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### ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Online Versus Face-to-Face Pulmonary Rehabilitation for Patients with Chronic Obstructive Pulmonary Disease: Randomised Controlled Trial</th>
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<tr>
<td>AUTHORS</td>
<td>Bourne, Simon; DeVos, Ruth; North, Malcolm; Chauhan, Anoop; Green, Ben; Brown, Thomas; Cornelius, Victoria; Wilkinson, Tom</td>
</tr>
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</table>

### VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Brenda O'Neill</th>
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<td>SCHOOL HEALTH SCIENCES, ULSTER UNIVERSITY, NORTHERN IRELAND</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>16-Oct-2016</td>
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### GENERAL COMMENTS

This interesting RCT compares online versus face to face pulmonary rehabilitation for patients with COPD. It explores if the online version of Pulmonary Rehabilitation is non inferior to the traditional face to face Pulmonary Rehabilitation model. This represents a substantial research study and it will add to the debate about the format for the delivery of PR, as well creating choice for patients with COPD for accessing pulmonary rehabilitation. I have summarised a few points below for consideration by the authors.

Access to an accompanying completed CONSORT checklist would be helpful for this manuscript.

Abstract: The abstract provides a brief overview of the study and any relevant revisions made to the main manuscript should be incorporated.

Introduction: The introduction clearly presents the rationale for the proposed trial. Inclusion of reference to the recent Cochrane review of the effects of PR should be considered (para 2) (Ref 1). Para 4 relates to components of PR and the lines about the educational component could be more clearly articulated. There should be a clear statement of the study aims and objectives at the end of the introduction.

Design: Please include an indication of ethics approval/ethics approval number and also an indication that signed informed consent was received from participants. It would be interesting to note any pilot work testing the ‘myPR’ application in advance of the RCT if this is available. Further information about patient training to use the intervention would be helpful, as well as whether they received advice about when to do the exercises specifically and how to make any modifications if an exercise was not suitable. Para 3, indicates that randomisation 2:1 is justified in relation to costs but it not clear which programme is more costly and further
clarification would be helpful. Please also indicate if there was concealed allocation.

In the statistical methods or results section it would be helpful to include information about what measures were used in the adjusted analysis and the rationale for the selection.

Results and discussion: Results and further discussion about the actual dose received by patients in each intervention is important. The methods indicate an expectation for online myPR of a min of x 2 sessions and up to 5 sessions per week; and for the face to face PR x 2 face to face sessions plus carry out the exercises at home an additional 3 times; Table 6 provides further information, yet overall it is difficult to compare the dose received for each intervention. For the per protocol analysis was there any rationale for choosing only participants who took up the offer of at least 1 face to face session per week/accessed online 1/week. Various suggestions relating to adherence have been previously considered e.g. completion of 75% of expected sessions (ref 2).

For the face to face PR, participants were asked to attend x 2 sessions and complete x 3 at home; were the 3 home based sessions monitored in any way? It would also be helpful to report any patient initiated contact with the HPs from the myPR group as well as the nature of these and any problems (or absence of) with the technology during the study. Any clarifications could inform the discussion.

Conclusion: The final lines of the conclusion are less specific to the results of this study, but are perhaps relevant for consideration in a future study e.g. in relation to cost analysis.

Tables: Table 5 has some extra words/notes underneath the table

References:


REVIEWER
Elizabeth Rivard
Haut-Richelieu-Rouville hospital, Canada
The hospital is affiliated to University of Sherbrooke

REVIEW RETURNED 24-Nov-2016

GENERAL COMMENTS
Very interesting paper with a RCT!

As said in the paper, it is difficult to establish the best length for PR and the optimal program. Was the exercise incremental in nature? (versus endurance?)

Was there in any way a method for the people in the online PR group to ask or discuss with someone after the learning videos?

In the ERS/ATS guidelines of 2014 on field walking test, the cutoff
now used is 30 meters to establish the minimal clinical difference. I see that the cutoff used was of 54 meters because it is the MCID for perceived amelioration. I would still talk about both cutoffs, saying that one covers the other one.

Dates in page 9 aren't logical (from September 2016 til January 2016...)

Well done!

**REVIEWER**

Alan Batterham  
Teesside University, UK.

**REVIEW RETURNED**

24-Jan-2017

**GENERAL COMMENTS**

In this paper the authors present the results of an RCT on Online Versus Face to Face Pulmonary Rehabilitation for Patients with COPD. This work makes a very good contribution to the literature. The trial is well designed and conducted rigorously. It is refreshing to see an estimation approach (rather than null hypothesis significance testing), and to see a principled method applied for missing data (the multiple imputation). Also, given that this is a non-inferiority trial, it is good to see a per-protocol sensitivity analysis alongside, as ITT analyses often favour a conclusion of non-inferiority, of course, due to dilution of treatment effects. I appreciate how difficult it is to conduct trials with patient populations like this one, and the authors are to be commended. I have two main (related) points, below, for the authors to consider.

1. My primary concern is the linked issue of sample size planning and subsequent clinical inference. The authors pre-specified a minimum clinically important difference (MCID) as a change in 6MWT distance of 54 m, based on the Redelmeier et al. (1997) study. In the current non-inferiority trial, the authors conclude that the online intervention is not inferior to the face-to-face intervention. However, an implicit assumption in a non-inferiority trial is that the reference treatment (face-to-face) is superior to just doing nothing, and that the comparator treatment preserves a good proportion of this benefit. Therein lies the problem with the pre-specified MCID. In the current study, based on the raw means presented in Table 3 (not adjusted means from the ANCOVA), the mean improvement in 6MWT distance the face-to-face group is 28.6 m vs. 44.9 m in the online group. Both of these mean improvements are somewhat smaller than the MCID of 54 m, so the online intervention is not inferior to the face-to-face, but there is not strong evidence for either being clinically significant, arguably. Similarly, the mean improvement in CAT score in the active control intervention (face-to-face) does not meet the MCID threshold of 1.8. Selecting an MCID from the early literature of 54 m enabled the authors to derive a relatively small sample size requirement, notwithstanding the fact that they still selected a non-inferiority margin of 75% of the MCID (which is atypically high, as the authors acknowledge; I shall return to this issue below). However, the high MCID of 54 m then becomes a hindrance when it comes to making inferences, subsequently, as neither the reference or online treatments resulted in substantial mean improvements relative to the MCID – the online was non-inferior to the face-to-face, but neither worked very well. The problem here is that the MCID of 54 m for the 6MWT, although claimed by the authors to be “widely accepted”, has been thoroughly debunked in the more recent literature. See, for example, Puhan
MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J 2011; 37: 784-90; Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the Minimal Important Difference for Six-Minute Walk Distance in Patients With Chronic Obstructive Pulmonary Disease. Arch Phys Med Rehabil 2010; 91: 221-5; Polkey MI, Spruit MA, Edwards LD, et al. Six-minute-walk test in chronic obstructive pulmonary disease: Minimal clinically important difference for death or hospitalization. Am J Respir Crit Care Med 2013; 187: 382-6. In all of these papers, the MCID is reported as 25-30 m; around half of the MCID adopted in the current study. (See the Puhan et al. paper for a thorough critique of the "widely accepted" 54 m value.) Against an MCID of 25-30 m, the results in the current trial look much more promising from a clinical-inference perspective. The authors should address this issue in the paper and make cautious inferences accordingly (caveat: see Point 2, below).

2. Related to the above issues, this trial is really an external pilot and I feel it should be labelled explicitly as such. At various points in the paper a pilot trial is hinted at with terms like "explore" and "preliminary", and in the trial protocol the term "exploratory clinical" is used as a descriptor. Also, the authors state that the results will inform the sample size planning and the design for a subsequent definitive trial. So, it is a pilot, it should be labelled as a pilot explicitly in the Title, Abstract, and Methods, and success criteria for a pilot/feasibility study should be presented. That is, on what basis would this trial be considered a success and therefore imply that a definitive trial was warranted? If it is a pilot, the formal sample size estimation is not required and I suggest this be removed from the paper, as it looks somewhat contrived in light of the MCID issue and the liberal non-inferiority margin. Indeed, a non-inferiority margin of 40.5 m against a more robust MCID of 25-30 m is inappropriate. I suggest the authors report the study as a pilot and follow the CONSORT extension for pilot studies: Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. BMJ (Online) 2016; 355.

3. Page 2, Strengths and Limitations of the Study, third bullet point. The authors state that larger studies are required to explore the health-economic benefits of this model. Given the above, is a larger study not required for effectiveness, too, not just for the health economics?

4. Page 3, What this study adds: “No differences were seen in the effects of key outcomes…” This statement is not robust given the acknowledged limitations of a study that is not powered to detect small differences. Assuming an MCID of 26 m from the Puhan et al, study, the current study had only around 44% power to detect a difference of 26 m between the two arms, so one cannot take the liberty of declaring “no differences” here. As the authors know, non-inferiority and “no differences” are not the same thing. I derived the power above using the data in the results using two methods that resulted in the same answer. First, by deriving the standard error for the effect from the 95% CI of -4.5 to 52.2 m, and then using the R code in the following article: Gelman A, Carlin J. Beyond Power Calculations: Assessing Type S (Sign) and Type M (Magnitude) Errors. Perspectives on Psychological Science 2014; 9: 641-51. Second, directly from the P value of 0.098 and the degrees of freedom using the inverse t distribution. The current study had <50% power to detect a difference of 26 m. I suggest amending the wording in this sentence.
This interesting RCT compares online versus face to face pulmonary rehabilitation for patients with COPD. It explores if the online version of Pulmonary Rehabilitation is non inferior to the traditional face to face Pulmonary Rehabilitation model. This represents a substantial research study and it will add to the debate about the format for the delivery of PR, as well creating choice for patients with COPD for accessing pulmonary rehabilitation. I have summarised a few points below for consideration by the authors.

- We thank the reviewer for their positive comments.
- Access to an accompanying completed CONSORT checklist would be helpful for this manuscript.
- A consort checklist has been included with the revised submission documents.

Abstract: The abstract provides a brief overview of the study and any relevant revisions made to the main manuscript should be incorporated.

- The abstract has been edited following the appropriate edits to the main paper in response to the reviewers comments.

Introduction: The introduction clearly presents the rationale for the proposed trial. Inclusion of reference to the recent Cochrane review of the effects of PR should be considered (para 2) (Ref 1). Para 4 relates to components of PR and the lines about the educational component could be more clearly articulated.

- The reference as suggested has been inserted in paragraph 2 of the introduction.
- Edits to paragraph 4 have been made to ensure clarity regarding the educational component of PR.
- The aims and objectives of the study are articulated now at the end of the introduction.

Design: Please include an indication of ethics approval/ethics approval number and also an indication that signed informed consent was received from participants.

- The ethics approval and consent process are now include in the revised methods section p 5.
- It would be interesting to note any pilot work testing the ‘myPR’ application in advance of the RCT if this is available. Further information about patient training to use the intervention would be helpful, as well as whether they received advice about when to do the exercises specifically and how to make any modifications if an exercise was not suitable.
- The ‘myPR’ application was developed as part of a web app ‘myCOPD’ that was developed in partnership with patients. Patients contributed to the content and appearance of the apps. The platform was tested for security and usability prior to the study but this was the first formal RCT of the platform- this point is discussed in the revised discussion section.

- Training regarding the use of myPR was given immediately on randomisation. After log-in details were generated, patients were shown how to use myPR in a brief 5-10 minute introduction. The programme is specifically designed to be self-explanatory and user-friendly, so little orientation to the programme is required. The methods section p 6 have been edited accordingly to capture this.

- Patients were advised to carry out the exercise at a time that was convenient to them and when they felt their energy levels were at their best. No specific advice was given regarding exercise modification, as this is built into the programme itself. The methods section p 6 have been edited accordingly to capture this.

Para 3, indicates that randomisation 2:1 is justified in relation to costs but it not clear which programme is more costly and further clarification would be helpful.

- Methods section paragraph three has been edited highlighting that face to face PR is the more costly arm. This is also discussed in the revised discussion section.

Please also indicate if there was concealed allocation.
Yes concealed-allocation to intervention was used with an online system. The revised method now include this.

In the statistical methods or results section it would be helpful to include information about what measures were used in the adjusted analysis and the rationale for the selection.

Disease severity in terms of FEV1% predicted and baseline 6mwt results were included in the adjusted analysis. This is because the baseline disease severity and functional capacity can influence the response to the intervention. The statistical section has been edited to capture this detail.

Results and discussion: Results and further discussion about the actual dose received by patients in each intervention is important. The methods indicate an expectation for online myPR of a min of x 2 sessions and up to 5 sessions per week; and for the face to face PR x 2 face to face sessions plus carry out the exercises at home an additional 3 times; Table 6 provides further information, yet overall it is difficult to compare the dose received for each intervention.

We agree it is difficult to compare exposure directly due to the different nature of interventions. We have provided mean data as comparisons but formal statistical comparison is not feasible.

For the per protocol analysis was there any rationale for choosing only participants who took up the offer of at least 1 face to face session per week/accessed online 1/week. Various suggestions relating to adherence have been previously considered e.g. completion of 75% of expected sessions (ref 2).

For the per protocol analysis we had to select a cut off which suited the different interventions. For face to face PR delivered at 2 sessions per week adherence was by default either 1 session ie 50% or two sessions 100%. As we wished to try and match to the equivalent digital intervention to avoid bias we selected 1 session. This is a conservative estimate of the per protocol effect but more realistic than using a 100% weekly adherence rate.

For the face to face PR, participants were asked to attend x 2 sessions and complete x 3 at home; were the 3 home based sessions monitored in any way?

Patients completing the face to face programme were asked to fill out a home exercise sheet three times a week, in addition to their two supervised sessions. These home exercise sheets were collected at the end of each week and added to their case report files.

It would also be helpful to report any patient initiated contact with the HPs from the myPR group as well as the nature of these and any problems (or absence of) with the technology during the study. Any clarifications could inform the discussion.

Background support was provided from the research team regarding any issues with IT related problems. The majority of these issues were resolved remotely and in one instance a dongle was provided to a patient who had limited data available on their wifi package. This area is covered in the revised discussion regarding resource implications.

Conclusion: The final lines of the conclusion are less specific to the results of this study, but are perhaps relevant for consideration in a future study e.g. in relation to cost analysis.

This section has been edited to clarify this issue.

Tables: Table 5 has some extra words/notes underneath the table

These words have been removed.

References:


Reviewer: 2 Reviewer Name: Elizabeth Rivard Institution and Country: Haut-Richelieu-Rouville hospital, Canada. The hospital is affiliated to University of Sherbrooke

Very interesting paper with a RCT!

We thanks the reviewer for their positive review.
As said in the paper, it is difficult to establish the best length for PR and the optimal program. Was the exercise incremental in nature? (versus endurance?)

• The exercise programme in myPR is incremental in nature, starting from one minute on each exercise in week one, rising by 30 seconds on each exercise on each of the six weeks, to 3½ minutes on each exercise in week six. This is highlighted in the revised methods section of the paper.

Was there in any way a method for the people in the online PR group to ask or discuss with someone after the learning videos?

• There was support available from the research staff to aid with any technological support, but no support was offered for patients wishing to discuss the content of the educational videos. However, patients weren’t specifically told they couldn’t contact the team with questions regarding the educational videos, and it was noted that throughout the study no patient sought any further advice. In the revised discussion section we have augmented the discussion regarding support for the online platform and its resource implications.

In the ERS/ATS guidelines of 2014 on field walking test, the cutoff now used is 30 meters to establish the minimal clinical difference. I see that the cutoff used was of 54 meters because it is the MCID for perceived amelioration. I would still talk about both cutoffs, saying that one covers the other one.

• We thank the reviewer for this point. We agree the accepted standard is now 30m. We originally used 54m the previous clinical standard as it was recommended by our national (BTS) guidelines. In the revised manuscript we now address this issue in the statistical methods results section and indeed using the 30m cut off establish that the online platform achieves this MCID and that non-inferiority findings are still present.

Dates in page 9 aren’t logical (from September 2016 til January 2016...)

• The dates have been amended appropriately

Well done!

• Thank you!

Reviewer: 3 Reviewer Name: Alan Batterham Institution and Country: Teesside University, UK.

In this paper the authors present the results of an RCT on Online Versus Face to Face Pulmonary Rehabilitation for Patients with COPD. This work makes a very good contribution to the literature. The trial is well designed and conducted rigorously. It is refreshing to see an estimation approach (rather than null hypothesis significance testing), and to see a principled method applied for missing data (the multiple imputation). Also, given that this is a non-inferiority trial, it is good to see a per-protocol sensitivity analysis alongside, as ITT analyses often favour a conclusion of non-inferiority, of course, due to dilution of treatment effects. I appreciate how difficult it is to conduct trials with patient populations like this one, and the authors are to be commended. I have two main (related) points, below, for the authors to consider.

• We thank the reviewer for their positive comments.

1. My primary concern is the linked issue of sample size planning and subsequent clinical inference. The authors pre-specified a minimum clinically important difference (MCID) as a change in 6MWT distance of 54 m, based on the Redelmeier et al. (1997) study. In the current non-inferiority trial, the authors conclude that the online intervention is not inferior to the face-to-face intervention. However, an implicit assumption in a non-inferiority trial is that the reference treatment (face-to-face) is superior to just doing nothing, and that the comparator treatment preserves a good proportion of this benefit. Therein lies the problem with the pre-specified MCID. In the current study, based on the raw means presented in Table 3 (not adjusted means from the ANCOVA), the mean improvement in 6MWT distance the face-to-face group is 28.6 m vs. 44.9 m in the online group. Both of these mean
improvements are somewhat smaller than the MCID of 54 m, so the online intervention is not inferior to the face-to-face, but there is not strong evidence for either being clinically significant, arguably. Similarly, the mean improvement in CAT score in the active control intervention (face-to-face) does not meet the MCID threshold of 1.8. Selecting an MCID from the early literature of 54 m enabled the authors to derive a relatively small sample size requirement, notwithstanding the fact that they still selected a non-inferiority margin of 75% of the MCID (which is atypically high, as the authors acknowledge; I shall return to this issue below). However, the high MCID of 54 m then becomes a hindrance when it comes to making inferences, subsequently, as neither the reference or online treatments resulted in substantial mean improvements relative to the MCID – the online was non-inferior to the face-to-face, but neither worked very well. The problem here is that the MCID of 54 m for the 6MWT, although claimed by the authors to be "widely accepted", has been thoroughly debunked in the more recent literature. See, for example, Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J 2011; 37: 784-90; Holland AE, Hill CJ, Rasekaba D, Naughton MT, McDonald CF. Updating the Minimal Important Difference for Six-Minute Walk Distance in Patients With Chronic Obstructive Pulmonary Disease. Arch Phys Med Rehabil 2010; 91: 221-5; Polkey MI, Spruit MA, Edwards LD, et al. Six-minute-walk test in chronic obstructive pulmonary disease: Minimal clinically important difference for death or hospitalization. Am J Respir Crit Care Med 2013; 187: 382-6. In all of these papers, the MCID is reported as 25-30 m; around half of the MCID adopted in the current study. (See the Puhan et al. paper for a thorough critique of the "widely accepted" 54 m value.) Against an MCID of 25-30 m, the results in the current trial look much more promising from a clinical-inference perspective. The authors should address this issue in the paper and make cautious inferences accordingly (caveat: see Point 2, below).

• We thank the reviewer for their detailed assessment of this issue and their suggested approach to address this in the revised paper. The reviewer is correct in highlighting the evolution of accepted MCID for 6MWT and helpful in suggesting appropriate references to evidence this. The original value was taken from the then valid national guidance (BTS). We agree that a revision acknowledging the new MCID of 30m is useful and strengthens the nature of the clinical inference of the results. We have made the appropriate changes to the manuscript in the methods and interpret the data with respect to both this and original criteria.

2. Related to the above issues, this trial is really an external pilot and I feel it should be labelled explicitly as such. At various points in the paper a pilot trial is hinted at with terms like "explore" and "preliminary", and in the trial protocol the term "exploratory clinical" is used as a descriptor. Also, the authors state that the results will inform the sample size planning and the design for a subsequent definitive trial. So, it is a pilot, it should be labelled as a pilot explicitly in the Title, Abstract, and Methods, and success criteria for a pilot/ feasibility study should be presented. That is, on what basis would this trial be considered a success and therefore imply that a definitive trial was warranted? If it is a pilot, the formal sample size estimation is not required and I suggest this be removed from the paper, as it looks somewhat contrived in light of the MCID issue and the liberal non-inferiority margin. Indeed, a non-inferiority margin of 40.5 m against a more robust MCID of 25-30 m is inappropriate. I suggest the authors report the study as a pilot and follow the CONSORT extension for pilot studies: Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. BMJ (Online) 2016; 355.

• We recognise that the study is an early phase assessment of a novel method of delivering and established intervention, however the study was not designed nor ethically approved as a pilot. A pilot study is not a hypothesis testing study and safety, efficacy and effectiveness are not evaluated in a pilot and hence this term is not appropriate as a descriptor for a study which did formally address these issues. The study is relatively small but compares favourably with a large number of intervention studies for conventional PR. The sample size and power calculation were performed
exactly because we were seeking to establish non-inferiority and the value selected was driven by national standards of care.

We accept the complexity this raises but do not feel it would be reasonable to delete the formal sample size estimation as this was an integral part of the original sample design. The terms explore and preliminary refer to the fact that this is an early phase study seeking to explore efficacy and safety. As with any clinical development programme larger later phase studies are indicated (a phase 3 study after a phase 2 study). The aims of larger studies would be to explore efficacy and safety data across centres and varying healthcare systems. To determine predictors of response and adherence and to capture data on long term outcomes and rare events eg hospitalisations not possible in this study. We have carefully addressed these points in the limitations section and discussion.

3. Page 2, Strengths and Limitations of the Study, third bullet point. The authors state that larger studies are required to explore the health-economic benefits of this model. Given the above, is a larger study not required for effectiveness, too, not just for the health economics?

• We address this point in the revised manuscript discussion and response to point 3 above. We expand on the utility of a larger scale study highlighting where it would add additional information and why.

4. Page 3, What this study adds: “No differences were seen in the effects of key outcomes…” This statement is not robust given the acknowledged limitations of a study that is not powered to detect small differences. Assuming an MCID of 26 m from the Puhan et al, study, the current study had only around 44% power to detect a difference of 26 m between the two arms, so one cannot take the liberty of declaring “no differences” here. As the authors know, non-inferiority and “no differences” are not the same thing. I derived the power above using the data in the results using two methods that resulted in the same answer. First, by deriving the standard error for the effect from the 95% CI of -4.5 to 52.2 m, and then using the R code in the following article: Gelman A, Carlin J. Beyond Power Calculations: Assessing Type S (Sign) and Type M (Magnitude) Errors. Perspectives on Psychological Science 2014; 9: 641-51. Second, directly from the P value of 0.098 and the degrees of freedom using the inverse t distribution. The current study had <50% power to detect a difference of 26 m. I suggest amending the wording in this sentence.

• We accept this point that non-inferiority rather than ‘no difference’ was demonstrated and have removed the text on P3.
Online versus face-to-face pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: randomised controlled trial

Simon Bourne, Ruth DeVos, Malcolm North, Anoop Chauhan, Ben Green, Thomas Brown, Victoria Cornelius and Tom Wilkinson

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