PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a feasibility trial to inform the development of a breathlessness rehabilitation programme for Chronic Obstructive Pulmonary Disease and Chronic Heart Failure (The COHERE Trial)
AUTHORS	Jones, Amy; Evans, Rachael; Esliger, Dale; Sherar, Lauren; Singh, Sally

VERSION 1 – REVIEW

REVIEWER	Natasha Smallwood Royal Melbourne Hospital & University of Melbourne Australia
REVIEW RETURNED	15-Feb-2019

GENERAL COMMENTS	This is an extremely well written paper on an incredibly important topic. The feasibility trial is well described and will use mixed methods to appropriately identify both relevant quantitative data as well as qualitative data regarding patients' and health professionals' experiences of both the trial and rehabilitation program. My main comments are: On page 7, lines 10-12 under eligibility criteria the paper reports that “patients with a confirmed diagnosis of COPD/CHF or combined diagnoses” will be included. Can you please state how diagnosis will be confirmed i.e. for COPD patients will spirometry measured before referral (demonstrating obstruction) be required to confirm the diagnosis or will a medical practitioner diagnosis be sufficient (GP or specialist?). Notably in practice, the latter is not always correct. Therefore spirometry before referral would be better. Similarly for CHF patients will the diagnosis be confirmed by ECHO or other measures before referral? Also will this trial include patients with CHF and LV systolic dysfunction and will patients with HF-PEF also be eligible? If the latter are included, how will their diagnosis be confirmed before referral? In the eligibility criteria any patient with MRC 2 or greater will be included. Whilst I realise this is being very inclusive, this translates to relatively mild breathlessness, which even unfit people without any medical conditions frequently report experiencing. Once you reach the next stage of a full trial, using such a low MRC may make it harder to find a significant improvement and will increase the sample size required. Regarding the qualitative interviews, the eligibility criteria only refer

	to health professionals involved in the program, however this group is likely to be fairly invested in the program and thus biased. Thus it might be worth including other health professionals too e.g. high frequency referrers (GPs, hospital cardiologists or respiratory physicians), to ascertain their thoughts on the program after a few of their patients have completed it. Similarly it would be worth interviewing carers as well as participants (particularly if carers are allowed to attend the education component), to examine their experiences of the trial and program. Lastly Table 1 lists the education topics, however smoking cessation does not seem to be included. Presumably smokers are not excluded from attending breathlessness rehabilitation? Given the immense immediate and long-term benefits of smoking cessation both generally, but particularly on dyspnoea, surely this requires a stand alone topic in your education program. To try to include it within one of the topics would not do it justice. I look forward to seeing the results of both the feasibility trial and later full trial.

REVIEWER	Prof. Tim McDonnell St. Vincent's University Hospital, Elm Park, Dublin Ireland D04 T6F4
REVIEW RETURNED	16-Feb-2019

GENERAL COMMENTS	This study addresses the value and assessment of rehabilitation for patients with COPD, CHF, and combined disease. In particular, the value of rehabilitation for patients with CHF has been a relatively neglected area and patients with CHF have poor access to the service. One way of addressing this is to combine COPD and CHF patients in a dyspnoea rehab programme which has been pioneered by this group which has a track of conducting innovative studies in pulmonary rehabilitation. The inclusion and exclusion criteria in this study might benefit from being expanded. How will the diagnosis of COPD and CHF be confirmed? Presumably, spirometry will be used to confirm the diagnosis of COPD patients but what will be used for objective confirmation of the CHF diagnosis. Again presumably unstable patients such as those with angina will be excluded. Will results be analysed by disease severity? Differences between the COPD and CHF patients will be of interest. There is no mention of the timescale for conducting the study, the estimated timeframe for initiation and completion of the study should be included.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

This is an extremely well written paper on an incredibly important topic. The feasibility trial is well described and will use mixed methods to appropriately identify both relevant quantitative data as well as qualitative data regarding patients' and health professionals' experiences of both the trial and rehabilitation program.

Many thanks for your positive comments.

Specific comment 1- On page 7, lines 10-12 under eligibility criteria the paper reports that “patients with a confirmed diagnosis of COPD/CHF or combined diagnoses” will be included. Can you please state how diagnosis will be confirmed i.e. for COPD patients will spirometry measured before referral (demonstrating obstruction) be required to confirm the diagnosis or will a medical practitioner diagnosis be sufficient (GP or specialist?). Notably in practice, the latter is not always correct. Therefore, spirometry before referral would be better.

Response specific comment 1- The inclusion criteria required a clinically confirmed diagnosis of either COPD or CHF in the referral letter to the service. COPD is confirmed as part of the trial process through spirometry and to date, nobody has been excluded due to a misdiagnosis. With respect to CHF, patients are referred through the hospital or community heart failure service, where an echocardiogram is routinely included. BNP is measured at baseline in all participants and a repeat echocardiogram on all participants is beyond the scope of this study.

Specific comment 2- Similarly for CHF patients will the diagnosis be confirmed by ECHO or other measures before referral? Also will this trial include patients with CHF and LV systolic dysfunction and will patients with HF-PEF also be eligible? If the latter are included, how will their diagnosis be confirmed before referral?

Response specific comment 2- All CHF patients will come through the hospital or community heart failure service and will routinely have an echocardiogram to confirm CHF. To date, we have only recruited HFREF, but will consider extending our criteria to HFPEF. A BNP level is analysed at baseline.

Specific comment 3- In the eligibility criteria any patient with MRC 2 or greater will be included. Whilst I realise this is being very inclusive, this translates to relatively mild breathlessness, which even unfit people without any medical conditions frequently report experiencing. Once you reach the next stage of a full trial, using such a low MRC may make it harder to find a significant improvement and will increase the sample size required.

Response specific comment 3- Thank you for this comment and thought. We took guidance from national guidelines (Bolton et al., Thorax 2013) to include anyone with an MRC2 (who is functionally limited) or greater. Our previous work showed that patients MRCpresenting to pulmonary rehabilitation did as well as those MRC3-5 (Evans et al., Resp Med 2009). We will only be recruiting those that have already been referred to PR. It also aligns with NYHA class II used to include patients with heart failure.

Specific comment 4- Regarding the qualitative interviews, the eligibility criteria only refer to health professionals involved in the program, however this group is likely to be fairly invested in the program and thus biased. Thus it might be worth including other health professionals too e.g. high frequency referrers (GPs, hospital cardiologists or respiratory physicians), to ascertain their thoughts on the program after a few of their patients have completed it. Similarly, it would be worth interviewing carers as well as participants (particularly if carers are allowed to attend the education component), to examine their experiences of the trial and program.

Response specific comment 4- Thank you for these comments. We agree this would be beneficial and will seek to amend the trial protocol to allow us to conduct more interviews/ focus groups in these groups.

Specific comment 5- Lastly Table 1 lists the education topics, however smoking cessation does not seem to be included. Presumably smokers are not excluded from attending breathlessness rehabilitation? Given the immense immediate and long-term benefits of smoking cessation both generally, but particularly on dyspnoea, surely this requires a standalone topic in your education program. To try to include it within one of the topics would not do it justice.

Response specific comment 5- We fully agree with the reviewer's comment in that smoking cessation is an integral part of the education within the COPD pathway. Smokers are not excluded from attending breathlessness rehabilitation and are routinely referred to our smoking cessation services. In the past, we have delivered education sessions on smoking cessation, but, it was only relevant to a minority of participants. We therefore deliver this education at an individual level during the classes.

Reviewer 2:

This study addresses the value and assessment of rehabilitation for patients with COPD, CHF, and combined disease. In particular, the value of rehabilitation for patients with CHF has been a relatively neglected area and patients with CHF have poor access to the service. One way of addressing this is to combine COPD and CHF patients in a dyspnoea rehab programme which has been pioneered by this group which has a track of conducting innovative studies in pulmonary rehabilitation.

We thank the reviewer for their positive comments.

Specific comment 1-The inclusion and exclusion criteria in this study might benefit from being expanded. How will the diagnosis of COPD and CHF be confirmed? Presumably, spirometry will be used to confirm the diagnosis of COPD patients but what will be used for objective confirmation of the CHF diagnosis. Again presumably unstable patients such as those with angina will be excluded. Will results be analysed by disease severity? Differences between the COPD and CHF patients will be of interest.

Response specific comment 1- Thank you for your comments.

COPD is confirmed as part of the trial process through spirometry and to date, nobody has been excluded due to a misdiagnosis. With respect to CHF, patients are referred through the hospital or community heart failure service, where an echocardiogram is routinely included. A BNP level is analysed at baseline. A repeat echocardiogram on all participants is beyond the scope of this study. With respect to the exclusion criteria, we used the rehabilitation service exclusion criteria, which would include unstable cardiovascular disease.

We have previously reported the differences in COPD and CHF participating in a conventional pulmonary rehabilitation programme (Evans et al., Respir Med. 2010). We will extend this data by also including those with mixed disease. As this is a feasibility trial, the results will be presented to reflect this so no definitive conclusions will be drawn regarding responses based on diseaseeverity even though we agree this is of interest.

There is no mention of the timescale for conducting the study, the estimated timeframe for initiation and completion of the study should be included.

Response specific comment 2- This has now been included to also comply with the CONSORT extension checklist for feasibility trials. This has been included within the sub-heading ‘Data collection’. Recruitment will occur from May 2018 to June 2020, with data collection ongoing until August 2020.

VERSION 2 – REVIEW

REVIEWER	Prof. TIm McDonnell Dept. Of Respiratory Medicine, St. Vincent's University Hospital, Elm Park, Merrion Road, Dublin , Ireland D04 T6F4
REVIEW RETURNED	20-Apr-2019

GENERAL COMMENTS	The authors have addressed satisfactorily my comments raised in my previous review