in HFpEF, we are collecting feedback from the patients and caregivers on the study information, clinic visits, outcome burden, and acceptability of other specific outcome measures that could be problematic for some participants, e.g. the incremental shuttle walk test.

3. What was the rationale for the 4 month and 6 month time points?

As described in the paper, the 4-month time point coincides with the planned end of the 3-month intervention delivery period for participants in the intervention arm. This allows a 1 month period after the baseline visit for completion of randomisation and referral processes. Due to funding and time constraints, we were not able to include a 12 month time point that might match the primary time point of a full trial. However, we have chosen 4 and 6 months to align with our full sister trial.

4. Is there a rationale for EF>45 rather than say >50?

In designing our HFrEF and HFpEF trials, we were well aware of the different ejection fraction cut-offs being adopted to differentiate between HFpEF and HFrEF that are being applied by previous and ongoing HF trials. At the advice of our clinical leads (Professor Lang and Drs Davis and Van Lingen), we opted for the cut off of >45% for our HFpEF study population. It should be noted that as reported by Kelly et al, the EF cut off of >45% is also being applied in the large multi-country PARAMOUNT and TOPCAT trials (Kelly JP, Mentz RJ, Mebazaa A, et al. Patient Selection in Heart Failure With Preserved Ejection Fraction Clinical Trials. J Am Coll Cardiol. 2015;65(16):1668-1682. doi:10.1016/j.jacc.2015.03.043.).

## VERSION 2 – REVIEW

| | |
|---|---|
| **REVIEWER** | Donal, Erwan<br>CHU Rennes France |
| **REVIEW RETURNED** | 16-Aug-2016 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thanks for answering to most of our remarks.<br>This is a valuable study and the design paper is valuable to publish<br>The end points and the many QoL questionnaire are something that could be discussed but, let's wait for the results! |