Author’s response to reviews

Title: Pulmonary Rehabilitation after exacerbation of bronchiectasis: a pilot randomized controlled trial

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Version: 1 Date: 19 Dec 2018

Author’s response to reviews:

Dear colleagues

Thank you for your comments. We attach here a revised version of the paper and below you will see a point by point response to the reviewers comments

Best wishes

James Chalmers, on behalf of the authors

PULM-D-18-00439

Pulmonary Rehabilitation after exacerbation of bronchiectasis: a pilot randomized controlled trial
James Chalmers, MD, PhD; Megan L Crichton, MSc; Gill Brady; Simon Finch, MD; Michael Lonergan, PhD; Thomas C Fardon, MD BMC Pulmonary Medicine
Dear Dr Chalmers,

Your manuscript "Pulmonary Rehabilitation after exacerbation of bronchiectasis: a pilot randomized controlled trial" (PULM-D-18-00439) has been assessed by our reviewers. They have raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in BMC Pulmonary Medicine.

Their reports, together with any other comments, are below. Please also take a moment to check our website at https://pulm.editorialmanager.com/ for any additional comments that were saved as attachments.

If you are able to fully address these points, we would encourage you to submit a revised manuscript to BMC Pulmonary Medicine.

Once you have made the necessary corrections, please submit online at:

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A decision will be made once we have received your revised manuscript, which we expect by 28 Dec 2018.

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I look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Marco Idzko

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Technical Comments:

Editor Comments:

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Reviewer reports:

Andreas Rembert Koczulla (Reviewer 1): Chalmers and co-authors presented the study "Pulmonary Rehabilitation after exacerbation of bronchiectasis: a pilot randomized controlled trial"

The study raised some fundamental questions.

1. What is the proposed number of patients that should be included in the study based on the power calculation? Was the power calculation adequate for the primary endpoint?
This was a pilot study and the purpose of such a study is to establish the sample size required for a definitive trial. A priori, there was therefore no power calculation.

2. Please clarify the discrepancy between the power calculation of thousands of subjects which were needed to fulfill the power calculation and the result of 9 patients in the rehab group. Due to this numeric imbalance, it seems problematic to draw reliable conclusions from the detected results of this study.

This was a pilot study, the purpose of which was to determine the feasibility and number of subjects required to perform a definitive trial. The original objective of our study was not to recruit thousands of patients (clearly) but to determine the mean and standard deviation changes in the primary endpoint in a small number of subjects to then power a definitive trial. Based on our results, such a trial would require a prohibitive number of patients.

3. Please explain the difference of number of subjects after randomization in the groups. A differential drop-out is not described

We have explained in the manuscript that this is due to imbalanced randomization. Unfortunately, since randomization is random, it is possible for more patients to be randomized to one group rather than the other. We have explained this in the study.

4. You mentioned 2 times of training and 2 homework trainings- what was the participation rate of the patients in the pulmonary rehab group?

This has been added to the manuscript. Adherence was 100% for those randomized to rehabilitation in terms of attending supervised rehabilitation. Home training was unsupervised and compliance cannot be assessed.

5. How did you control the home training was performed? Please provide the average training time duration for the patients

We have added to the limitations section of the manuscript that compliance with home training is not monitored and so we cannot demonstrate the level of compliance with this.

6. Since rehab is more than training the title should be changed to pulmonary training after exacerbations.
Pulmonary rehabilitation is the recognised term for this intervention and in addition the registration of our trial uses this term and according to ICMJE guidelines and reporting standards, the title of our paper should match the original study design and registration.

7. Please provide blood gas analysis (pO2), LTOT supply, and heart insufficiency as comorbidity in regards of the characterization of the patients

None of the patients were receiving long term oxygen therapy and blood gas analysis is not part of the standard workup for bronchiectasis patients attending pulmonary rehabilitation and was therefore not performed in this study. None of the patients had a history of heart failure.

8. You refer to Greening and colleagues in regards to mortality of rehab.- the per protocol analysis of the study did not show a difference in mortality, suggesting that those who actually received the intervention were not those who came to harm. (Spruit et al. Eur Respir J. 2018 Jan 11;51(1).)

Thank you for this useful insight which we have incorporated into the discussion section of the manuscript.

9. The 6 MWD difference in the groups is small. That raises again the question of the quality and frequency of the training participation. Please provide more data on training participation

As above, compliance with supervised exercise was 100% but home training is not supervised and compliance cannot be determined. This is listed as a limitation of the study.

10. No drop-outs in the exacerbated patients- please comment.

Our study was small and so we were fortunate that patients were able to complete the intervention. We acknowledge drops out may be an issue in future larger studies.

11. How did you rule out training in the control group? Where there any differences - for example, in the weekly performed steps in the control group and training group? How do you explain the increase in 6 MWD in the control group?
This is a relevant question- patients in the control group did not attend pulmonary rehabilitation and received no other intervention. Nevertheless they are recovering from an exacerbation and so some recovery is expected simply as a result of antibiotic treatment. I think this is what we are seeing, and pulmonary rehabilitation is having minimal additional benefit on top of this.

Samantha Harrison (Reviewer 2): This is a well-written manuscript describing an interesting pilot trial. Such a study is difficult to perform prospectively and this is a challenging population to engage in active intervention.

Background

Pg 1, line 46 - PR has been found to be very successful for people who complete following an exacerbation of COPD but attendance rates are very poor. Please provide a comment on this.

This is an excellent comment, we have added this to the paper. There is an important difference between the results of trials and real-life.

Reference is made to the study by Greening et al 2014. Please add more details. Are you saying that 20/389 patients enrolled had bronchiectasis? Currently this is not clear.

Thank you, we have added a further discussion of this paper.

If only 5% (20/389) of people with respiratory disease are admitted to hospital with an exacerbation of bronchiectasis please provide a rationale for why we should be attending to this particular sub-population. I agree we should be providing focused care for people post-exacerbation of bronchiectasis but this needs to be made clear.

We have added this. I am not sure that the Greening study can be taken as representative since it was primarily focused on COPD. The current prevalence estimates suggest that bronchiectasis is common and increasing rapidly and therefore we feel as the reviewer says, that we should be looking at interventions post-exacerbation.
Methods

Please add pilot to the study design section.

Done

If this was indeed a pilot study the primary aim should not be concerned with effectiveness. Rather the aim of a pilot study is to test the feasibility of an approach to be applied in a future larger trial. Please rephrase.

Agreed, this has been added to the objectives section.

Did you monitor adherence to the 'homework' (unsupervised sessions)?

No and this has been listed as an important limitation of the study.

If PR program is 6 weeks why are outcomes assessed at 8 weeks rather than immediately following completion of the program?

This is to allow a small window of feasibility around starting rehabilitation and attending for the 8 week visit.

Results

If this is a pilot study some of the main results should comment on recruitment rates, willingness to be randomised, adherence, time required to complete the assessment, safety.

We have added more details on this.

Do you know how many took up maintenance programs?

This was not recorded.

Discussion

Did all those randomised to PR complete?

yes
If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

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