Author's response to reviews

Title: Efficacy of a Physical Exercise Training Programme COPD in primary care: study protocol of a randomized controlled trial

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Version: 3
Date: 10 July 2014

Author's response to reviews: see over
Author's response to reviews

Title: Efficacy of a Physical Exercise Training Programme COPD in primary care: study protocol of a randomised controlled trial

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Version: 2 Date: 10 July 2014
Author's response to reviews: see over
Reviewer’s report

Title: Efficacy of a Physical Exercise Training Programme COPD in primary care: study protocol of a randomised controlled trial

Version: 2 Date: 10 April 2014

Reviewer: Marie Williams

Reviewer's report:
A useful and much needed study which will address the use of exercise training in primary care.

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
  - I was very interested to see that breathing exercises were included as part of the active intervention. This seems an odd choice, when the rest of the intervention has very high level evidence to support inclusion. There is fairly unconvincing evidence to support the inclusion of breathing exercises and it’s unclear for what purpose these are included? “Breathing exercise is an embracing term for a range of exercises such as active expiration, slow and deep breathing, pursed lips breathing, and diaphragmatic breathing [38].”

Reviewer 1 is right in her statement that there is no convincing evidence for the effectiveness of breathing exercises in reducing dyspnoea. However, a few studies have shown that patients who undergo breathing training are able to adopt a slower, deeper pattern of breathing (Nield, 2007, Pomidori, 2009). For example, pursed lip breathing was successful in reducing dyspnoea after a 6-minute walk (Nield, 2007). The rationale is that some patients with COPD might be limited in exercise capacity because of dynamic hyperinflation. Breathing training focuses on slowing the respiratory rate, primarily through prolonged expiration, and it might be beneficial in reducing dyspnoea via reducing exercise-induced dynamic hyperinflation (Collins, 2008). Overall, the ATS/ERS Statement on Pulmonary Rehabilitation indicates that expert opinion strongly supports the use of breathing training, despite the small sample of studies focusing on breathing strategies (Spruit, 2013, page e23). Because of this recommendation, we included breathing exercises in our intervention.

- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
  - Minor sentence structure revisions and suggestions for improving clarity and reducing complexity of sentence structure I have bolded the changed word/s and used strike through for words which could be removed:
    • Only a few trials have investigated the effect of exercise training on changes in daily physical activity [7-11]. (Page 4)
• However, also patients with moderate COPD also have impairments in exercise capacity, respiratory muscle function, limb muscle force and quality of life [15-18]. (Page 5)

• Exercise training programmes in patients with moderate to severe COPD when incorporated in (self)-management programmes or integrated disease management programmes in primary care result in improvements in health-related quality of life, breathlessness, exercise capacity, muscle strength and daily physical activity [9, 21, 22]. (Page 5)

• To our knowledge hardly any data are available on the efficacy of physical exercise training programmes in patients with mild to moderate COPD that are recruited and treated solely in primary care. (Page 5)

• From a patients’ perspective, an increase in exercise capacity and daily physical activity during the early stage of the disease could be beneficial in order to stop the downward spiral of symptom-induced inactivity, deconditioning, muscle weakness, the fear of movement and reduced quality of life. (Page 6)

• It seems advantageous to initiate exercise training when the symptoms of dyspnoea and deconditioning are not very pronounced yet. (Page 6)

• The Practice Guideline COPD of the Dutch College of General Practitioners (NHG standard, 2007) recommends general practitioners (GP’s) to advise all patients with COPD to be sufficient physically active [5]. (Page 6)

• The implementation of this disease management programme for COPD is encouraged by the reimbursement through so-called chained diagnose-treatment combination (DTC) [27]. (Page 7)

• Although in some regions in the Netherlands these disease management programmes for COPD are already implemented and serve as current daily care, no evidence on the effectiveness of these programmes is available. (Page 7)

We adopted all the above mentioned language and sentence structure suggestions.

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
  - Sham-intervention. I understand the intent of the sham is to provide similar experience in a physiotherapy setting and with the exercise prescription at a level unlikely to result in physiologic training stimulus. The difficulty I have is the clear mismatch in “group exposure” between the active and sham intervention (Active intervention, 60-90 minutes sessions x 2 a week whereas the Sham groups patients participants in one 30 minutes sessions per week). Assuming 16 week intervention, this means that the Sham participants have potential exposure in group exercise sessions for 480 min max (16 x 30 min.) whereas the Active intervention participants have 1920 to 2880 minutes (2 sessions a week =32 x 60 or 90 minutes). Perhaps the duration of exposure
might have a greater influence or at least could confound the content of the interventions?

Our main purpose was to assess the difference in effectiveness between a training programme + advises on becoming physically more active and advises on becoming physically more active alone. The control group in our study receives more (training) exposure than patients receive in current daily care in which they only get advises on physical activity from the general practitioner and/or nurse practitioner. Furthermore they receive more training exposure than in many other pulmonary rehabilitation studies (Effing, 2010, Roman, 2013, Troosters, 2000, van Wetering, 2009). From an ethical and financial point of view, we found it undesirable to enlarge the exposure even more than we already did. For ethical reasons, because patients are spending time to come to a physiotherapy practice and to execute a programme, while there is no training stimulus. For financial reasons, because the physiotherapists are paid for their consultations. But, we are quite well aware of the difference in duration of the exposure in both groups and in the discussion of the results we will take into account that this could be a confounding factor.

- Clarify use of the term “success” within the secondary objective (“The secondary objective is to assess the main determinants for success of treatment”). The does not appear to be an a priori definition for “success” - apologies is I have missed this? And the planned analysis assesses the effect of modifiers rather than identifying “success” – “…… MRC dyspnoea score, walking distance, peripheral muscle strength, level of daily physical activities and compliance with the training programme”.

The reviewer is right in her comments, we indeed will assess the effect of modifiers rather than identifying “success”. Therefore, the secondary objective of the study has been changed to “The secondary objective is to assess how patient characteristics and baseline burden of disease modify the effect of a physical exercise training programme on functional exercise capacity in patients with mild to moderate COPD in primary care.” (Page 7).

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
'I declare that I have no competing interests'
Reviewer's report

Title: Efficacy of a Physical Exercise Training Programme COPD in primary care: study protocol of a randomised controlled trial

Version: 2 Date: 19 May 2014

Reviewer: miguel roman

Reviewer's report:
This is a well designed randomized controlled trial situated in the primary care setting to evaluate the efficacy of a physical exercise training programme at a local physiotherapy practice in patients with mild to moderate COPD on exercise capacity, physical activity, dyspnoea and quality of life. The intervention group receives a well designed 4-month physical exercise training programme according to Dutch guidelines and primary outcome is functional exercise capacity at 4-months measured on the six-minute walk distance. Thought I'm not an statistics expert it seems that a review has been made on that issue and the data-analysis plan seems to be robust.

The study faces an important issue for COPD management in primary care and it's original research.

We have some suggestions that could improve the publication

- Major Compulsory Revisions
  - Inclusion criteria

Page 4: Inclusion criteria are not well explained and this is one of the main problems of the design. They will recruit COPD patients visiting their general practitioner because of dyspnoea, impaired exercise capacity and a low level of self-reported physical activity. They should explain which level of dyspnea or impaired exercise capacity or physical activity is needed to be eligible for the study. Otherwise the inclusion criteria will be widely open and hardly reproducible and as commented in the discussion will bias the sample because they will very much depend on the doctor and nurses aims and encouragement to include patients. An strategy (well defined inclusion criteria) should have been built on to minimize this possible bias.

We understand the problem of possible bias and we have well defined the inclusion criteria (see page 9), “Inclusion will be based on patients with a clinical diagnosis of mild to moderate COPD (post-bronchodilator FEV₁/FVC ratio < 0.7 and FEV₁ ≥ 50% of predicted); who not have a minimum of 30 minutes of physical activity at moderate intensity, on at least 5 days per week, according to the ACSM-recommendation (Haskell, 2007); having a stable situation (no exacerbations in the last 8 weeks) and adequate and optimal inhalation technique, are competent enough to understand and speak the Dutch language and having provided written informed consent.”
Page 4. The population in Limburg is the least physically active population of the Netherlands. This could lead to a lack of external validity and should be comment on the discussion.

The following sentence is added in the Discussion section (page 17): “As the population in Limburg is the least physically active population of the Netherlands, this might influence the external validity of the study.”

Page 4. The inclusion criteria includes an adequate and optimal inhalation technique but there’s no mention on how it will be measured. Which is the added value of this criteria for the study to be an inclusion criteria?

The general practitioner or nurse practitioner will check and report the inhalation technique during their consults. In our opinion it is important for the patients to have an optimal inhalation technique, because pharmacologic therapy is one of the key components of disease management, used to prevent and control symptoms, reduce exacerbations and improve exercise capacity and health status (Rabe, 2007). With optimal bronchodilation, the primary locus of exercise limitation may change from dyspnoea to leg fatigue, thereby allowing patients to exercise their peripheral muscles to a greater degree. This illustrates the potential synergy between pharmacologic and nonpharmacologic treatments (Spruit, 2013).

- Duration of intervention

Page 11: Most rehabilitation programs are conducted over 12 weeks. It is not well explained why in this study the duration of the intervention will be 4 months. We need some arguments to the duration of the intervention

There remains no consensus on the optimal duration of pulmonary rehabilitation. However, longer programmes are thought to produce greater gains and maintenance of benefits, with a minimum of 8 weeks (Beauchamp, 2011). Especially, when changes in physical activity are aimed, it is suggested that longer programme duration (>3 months) is required to achieve change in health-enhancing behaviour (Pitta, 2008, NG, 2012).

- Minor Essential Revisions
- Background

We miss two important references about rehabilitation in primary care very recently published:
Kruis AL, Smidt N, Assendelft WJJ, Gussekloo J, Boland MRS, Rutten-van Mölken M, Chavannes NH. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD009437. Metaanalysis showing that integrated disease management interventions not only improved disease-specific QoL and exercise capacity, but also reduced hospital
admissions and hospital days per person.


We added the two references in the background section (page 5) as indicated by the reviewer. (We were not able to include these references before, because this manuscript has been submitted to BMC more than a year ago).

On page 7 authors say "Although in some regions in the Netherlands these disease management programmes COPD are already implemented and serve as current daily care, no evidence on the effectiveness of these programmes is available" The authors are not making a cost-effectiveness analysis so this sentence is out of place here.

We are not sure what is meant by this comment of the reviewer. In our view, implementation of the programme (as it already is) is unrelated to a cost-effectiveness analysis.

Page 13: "The six-minute walk test (6MWT) will be performed in accordance with the ATS Statement: guidelines for the 6MWT [43], except that a standard 30-meter corridor will not always be feasible in a primary care physiotherapy practice, but the minimal track will be 10 meter" This could lead to wrong results and should be mentioned in the limitations.

We are well aware of this problem and we have mentioned it in the Discussion section as limitation (page 17).


A main purpose of our study was to assess physical activity in daily life. We have chosen to assess this with a subjective tool (a questionnaire) and an objective instrument (activity monitor). In the review of Benzo (2009) it is stated that there is no specific questionnaire that is optimal to use in COPD. So, we relied on the recommendations in the Practice Guideline COPD of the Dutch College of General Practitioners (NHG standard, 2007) and the Dutch Guideline Physiotherapy in COPD (2008) where, amongst others, the brief physical activity assessment tool of Marshall is recommended and therefore familiar in Dutch
primary care organizations. The brief physical activity assessment tool is a reliable instrument, with validity similar to that of more detailed self-report measures of physical activity.

Page 17: "As a consequence, general practitioners or practice nurses will have a lack of information on this topic and will not consider a follow-up strategy, including referral to a physical exercise training programme”. This is an assumption that should be deleted.

This sentence was added within the scope of potential barriers in the recruitment of patients. As objective physical activity monitoring by accelerometers is not common in general practice, general practitioners and practice nurses have to rely on assessment by questionnaires (self-report). Although the results of these subjective methods may be useful as a group estimate, they lack accuracy and show a large individual variability. Therefore, relying on individual results is not recommended (Pitta, 2006). That is why we assume that lack of objectified insight in physical activity patterns might be a barrier in the recruitment of patients. We have replaced the word ‘will’ by ‘might’ (page 18).

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report

Title: Efficacy of a Physical Exercise Training Programme COPD in primary care: study protocol of a randomised controlled trial

Version: 2 Date: 24 June 2014

Reviewer: Carl J Lombard

Reviewer's report:

1. The authors provide no rational for doing a individually randomised trial with the strong possibility of contamination due to the design of the same physiotherapist delivering the intervention to participants from both arms. A simple cluster randomised design of say 20 physiotherapy setting with 8 participants would be able to answer the same question with the same power (icc=.05).

We agree with the reviewer that, from a methodological point of view, a cluster randomized design would be the most sound design for the study. We initially planned to perform a cluster randomized design, but during a pilot study of this trial (Fastenau et al., 2007), we discovered that physiotherapists were not very keen to deliver a treatment without a proper training programme, although hard evidence of efficacy of a physical exercise training programme COPD was still lacking. Therefore, it would have been impossible to recruit sufficient physiotherapy practices with treating only control patients. We are very dependent on the participation of physiotherapists, since they play a dominant role in our study. We have found a solution to this problem by allowing the physiotherapist offering the possibility for patients in the control group to participate in the physical exercise training programme after the study-period, in case the intervention has proven to be efficacious.

To tackle contamination, we have trained and instructed the physiotherapists thoroughly in advance of the study and monitored and instructed them throughout the intervention period. We have well explained that there is still no evidence for the efficacy of such a training programme for patients with mild to moderate COPD, and that the physiotherapists could only participate if they were willing to deliver both the intervention treatment and sham-treatment. Another strategy to minimize contamination was that patients of the intervention and control group were not in the same physiotherapy setting at the same time. So, the physiotherapists could focus their mind on just one treatment at the time.

Finally, in an individually randomized trial less patients have to be included for the same power. With our design we needed to include 104 patients, according to the option of the reviewer we should have needed to include 160 patients. We have added the abovementioned rationale for doing an individually randomized trial instead of a cluster randomized trial in the limitation section of the manuscript (see page 16).
2. Since multiple sites will handle participants it is not clear how randomisation will be implemented across the sites - will they contact a centralised person who has a concealed list? No reference to Figure 1 in this section which seems to be indicated that the researcher will do the allocation which is not desirable.

Randomization is performed by a centralized and independent person who has a concealed list. The researcher is not involved in allocation to treatment group or setting. We have added these sentences in the randomization part of the manuscript (page 10).

3. What is meant by the statement that participants from both groups will not be in the same physiotherapy setting for treatment at the same time. (p10)?

Participants from the control group will not be treated at the same hour of the day in the same physiotherapy setting as the intervention group. So, it will not occur that participants from one group see the treatment of the other group. Furthermore, physiotherapists can focus on either the intervention treatment or sham- treatment.

4. Will the same physiotherapist be dealing with a participant for the whole period?

The same physiotherapist will be dealing with a participant for the whole period.

5. How many physiotherapist will be participating in the trial?

We have estimated that 18 physiotherapy practices will be eligible to participate in the trial.

6. Given the fact that participants from both arms will be nested within the same physiotherapist setting this random effect should also be evaluated. The variability due to this factor may large and have an influence on the power.

We will check the random effect in our effect evaluation as indicated by the reviewer. We have added this point in the section of data analysis on page 15.

7. Descriptive statistics should be presented by group.

Descriptive statistics will be presented for the total group, as well as for the separate groups. We will have added this sentence in the data analysis section as indicated by the reviewer (page 15).

8. The measurement of the primary outcome should be standardised across all settings. If one facility can only do the test in a 10 m passage this length should be used across all settings. This will reduce variability.
Since we have submitted this manuscript to BMC more than a year ago, six-minute walk tests are already performed and we now cannot make adaptations to the realizations. (We do know that a vast majority of physiotherapy practices has a track of 10 meters.) An advantage of the randomization on patient level instead of physiotherapy practice level is that patients are assigned to smaller and longer passages in a non-differential manner and an equal distribution of patients from the intervention group and control group can be expected per physiotherapy practice. Since we are interested in the difference scores (4 or 6 months minus baseline measurement) and participants are assessed in the same passage on all occasions, we think that the variability is acceptable. We will take this point in account for future studies. We have mentioned this point in the limitations (page 17).

9. Using the 4 month time point as the primary outcome is the best case scenario for the efficacy of the program but the 6 month time point will be the more pragmatic one. No rational for not using the 6 month time point is given.

We were primarily interested in the effect of the physical exercise training programme. In other words, was it possible at all for patients with mild to moderate COPD to benefit from a training programme? So, that’s why the 4 month time point was our primary outcome. The 6 month time point is indeed a more pragmatic one, as it aimed at gaining more insight into the lasting of the effects. So, we do agree with the reviewer and we will add this information in the objectives section (page 7).

10. A increase of 52 meters in 6mwd represents a approximate increase of 10% on the average of 475m. As non- specialist in this field it is hard to see how walking an extra 50 meters when you can already walk nearly half a km will have an impact on regaining social contacts (p16)?

First of all, Redelmeier et al (1997) assessed a threshold of 54 m at which a difference in 6MWT was associated with a noticeable difference in perceived walking ability for patients with COPD. Furthermore, it is assumed that a rehabilitation programme learns patients with COPD how to manage their disease. A rehabilitation programme is believed to counteract the negative spiral of dyspnoea and deconditioning (Chavannes, 2009). So, the benefits of such a programme surpass the pure physiologic changes that occur and have a wider impact.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

'I declare that I have no competing interests