The setting of pulmonary rehabilitation for Chronic Obstructive Pulmonary Disease (COPD), a systematic review

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National Clinical Effectiveness Committee (NCEC)

Clinical effectiveness is a key component of patient safety and quality. The integration of best evidence in service provision, through clinical effectiveness processes, promotes healthcare that is up to date, effective and consistent.

The National Clinical Effectiveness Committee (NCEC) is a Ministerial committee established in 2010 as part of the Patient Safety First Initiative. The NCEC is supported by the Clinical Effectiveness Unit (CEU), Department of Health. The NCEC is a partnership between key stakeholders in patient safety and its mission is to provide a framework for national endorsement of clinical guidelines and audit to optimise patient and service user care.

Invitations to tender were issued in July 2015 and a public procurement competition held for the provision of systematic literature reviews and budget impact analysis to support the development of National Clinical Guidelines. Subsequently, a series of reports were commissioned by the CEU/NCEC Department of Health. This report is the second published under this contract. It supports the development of a National Clinical Guideline on the *Management of Chronic Obstructive Pulmonary Disease (COPD)*. The guideline proposal was submitted to the NCEC by the HSE National Clinical Programme for COPD and was prioritised for development as a National Clinical Guideline.

COPD is a common progressive lung disease and is the commonest disease-specific cause of emergency admissions of adults to hospital in Ireland. COPD has a significant impact on the individual, and on primary and secondary care service providers. In 2013, (the latest year for which OECD data are currently available), the hospitalisation rate for Ireland was the highest rate among selected OECD countries.

Further information on the NCEC and National Clinical Guidelines is available at www.health.gov.ie/patient-safety/ncec

Abstract

Background

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease, characterized by persistent airflow limitation leading to symptoms of persistent breathlessness, chronic productive cough, fatigue and an increased susceptibility to respiratory infections. The global prevalence of COPD is estimated at 11.7% (8.4%–15.0%) and COPD will, according to the World Health Organisation, become the fifth largest disease burden and the third greatest cause of death by 2020. Pulmonary rehabilitation (PR) improves symptoms, health-related quality of life (HRQoL) and exercise capacity, but the optimal setting for PR is unknown.

Aim

To compare the effects of PR in different settings on HRQoL and functional and maximal exercise capacity in people with COPD.

Search methods

We identified trials on 5th July 2016 from the Cochrane Airways Group Specialised Register (CAGR), clinical trial registries ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We also searched PubMed from 01/01/2016-05/07/2016 to capture publications 'in press' and 'ahead of print', not yet indexed in Medline (Ovid). The Epistemonikos database was searched for systematic reviews to ensure no previous reviews addressing an identical question had been done.

Selection criteria

We included randomised controlled trials (RCTs) that included a direct comparison of the effectiveness of at least two different settings in which PR was delivered to patients with stable COPD and who did not have an acute exacerbation in the four weeks prior to the start of the programme. We defined PR as exercise therapy with or without any form of education and/or psychological support for at least four weeks' duration. Outcomes of interest included Health-related Quality of Life (HRQoL), exercise capacity and cost-effectiveness.

Data collection, analysis and quality assessment

We selected studies and extracted data with two independent reviewers. We calculated mean differences (MD) with 95% confidence intervals (CI). We assessed the quality of evidence using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.

Main results

We extracted data for nine trials involving 884 participants, six comparing outpatient and home-based PR, and three comparing outpatient and community-based PR. A total of 461 patients were randomly allocated to outpatient hospital PR, 294 to home-based PR, and 129 to community-based PR. Groups were comparable at baseline and the length of programmes varied from six weeks to three months.

Blinding of participants and personnel was not possible due to the nature of PR programmes. Two studies had high attrition bias, four had unclear random sequence generation and five did not specify if allocation was concealed.

For the comparison of hospital (outpatient) PR and home-based PR, there was no difference in HRQoL on the four domains of the Chronic Respiratory Questionnaire (CRQ) (Dyspnoea: MD -0.09, 95% CI -0.28 to 0.10, four trials, 473 participants, moderate quality evidence; Fatigue: MD -0.00, 95% CI -0.18 to 0.17, four trials, 473 participants, moderate quality evidence; Emotional: MD 0.10, 95% CI -0.24 to 0.45, four trials, 473 participants , moderate quality evidence; and Mastery: MD -0.02, 95% CI -0.28 to 0.25, four trials, 473 participants, moderate quality evidence). Similarly, there was no difference between the two settings in overall health, daily life, and perceived well-being as measured by the St George's Respiratory Questionnaire (SGRQ) (MD 1.4, 95% CI -1.5 to 4.3, one trial, 233 participants, moderate quality evidence). There was no difference in exercise capacity between outpatient and home PR as measured using the 6-minute walking distance (6MWD) (MD -0.39, 95% CI -16.61 to 15.83, four trials, 488 participants, low quality evidence) and measured using incremental cycle ergometry (MD, -9.0, 95% CI -109.8 to 91.8, 1 trial, 233 participants, low quality evidence).

Hospital (outpatient) and community-based PR programes were equally effective at improving HRQoL (CRQ Dyspnoea: MD 0.29, 95% CI -0.05 to 0.62, two trials, 195 participants, moderate quality evidence; Fatigue: MD -0.02, 95% CI -1.09 to 1.05, two

trials, 200 participants, low quality evidence; Emotional: MD 0.10, 95% CI -0.40 to 0.59, two trials, 198 participants, moderate quality evidence; and Mastery: MD -0.08, 95% CI -0.45 to 0.28, two trials, 198 participants, moderate quality evidence). Similarly, there was no difference in improvement in incremental cycle ergometry (MD 4.0, 95% CI -11.0 to 19.0, one trial, 30 participants, low quality evidence), endurance shuttle walking distance (MD 67.3m, 95% CI -40.8 to 175.4, 1 trial, 161 participants, low quality evidence) and time walked (MD 1.1minutes, 95% CI -0.7 to 2.9, 1 trial, 160 participants, low quality evidence) between hospital (outpatient) and community-based PR programes.

Conclusion

The setting in which PR is provided does not appear to impact its effectiveness. In meeting current international clinical guidelines that recommend the use of PR in the management of COPD, health services could tailor the setting of any PR programme to best suit the local context, health services resources and patients' needs. No clear conclusion could be drawn regarding the cost-effectiveness of different PR settings due to a lack of studies.

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List of abbreviations

6MWD	6 Minutes Walking Distance test
CAGR	Cochrane Airways Group Specialised Register
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory Disease Questionnaire
ESWT	Endurance Shuttle Walk Test
FEV_1	Forced Expiratory Volume after one second
FVC	Forced Vital Capacity
HRQoL	Health-Related Quality of Life
ISWT	Incremental Shuttle Walk Test
MD	Mean Difference
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
ROB	Risk of Bias
SGQR	St George's Respiratory Questionnaire

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Outpatient hospital-based PR compared to Home-based PR for stable COPD

Patient or population: COPD

Setting: Outpatient hospital-based or home-based

Intervention: Outpatient hospital-based PR

Comparison: Home-based PR

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Home-based PR	**Risk with Outpatient hospital-based PR**				
Change in HRQoL - CRQ (dyspnoea)	The mean change in HRQoL - CRQ (dyspnoea) was **0**	The mean change in HRQoL - CRQ (dyspnoea) in the intervention group was -0.09 lower (-0.28 lower to 0.1 higher)	-	473 (4 RCTs)	⨁⨁⨁◯ MODERATE [1]	
Change in HRQoL - CRQ (fatigue)	The mean change in HRQoL - CRQ (fatigue) was **0**	The mean change in HRQoL - CRQ (fatigue) in the intervention group was -0 (-0.18 lower to 0.17 higher)	-	473 (4 RCTs)	⨁⨁⨁◯ MODERATE [1]	
Change in HRQoL - CRQ (emotional)	The mean change in HRQoL - CRQ (emotional) was **0**	The mean change in HRQoL - CRQ (emotional) in the intervention group was 0.1 higher (-0.24 lower to 0.45 higher)	-	473 (4 RCTs)	⨁⨁⨁◯ MODERATE [1]	
Change in HRQoL - CRQ (mastery)	The mean change in HRQoL - CRQ (mastery) was **0**	The mean change in HRQoL - CRQ (mastery) in the intervention group was -0.02 lower (-0.28 lower to 0.25 higher)	-	473 (4 RCTs)	⨁⨁⨁◯ MODERATE [1]	

Outpatient hospital-based PR compared to Home-based PR for stable COPD

Patient or population: COPD

Setting: Outpatient hospital-based or home-based

Intervention: Outpatient hospital-based PR

Comparison: Home-based PR

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Home-based PR	**Risk with Outpatient hospital-based PR**				
Change in SGRQ total (units)	The mean change in SGRQ total (units) was **0**	The mean change in SGRQ total (units) in the intervention group was 1.4 higher (-1.5 lower to 4.3 higher)	-	233 (1 RCT)	⨁⨁◯◯ LOW [1,2]	
Change in Incremental Cycle Ergometry Distance (m)	The mean change in Incremental Cycle Ergometry Distance (m) was **0**	The mean change in Incremental Cycle Ergometry Distance (m) in the intervention group was -9 lower (-109.8 lower to 91.8 higher)	-	233 (1 RCT)	⨁⨁◯◯ LOW [1,2]	
Chang 6MWD (m)	The mean chang 6MWD (m) was **0**	The mean change 6MWD (m) in the intervention group was -0.39 lower (-16.61 lower to 15.83 higher)	-	488 (4 RCTs)	⨁⨁◯◯ LOW [1,2]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Blinding not performed in 4 out of 4 RCTs included in analysis. This is an inherent problem due to the nature of the intervention in PR
2. Wide CI that includes appreciable benefit and harm

2. Summary of Findings for comparison outpatient versus community-based PR pulmonary rehabilitation

Outpatient hospital-based PR compared to Community-based PR for stable COPD

Patient or population: COPD

Setting: Outpatient hospital-based or community-based

Intervention: Outpatient hospital-based PR

Comparison: Community-based PR

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Community-based PR	**Risk with Outpatient hospital-based PR**				
HRQoL - CRQ (dyspnoea)	The mean hRQoL - CRQ (dyspnoea) was **0**	The mean hRQoL - CRQ (dyspnoea) in the intervention group was 0.29 higher (-0.05 lower to 0.62 higher)	-	195 (2 RCTs)	⨁⨁⨁◯ MODERATE [1]	
HRQoL - CRQ (fatigue)	The mean hRQoL - CRQ (fatigue) was **0**	The mean hRQoL - CRQ (fatigue) in the intervention group was -0.02 lower (-1.09 lower to 1.05 higher)	-	200 (2 RCTs)	⨁⨁◯◯ LOW [1,2]	
HRQoL - CRQ (emotional)	The mean hRQoL - CRQ (emotional) was **0**	The mean hRQoL - CRQ (emotional) in the intervention group was 0.1 higher (-0.4 lower to 0.59 higher)	-	198 (2 RCTs)	⨁⨁⨁◯ MODERATE [1]	
HRQoL - CRQ (mastery)	The mean hRQoL - CRQ (mastery) was **0**	The mean hRQoL - CRQ (mastery) in the intervention group was -0.08 lower (-0.45 lower to 0.28 higher)	-	198 (2 RCTs)	⨁⨁⨁◯ MODERATE [1]	

Outpatient hospital-based PR compared to Community-based PR for stable COPD

Patient or population: COPD

Setting: Outpatient hospital-based or community-based

Intervention: Outpatient hospital-based PR

Comparison: Community-based PR

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Community-based PR	**Risk with Outpatient hospital-based PR**				
Change in 6MWD (m)	The mean change in 6MWD (m) was **0**	The mean change in 6MWD (m) in the intervention group was 66.9 higher (-0.4 lower to 134.2 higher)	-	31 (1 RCT)	⨁⨁◯◯ LOW [1,3]	
Change in ESWD (m)	The mean change in ESWD (m) was **0**	The mean change in ESWD (m) in the intervention group was 67.8 higher (-40.8 lower to 175.4 higher)	-	161 (1 RCT)	⨁⨁◯◯ LOW [1,2]	
Incremental cycle ergometry	The mean incremental cycle ergometry was **0**	The mean incremental cycle ergometry in the intervention group was 4 higher (-11 lower to 19 higher)	-	30 (1 RCT)	⨁⨁◯◯ LOW [1,3]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Blinding not performed in 2 out of 2 RCTs included in analysis. This is an inherent problem due to the nature of the intervention in PR
2. Wide CI that includes appreciable benefit and harm
3. Small number of participants and wide confidence interval

3. Background

Chronic Obstructive Pulmonary Disease (COPD) is "a common, preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases".[1] Airway obstruction is caused by small airways disease (chronic bronchitis) and/or lung destruction (emphysema). In chronic bronchitis, mucociliary dysfunction resulting from airway inflammation with the consequences of ciliary damage and mucus hypersecretion leads to symptoms of persistent breathlessness, chronic productive cough, fatigue, and an increased susceptibility to respiratory infections. In emphysema, destruction of the lung parenchyma, also by chronic inflammation, leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil.[1] Systemic effects of COPD may include skeletal muscle dysfunction, weight loss, osteoporotic changes, depression, cardiovascular and neurological changes; these are thought to result from extrapulmonary inflammation, tissue hypoxia, oxidative stress and reduced physical activity.[2] A diagnosis of COPD is reached based on a person's symptoms and a post-bronchodilator ratio of the Forced Expiratory Volume in one second to the Forced Vital Capacity (FEV_1/FVC) of less than 0.70.[1]

The global prevalence of COPD was estimated at 11.7% (8.4%–15.0%) in 2010, with a higher prevalence amongst men and urban dwellers, an overall increasing trend, and expected underreporting.[3] According to the World Health Organisation, COPD will become the fifth largest disease burden and the third greatest cause of death by 2020, making is a major public health problem and cost.[4, 5] The prevalence of COPD varies across countries depending on levels of tobacco smoking, but indoor and outdoor air pollution, occupational dust and chemicals are also contributory factors.[6]

Pulmonary Rehabilitation (PR) has been defined as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours".[7, (page e14)] The aim of PR in the management of COPD is to increase quality of life, reduce symptoms, and improve physical and emotional

participation.[8] A recent Cochrane review examining the effectiveness of PR for COPD compared to usual care concluded that PR leads to moderately large and clinically significant improvements in dyspnoea, fatigue, emotional function, health-related quality of life (HRQoL) and exercise capacity.[9] National and international guidelines recommend incorporating PR in the management of COPD.[1, 10]

Pulmonary rehabilitation can be provided in different settings, including hospital-based, community-based and home-based sessions.[11-13] McCarthy et al (2015) [9] conducted a subgroup analysis in their systematic review for hospital-based and community-based programmes which suggested a difference in treatment effect between these settings. However, in line with the scope of their review, only studies that compared PR to usual care were included and studies comparing PR in different settings only were excluded. To our knowledge, no systematic review of studies that directly compare the effectiveness of PR in different settings has been done. To maximise the effectiveness of PR and target resources accordingly, it is essential to identify the optimal setting for delivering PR, providing a strong rationale for this systematic review.

4. Aim and Objectives

To compare the effects of PR in different settings on HRQoL and functional and maximal exercise capacity in persons with COPD.

5. Methods

5.1. Selection criteria

5.1.1. Population, Intervention, Comparison, Outcome (PICO)

P	We included Randomised Controlled Trials (RCTs) in whom 90% or more of participants had COPD defined as: • a clinical diagnosis of COPD; and • best recorded forced expiratory volume after one second (FEV_1)/forced vital capacity (FVC) (FEV_1/FVC) ratio of individual participants < 0.7. We included RCTs in which: • any or all participants were on continuous oxygen. We excluded RCTs that focussed on participants: • who were mechanically ventilated; or • who had an acute exacerbation within four weeks before commencement of the intervention.
I	<u>Pulmonary rehabilitation</u> Any in-patient, out-patient, community-based or home-based rehabilitation programme of at least four weeks' duration that included

	exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitation attributable to COPD. We included any exercise therapy that included physical activity considered to be aerobically demanding. We excluded: • interventions in which the physical activity component was considered not to be aerobically demanding (e.g. respiratory muscle training, breathing exercises, Tai Chi, yoga) (the degree of aerobic demand was assessed for each individual intervention by examining the detailed description of the intervention in identified studies); and • programmes of less than 4 weeks' duration.
C	For a study to be eligible for inclusion in this review, PR had to be compared in at least two different settings (in-patient, out-patient, community-based and/or home-based), i.e. pairwise comparison of PR in different settings.
O	We considered disease-specific HRQoL and/or maximal or functional exercise capacity (up to and including three months after the end of the intervention). We defined 'maximal exercise capacity' as the peak capacity measured by an incremental cycle ergometry test. 'Functional exercise capacity' was defined according to the results of timed walk tests.[14] <u>Primary outcomes</u> *Disease-specific health-related quality of life (HRQoL)* • Chronic Respiratory Disease Questionnaire (CRQ): A disease-specific instrument that measures the extent to which patients feel they can cope with the disease and its manifestations in four domains (dyspnoea, fatigue, emotional function and mastery). All four domains perform well in detecting small treatment effects[15] and a difference in score of 0.5 corresponds to the smallest difference in score that patients view as important and that would require a change in their management.[16] • St. George's Respiratory Questionnaire (SGRQ): A disease-specific questionnaire that has been validated in patients with all grades of respiratory diseases including advanced COPD.[17] The questionnaire consists of 76 items divided into three domains (symptoms, activity, and impact). Scores range from zero (perfect health) to 100 (worst possible) for each component. A change in score of 4 units is clinically significant.[18] • COPD Assessment Test (CAT): An 8-item disease-specific instrument that measures that measures the health status of patients with COPD.[19] A minimally clinically important difference is thought to be 2 or more.[20]

	Secondary outcomes
	Exercise testing
	The classification of exercise testing was divided into functional and maximal exercise groups, which included the following.[14]
	• Functional exercise capacity assessments.
	  ▪ Six-minute walk test/distance (6MWT/6MWD).
	  ▪ Incremental shuttle walk test/distance (ISWT/ISWT).
	  ▪ Endurance shuttle walk test/distance (ESWT/ESWD).
	• Maximal exercise tests.
	  ▪ Incremental cycle ergometry.
	
	Cost-effectiveness measures
	• Use of healthcare resources associated with PR in different settings including direct resource costs (e.g. staff time), indirect costs (associated with loss of productivity) and other non-medical costs (e.g. patient out of pocket expenses)
	• Cost savings, cost effectiveness measures such as Incremental Cost-Effectiveness Ratios (ICERs), Quality Adjusted Life Years (QALYs).

5.1.2. Types of studies

All RCTs in which participants are assigned randomly at the individual or cluster level and in which effects of PR in different settings is compared.

5.2. Search methods

The Information Specialist of the Cochrane Airways Group (ES) conducted the search for this review on 5th July 2016. We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is populated through comprehensive systematic searching of multiple sources, outlined in detail in Appendix 1. In addition, we conducted a search of the clinical trial registries ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). The Epistemonikos database was searched for systematic reviews to ensure no previous reviews addressing an identical question had been done. We also searched PubMed from 01/01/2016-05/07/2016 to capture publications 'in press' and 'ahead of print' that might not yet have been indexed in Medline (Ovid), the Medline (Ovid) searches being performed as part of the CAGR. Although we only included studies published in English, we did not apply any language restrictions to be able to detect any language bias.

5.3. Screening for inclusion

Study selection was conducted using the review software Covidence.[21] Four review authors (MC, FW, BM, MM) independently screened all citations based on the title and abstract so that each citation was independently reviewed by at least two authors. If there was a lack of clarity about the inclusion/exclusion of a citation or a lack of consensus, the citation was moved to full-text selection. Subsequently, the same reviewers (MC, FW, BM, MM) assessed study eligibility based on full-texts. Any disagreement was resolved through discussion and, where necessary, by involving another review author (DD).

5.4. Risk of bias assessment

Risk of bias (ROB) of all included studies was assessed using the Cochrane Risk of Bias tool for intervention studies.[22] Each included study was assessed by two reviewers independently (MC, FW, BM), using the guidance criteria provided in the Cochrane Handbook for Systematic Reviews of Intervention, for seven domains of potential risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias).[22] In case of any disagreements, consensus was reached through discussion or by getting a third opinion (DD).

5.5. Data extraction

Three review authors (MC, FW, BM) extracted data from the included studies independently. A data extraction form was created for this purpose and an overview of the data extraction for each study is presented in Table 1. Consensus on extracted data was reached by involving another author (DD). Where a study included multiple treatment arms, we excluded comparisons not related to PR settings.

Table 1. Overview of data extracted from included studies

1. Study authors, year, country/region
2. Characteristics and number of participants in each study arm
3. Characteristics of the PR programme (including setting, duration, elements)
4. Outcomes (Quality of life, exercise capacity) and corresponding results

5.6. Data analysis and synthesis

A priori specified primary (disease-specific health-related quality of life) and secondary outcomes (exercise capacity) measures are continuous variables. Therefore, for each outcome measure, the mean change (and standard deviation) from baseline to post-intervention follow up was abstracted from included studies. Where studies reported only the mean score at baseline and follow up, then the mean change was calculated by subtracting the two. In such case, we used the standard deviation of the follow up data as the standard deviation for the mean change. We conducted meta-analyses in Revman.[23]

Cluster-randomised trials

We did not identify any cluster randomised trials.

Multi-armed trials

For multi-armed trials, we only included the arms that received PR in any setting. Control groups were excluded. We planned to spit the 'shared group' to deal with multiple comparisons, but no trials were identified with more than two relevant groups for inclusion, hence no comparison had any intervention group in common.

Missing data

We examined the level of attrition and less than 80% of participants retained at follow up outcome assessment was considered high risk of attrition bias. If the mean change from baseline was not reported, and baseline and follow up data were provided, we calculated the mean change, but the missing Standard Deviation (SD) was substituted by the SD of the measurement at follow up.

Publication bias

We planned to assess publication bias using a funnel plot if 10 or more studies were included in the meta-analysis, but the number of studies included was less than 10 for all analyses.

Heterogeneity assessment

Statistical heterogeneity was considered substantial if Tau^2 was greater than zero and either I^2 was greater than 30%, or the p-value for the Chi^2 test for heterogeneity was less than 0.10.[22]

Subgroup analysis

We planned subgroup analysis for PR including both exercise and education components versus PR with exercise training alone, but insufficient studies were included.

5.7. Quality of evidence assessment (GRADE)

The quality of evidence for the outcomes HRQoL and exercise capacity was assessed by two reviewers (BM, MM) independently using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[24] The results are presented in two summary of findings tables (Section 1 and 2) and the complete GRADE profiles for all outcomes are provided in Appendix 5.

5.8. Reporting of the review

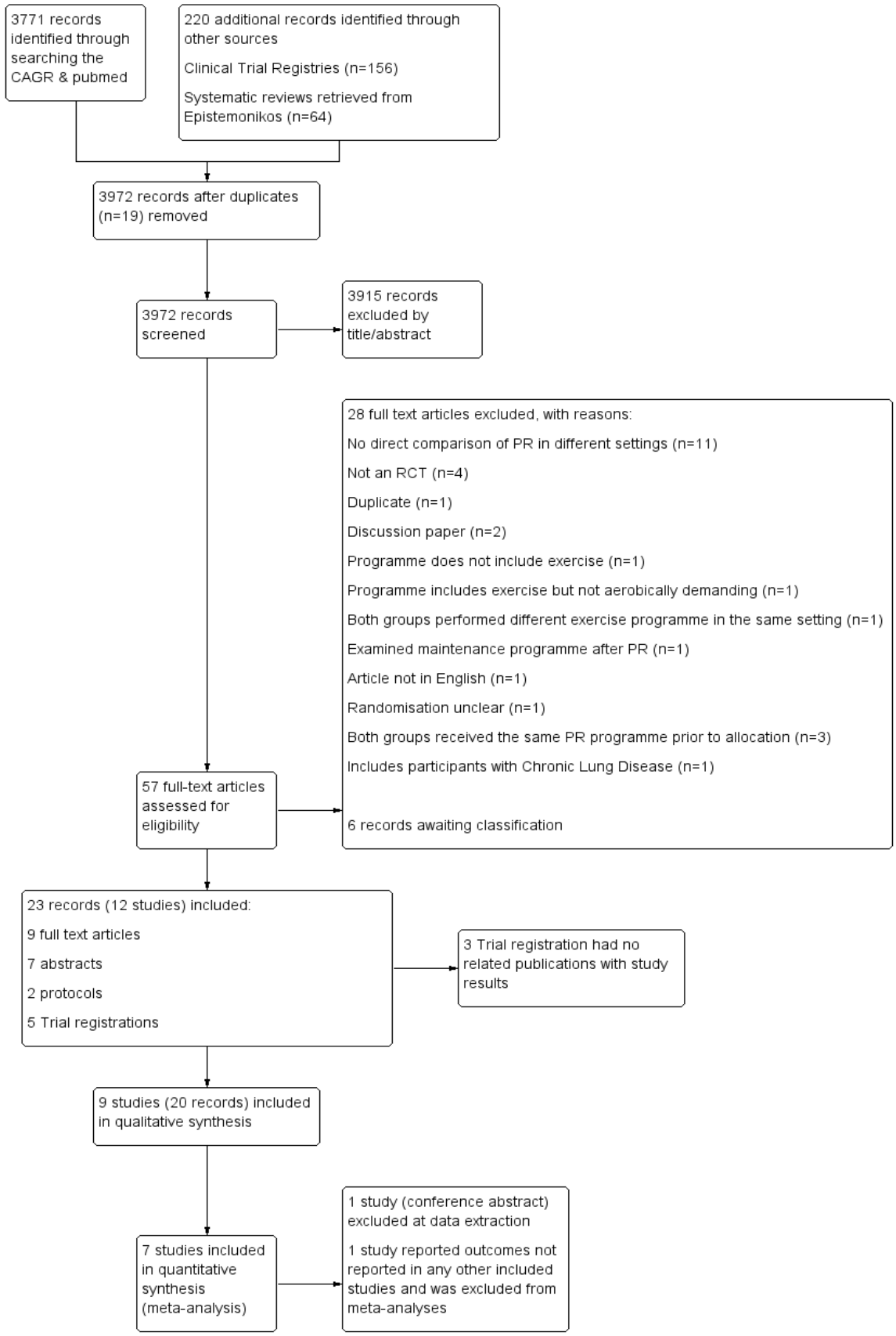
The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidance was followed for reporting this review.[25] The results of the search and study selection process were presented in a PRISMA flow diagram, constructed in Revman software.[23]

6. Results

6.1. Search results

We identified a total of 3991 records through our comprehensive search (3790 from the CAGR and PubMed, and 220 from other resources). After duplicate removal, 3972 records were screened by title and abstract, of which 57 were assessed by full text. The most common reasons for exclusion at full text selection were the absence of a direct comparison between two different settings for PR (n=11) or a study design other than a RCT (n=4). One article was excluded because it was in Spanish[26], and six abstracts did not include sufficient information to assess their eligibility for inclusion and the authors have not yet responded to the request for more information, hence we classified these studies as 'awaiting classification'. A total of 23 records were included relating to 12 studies, of which three were trial registrations, leaving a total of nine included studies to extract. A detailed overview of the study selection process is presented in Figure 1.

Figure 1. Search results and study selection flow chart



6.2. Characteristics of included studies

Twelve studies were included. Five were trial registrations of which three did not have any published findings yet,[27-29] hence, we extracted data for nine trials involving 884 participants. A total of 461 were randomly allocated to outpatient hospital PR, 294 to home-based PR, and 129 to community-based PR. Full characteristics of each included study are provided in appendix 2.

All nine trials included a group that completed a PR programme in an outpatient hospital setting, of which three compared this to a community setting and six to a home-based PR programme. Studies that examined the same comparison are colour coded the same in Tables 2 and 3. The duration of the PR programmes ranged from six weeks to three months (

). The frequency of sessions varied from daily exercises to twice per week.

Three studies included patients with severe or very severe COPD, but definitions varied from FEV_1 30-50% of predicted value according to the GOLD guidelines,[30, 31] FEV_1 of less than 50% of predicted value post bronchodilation,[32-34] to FEV_1 of less than 65% of predicted value post bronchodilation.[35-37] One study included participants with moderate to severe COPD, defined as FEV_1 of 34-70% of predicted value.[38, 39] Two studies just stated they included patients with COPD as per GOLD guidelines,[40-42] while Holland (2016) [43] included patients with a FEV_1/FVC ratio of less than 70%, and Maltais (2008) [44] included patients with FEV_1 of less than 70% of predicted value. Nygren-Bonnier (2002) [45] did not specify the inclusion criteria in their abstract, but participants had, on average, a FEV_1 of less than 41.5% of predicted value. The baseline characteristics of the participants of the included studies are presented in Table 2.

Table 2. Baseline characteristics of participants

Study	Setting[††] (A)	Sample size	Male	Female	Mean age (SD)	FEV_1 (SD)	Setting[††] (B)	Sample size	Male	Female	Mean age (SD)	FEV_1 (SD)
Elliot 2004;[38] Lake 1999[39]	O	30	14	16	66.4 (2.1); 68.7 (2.1)*	46.0 (3.9); 46.3 (4.4)*	C	13	9	4	62.5 (2.1)	42.7 (5.9)
Guell 2008;[30] Guell 2006[31]	O	29	NR	NR	63.2 (6.6)	37.5 (7.1)	H	23	NR	NR	66 (5.8)	39 (7.6)
Holland 2013;[46] Holland 2016a;[43] Holland 2016b;[47] La Trobe 2011[48]	O	86	51	35	69 (10)	49 (19)	H	80	48	32	69 (13)	52 (19)
Laval 2005;[49] Maltais 2005;[50] Maltais 2008[44]	O	126	72	54	66 (9)	43 (13)	H	126	68	58	66 (9)	46 (13)
Mendes de Oliviere 2010;[40] Oliviere 2011[41]	O	23	19	4	71.3 (6.7)	51.5 (23.9)	H	33	27	6	66.4 (9.5)	47.5 (23.3)
Nygren Bonnier 2002[45]	O	12	NR	NR	NR	41.5**	H	12	NR	NR	NR	41.5**
Puente Maestu 1996;[32] Puente Maestu 2000a;[33] Puente Maestu 2000b[34]	O	21	21	0	63.3 (4.3)	41 (6)	H	20	20	0	65.6 (4.7)	40 (6)
Strijbos 1996a;[35] Strijbos 1996b;[36] Strijbos 1999[37]	O	45[†] (total)	38	7	61.4 (6.2)	41.1 (13.8)	C	(only data for the total sample available)				
Waterhouse 2010[42]	O	129	63	66	69.1 (7.5)	48.3 (19.3)	C	111	62	49	68.7 (8.3)	45.1 (16.3)

*Data from the groups that received outpatient PR followed by home PR and data for group that received outpatient PR followed by community PR are reported separately. Only the first phase (outpatient PR) for both groups was included in this review, since they received another intervention (different setting of PR) in the second phase of the study.

**Only the average for the whole group before randomisation reported.

[†]Baseline data of 5 participants that dropped out during the programme not provided. A total of 50 participants enrolled initially.

[††]Outpatient (O); Community (C); Home (H)

Table 3. Study design characteristics of included studies

Study	Setting A	Setting B	Duration	Follow up; from start of programme	Programme type	Outcomes: HRQoL: CQR	HRQoL: SGRQ	Exercise capacity: 6MWD	Exercise capacity: Incremental cycle ergometry	Exercise capacity: ESWT (Time)	Exercise capacity: ESWD	Cost-effectiveness measures
Elliot 2004;[38] Lake 1999[39]	Outpatient	Community	3 months	3 months	Exercise + education	V		V				
Guell 2008;[30] Guell 2006[31]	Outpatient *	Home*	9 weeks	9 weeks	Exercise + education	V		V				
Holland 2013;[46] Holland 2016a;[43] Holland 2016b;[47] La Trobe 2011[48]	Outpatient	Home	8 weeks	9 weeks	Exercise	V		V				(V)
Laval 2005;[49] Maltais 2005;[50] Maltais 2008[44]	Outpatient	Home	8 weeks**	3 months	Exercise + education	V	V	V	V			
Mendes de Oliviere 2010;[40, 41] Oliviere 2011	Outpatient	Home	12 weeks	12 weeks	Exercise + education			V				
Nygren Bonnier 2002[45]	Outpatient	Home	12 weeks	12 weeks	Exercise							
Puente Maestu 1996;[32] Puente Maestu 2000a;[33] Puente Maestu 2000b[34]	Outpatient	Home	8 weeks	8 weeks	Exercise	V						
Strijbos 1996a;[35] Strijbos 1996b;[36] Strijbos 1999[37]	Outpatient	Community	12 weeks	12 weeks	Exercise + education			4 min test	V			
Waterhouse 2010[42]	Outpatient	Community	6 weeks	6 weeks	Exercise + education	V				V	V	V

*Both groups received same outpatient programme in week 1; **In addition to 4 weeks of education prior to the PR programme in both arms.

6.3. Characteristics of excluded studies

We excluded 28 records at full text selection. The most common reason for exclusion was the absence of a direct comparison of PR in different settings (n=11). Full details of the excluded studies are provided in Appendix 3.

6.4. Risk of bias in included studies

Figure **2** provides an overview of the ROB of the included studies. Full details and the justification of the judgments regarding the ROB of each included study are provided in Appendix 4.

Figure 2. Risk of bias of included studies

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Elliot 2004;[38] Lake 1999[39]	?	?	+	?	+	-	-
Guell 2008;[30] Guell 2006[31]	?	-	+	-	-	-	-
Holland 2013;[46] Holland 2016a;[43] Holland 2016b;[47] La Trobe 2011[48]	-	-	+	-	-	-	-
Laval 2005;[49] Maltais 2005;[50] Maltais 2008[44]	-	-	+	-	-	-	-
Mendes de Oliveira 2010;[40] Oliveira 2011[41]	-	?	+	?	+	-	-
Nygren Bonnier 2002[45]	?	?	+	?	?	+	?
Puente Maestu 1996;[32] Puente Maestu 2000a;[33] Puente Maestu 2000b[34]	?	?	+	?	-	-	-
Strijbos 1996a;[35] Strijbos 1996b;[36] Strijbos 1999[37]	-	?	+	-	-	-	-
Waterhouse 2010[42]	-	-	+	-	+	-	-

'?' = unclear ROB, '-' = low ROB, '+' = high ROB

6.4.1. Random sequence generation (Selection bias)

We judged five studies as having low risk of bias for random sequence generation; in four studies the random sequence was computer generated and in one study it was generated through a 'lottery procedure'. The other four studies did not state how the random sequence was obtained and were subsequently judged as having unclear risk of bias.

6.4.2. Allocation concealment (Selection bias)

Five studies did not specify if allocation was concealed. Two studies allocated participants using sealed envelopes, in one study participants were invited to the hospital for assessment without knowing their allocation,[42] and one study emailed the allocation to research staff not otherwise involved who then informed patients of their group allocation.[44, 49, 50]

6.4.3. Blinding of participants and personnel (Performance bias)

Pulmonary rehabilitation by nature is an intervention to which participants and personnel cannot be blind. For this reason, all studies had high risk of performance bias, which was unavoidable.

6.4.4. Blinding of outcome assessment (Detection bias)

In five studies, the outcome assessment was conducted by someone who was blind to the group assignment. The other four studies did not report clearly who conducted the assessment.

6.4.5. Incomplete outcome data (attrition bias)

Three studies had high attrition rates (>80%). In Waterhouse et al (2010) [42], there was 52% and 47% in the hospital and community groups respectively. Elliott et al (2004) [38] had retained 73% of participants at follow up in the hospital group and 69% in the community group. Mendes De Oliveira et al (2010) [40]had low attrition in the home PR group (79%) but high attrition in the outpatient group (50%).

6.4.6. Selective reporting (reporting bias)

Only one study was judged as having high risk of reporting bias, since this record was a conference abstract that reported only some outcomes specified in their methods.[45] All other studies reported all pre-specified outcomes and were considered at low risk of reporting bias.

6.4.7. Other bias

We did not identify any other biases in the included studies. Baseline characteristics were similar between groups. However, Nygren-Bonnier et al (2002) [45] did not report sufficient information in the abstract to assess for any other biases.

6.5. Effects of interventions

Meta-analyses were conducted for two comparisons: Outpatient versus home-based PR (6.5.1) and outpatient versus community-based PR (6.5.2). Home-based and community-based PR groups were analysed separately because of a clear distinction in the extent of supervision. Community-based PR was supervised by a physiotherapist while home-based PR was carried out by the patient independently (with the exception of training and monitoring sessions).

Nygren-Bonnier et al (2002) [45] was a conference abstract and contained limited information on the findings of this study. We contacted the author, but did not receive a response by time of completion of this review, hence this study did not contribute any outcome data. Another study[35-37] only reported outcome measurements (4 minutes walking test, incremental cycle ergometry) that were not reported in any of the other included studies of the same comparison, and was therefore not included in any of the meta-analyses.

6.5.1. Hospital-based (outpatient) versus home-based PR

Primary outcome: Health-related Quality of Life (HRQoL)

CRQ

There was no difference between hospital-based (outpatient) and home-based PR in HRQoL as measured by the CRQ domains of Dyspnoea (mean difference (MD) -0.09, 95% CI -0.28 to 0.10, four trials, 473 participants, I^2 0%, Figure 3), Fatigue (MD, -0.00, 95% CI -0.18 to 0.17, four trials, 473 participants, I^2 0%, Figure 4), Emotional (MD, 0.10, 95% CI -0.24 to 0.45, four trials, 473 participants, I^2 63%, Figure 5) and Mastery (MD, -0.02, 95% CI -0.28 to 0.25, four trials, 473 participants, I^2 38%, Figure 6). The evidence was assessed to be of moderate quality due to the high risk of bias resulting from the lack of blinding of participants and personnel in PR (Appendix 5).

Figure 3. Change in CRQ (Dyspnoea)

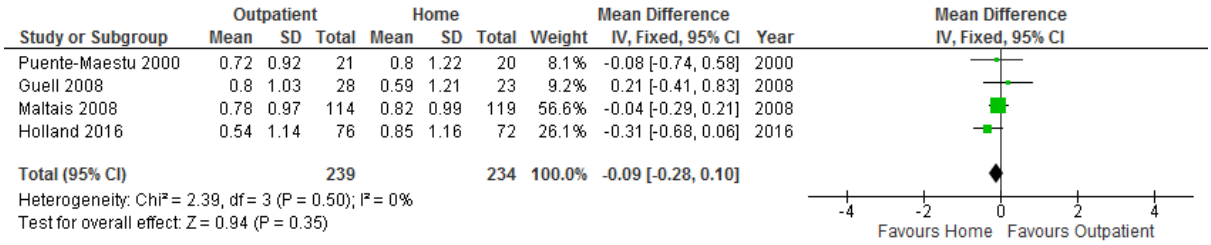


Figure 4. Change in CRQ (Fatigue)

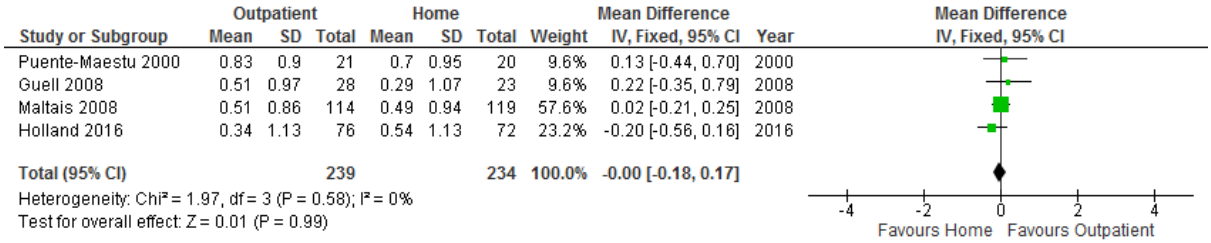


Figure 5. Change in CRQ (Emotional)

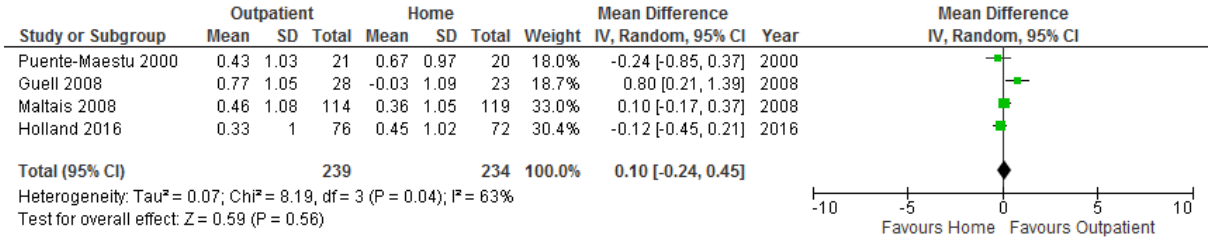
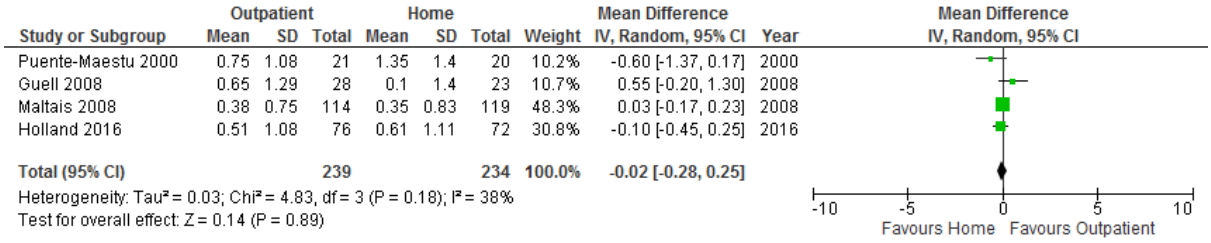


Figure 6. Change in CRQ (Mastery)



<u>*SGRQ*</u>

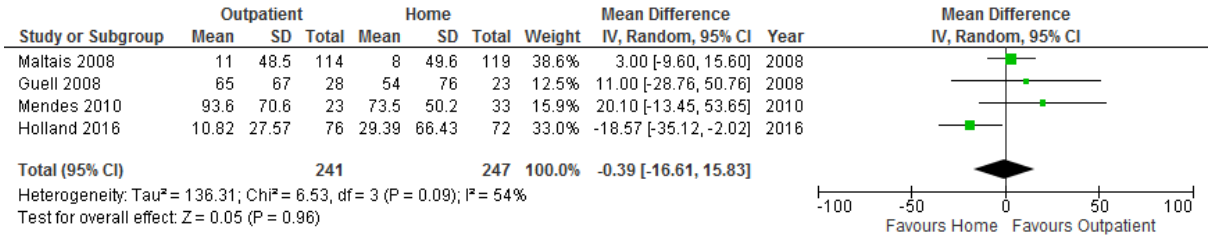
Only one study reported the outcome HRQoL as measured by the SGRQ.[44, 49, 50] There was no difference between hospital-based (outpatient) and home-based PR in HRQoL as measured by the SGRQ total (MD 1.4, 95% CI -1.5 to 4.3, one trial, 233 participants) and by SGRQ domains of Activity (MD 0.2, 95% CI -3.9 to 4.3, one trial, 233 participants) and Impact (MD 0.2, 95% CI -3.1 to 3.5, one trial, 233 participants). There was a greater improvement in SGRQ (symptoms) subscale in the home-based PR group (MD 6.1, 95% CI 1.3 to 10.9, one trial, 233 participants).

Secondary outcome: Exercise capacity

6MWD

Four studies assessed exercised capacity using the 6MWD. There was no significant difference in the 6MWD between outpatient and home-based PR programmes (MD, -0.39, 95% CI -16.61 to 15.83, four trials, 488 participants, I^2 54%, Figure 7). The evidence was judged to be of low quality due to imprecision and risk of bias from a lack of blinding of participants and personnel (Appendix 5).

Figure 7. Change in 6MWD



Incremental cycle ergometry

One study reported this outcome.[44, 49, 50] There was no difference in mean change from baseline to follow up between outpatient and home-based PR (MD, -9.0, 95% CI -109.8 to 91.8, 1 trial, 233 participants). Evidence was rated as low quality due to imprecision with only one study examining this outcome and relatively wide confidence intervals.

Cost-effectiveness outcomes

The search of published and unpublished economic literature, including scientific databases and numerous grey literature resources (Section 5.2), did not identify any such studies for inclusion in this review. As a result, no definitive conclusions can be drawn about the relative cost-effectiveness of PR delivered in these alternative settings. That said, some tentative implications for cost-effectiveness may be drawn from the clinical effectiveness literature detailed above. For example, Holland et al (2016) [47] found no significant difference between the two settings in terms of clinical and physical activity outcomes, but found that patients randomised to home-based therapy were more likely to complete the programme. Furthermore, the risk of hospitalisation (all-cause and respiratory-related) was lower among those that completed the programme compared to those that did not. This would be suggestive of reduced costs and improved cost-effectiveness for home-based

relative to hospital-based PR, holding all else equal. However, this theory is open to question and highlights the need for primary research studies to be conducted to directly evaluate the relative cost-effectiveness of hospital-based (outpatient) versus home-based PR programmes for the COPD patient population.

6.5.2. Hospital-based (outpatient) versus community-based PR

CRQ

There was no difference between outpatient and community-based PR in HRQoL as measured by the CRQ domains of Dyspnoea (MD 0.29, 95% CI -0.05 to 0.62, two trials, 195 participants, I^2 0%, Figure 9), Fatigue (MD, -0.02, 95% CI -1.09 to 1.05, two trials, 200 participants, I^2 68%, Figure 10), Emotional (MD, 0.10, 95% CI -0.40 to 0.59, two trials, 198 participants, I^2 47%, Figure 11) and Mastery (MD, -0.08, 95% CI -0.45 to 0.28, two trials, 198 participants, I^2 0%, Figure 12). The evidence was assessed to be of moderate quality due to serious risk of bias as it is impossible to blind participants and personnel in PR, except for the domain 'fatigue', which was of low quality due to imprecision in addition to serious ROB (Appendix 5).

Figure 8. Change in CRQ (Dyspnoea)

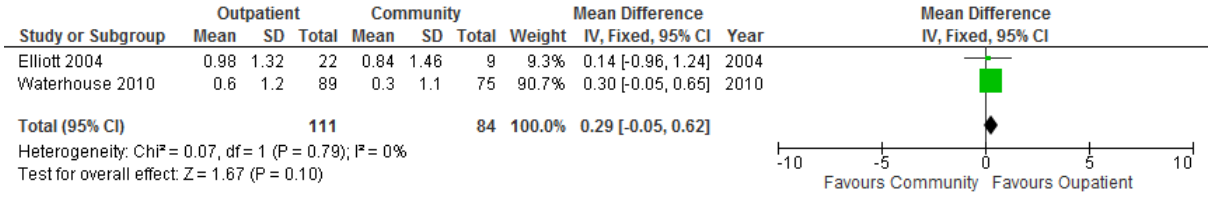


Figure 9. Change in CRQ (Fatigue)

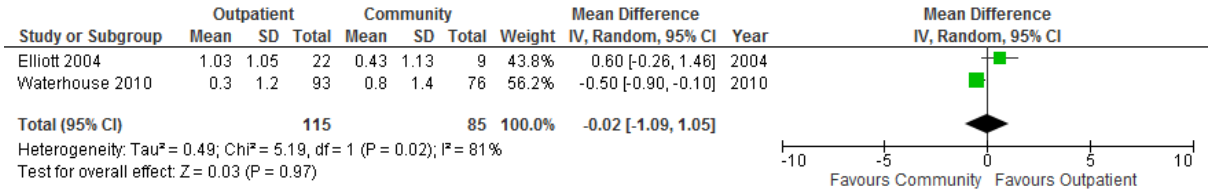


Figure 10. Change in CRQ (Emotional)

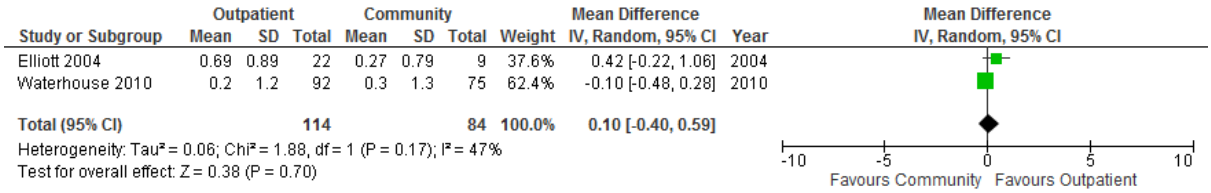
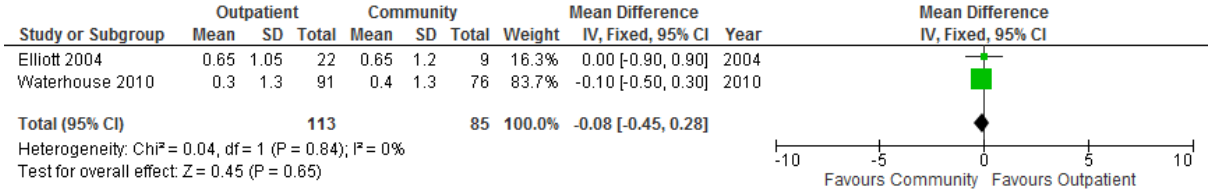


Figure 11. Change in CRQ (Mastery)



6MWD

One study[38, 39] examined the difference in change in 6MWD after community-based PR compared to outpatient PR. There was a larger increase in distance from baseline in the outpatient group, but the sample was small (MD 66.9m, 95% CI -0.4 to 134.2, one trial, 31 participants) and the evidence was of low quality due to imprecision and serious risk of bias related to blinding of participants and personnel (Appendix 5).

Another study[35-37] assessed the change in distance that participants could walk in 4 minutes before and after the programme, but found no difference in improvement between outpatient and community PR (MD 7.0m, 95% CI -37.1 to 51.1, one trial, 30 participants).

Incremental cycle ergometry

There was no difference in change in exercise capacity as measured by incremental cycle ergometry between hospital and community-based PR (MD 4.0, 95% CI -11.0 to 19.0, one trial, 30 participants) [35-37] The evidence to support these findings was of low quality due to imprecision and serious ROB resulting from lack of blinding (Appendix 5).

Endurance shuttle walking test: time (ESWT) and distance (ESWD) walked

Waterhouse et al (2010) [42] found no difference in the distance (MD, 67.3m, 95% CI -40.8 to 175.4, 1 trial, 161 participants) and time walked (MD, 1.1minutes, 95% CI -0.7 to 2.9, 1 trial, 160 participants) during the endurance shuttle walking test. The

evidence to support these findings was of low quality due to imprecision and serious ROB resulting from lack of blinding (Appendix 5).

Cost-effectiveness outcomes

We identified one study that assessed the cost-effectiveness of hospital (outpatient) versus community-based PR.[42] Cost-effectiveness was examined in terms of incremental healthcare costs, incremental quality adjusted life years (QALYs) and incremental cost-effectiveness ratios, and in terms of the uncertainty surrounding these point estimates. While the estimated mean costs and mean QALYs gained were higher for hospital-based PR relative to community-based PR, neither result was significant at the 5% level of statistical significance. That is, the evaluation showed similarity in the cost-effectiveness of community provision and hospital provision and did not favour either setting. Notably, from a solely healthcare resource perspective, the estimated mean cost for hospital-based PR was £4511.21 (SD: 3794.69) compared to £3643.74 (SD: 3314.42) for community-based PR. This suggests that, with a strong assumption of equivalence in health outcomes across the settings, the community setting has the greater potential to generate cost savings for healthcare budgets. This notwithstanding, the inclusion of only one study means that no definitive conclusions can be drawn about the relative cost-effectiveness of PR delivered in these alternative settings.

7. Conclusion

This review included nine trials involving 884 patients with COPD. Six studies compared outpatient hospital-based PR versus home-based PR and three studies compared outpatient hospital-based PR with community-based PR. The review found that, based on low to moderate quality evidence (appendix 5), it likely that the beneficial effects of PR as identified in the McCarthy et al (2015) [9] review can be obtained across settings and different settings probably result in little to no difference in HRQoL and exercise capacity.

Five studies included is this review took place in Europe, one in Canada, one in Brazil, and two in Australia. Spruit (2014) [51] identified that existing differences in content and organisation between jurisdictions are likely not to be reported in clinical trials and might contribute to the effect on outcomes.

7.1. Implications for practice

Whilst previous evidence strongly support the use of PR in the management of COPD to improve HRQoL and exercise capacity,[9] this review found that the setting in which PR is provided does not seem to impact its effectiveness.

Therefore, in meeting current international clinical guidelines that recommend clearly the use of PR in the management of COPD,[8, 52] health services could tailor the setting of any PR programme to best suit the local context, health services resources and patients' needs.

7.2. Implications for research

Only nine studies were identified that included a direct comparison of different settings for PR with some outcomes being only measured in one study. In assessing the quality of evidence (GRADE; Appendix 5), the main reasons for downgrading were imprecision and ROB due to lack of blinding. While blinding of participants and personnel is inherently not possible in PR, there is a need for additional studies comparing the effectiveness of PR in different settings to be able to draw a more definite answer and improve the precision of the effect estimates.

In addition to the setting, the length and frequency of the PR programme, and its relation to the setting to achieve optimal outcomes, warrants further investigation.

The near-absence of economic literature highlights the need for further primary research studies to be conducted to directly evaluate the relative cost-effectiveness of PR programmes for the COPD patient population in different settings.

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Appendix 1: Search strategy Cochrane Airways Group Specialised Register (CAGR)

a. Sources and search methods for the CAGR

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*the Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PubMed	Weekly (basic search)
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards (latest: 2015)
American Thoracic Society (ATS)	2001 onwards (latest: 2015)
Asia Pacific Society of Respirology (APSR)	2004 onwards (latest: 2015)
British Thoracic Society Winter Meeting (BTS)	2000 onwards (latest: 2015)
Chest Meeting	2003 onwards (latest: 2015)
European Respiratory Society (ERS)	1992, 1994, 2000 onwards (latest: 2015)
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards (latest: 2014 - biennial)
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards (latest: 2015)

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

b. Search string used to identify trials from the CAGR

Search terms	Comments
#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All #2 MeSH DESCRIPTOR Bronchitis, Chronic #3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) #4 COPD:MISC1 #5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW #6 #1 OR #2 OR #3 OR #4 OR #5 #7 MeSH DESCRIPTOR Rehabilitation Explode All #8 MeSH DESCRIPTOR Respiratory Therapy Explode All #9 MeSH DESCRIPTOR Physical Therapy Modalities Explode All #10 rehabilitat* or fitness* or exercis* or train* or *physiotherap* or "physical therap** #11 #7 or #8 or #9 or #10 #12 #6 AND #11	*MISC1 is the field in the record where the reference has been coded for condition.*

c. Search string used to identify trials from PubMed

("pulmonary disease, chronic obstructive"[mh] OR "bronchitis, chronic"[mh] OR COPD[tiab] OR COAD[tiab] OR COBD[tiab] OR AECOPD[tiab] OR "obstructive pulmonary"[tiab] OR "obstructive airways"[tiab] OR "obstructive lung"[tiab]) AND ("Rehabilitation"[mh] OR "Respiratory Therapy "[mh] OR "Physical Therapy Modalities "[mh] OR rehabilitat*[tiab] OR fitness*[tiab] OR exercis*[tiab] OR train*[tiab] OR physiotherap*[tiab] OR "physical therapy"[tiab] OR "physical therapist"[tiab]) AND ("randomized controlled trial"[pt] OR randomly*[tiab] OR randomised*[tiab] OR randomized*[tiab] OR trial[tiab] OR groups[tiab] OR placebo*[tiab]) AND (("2016/01/01"[PDat] : "3000/12/31"[PDat]))

d. Search string used to identify trials from ClinicalTrials.gov

Search Field	Search term
Study type	Interventional
Condition	COPD
Intervention	Pulmonary rehabilitation

e. Search string used to identify trials from Epistimonikos

(title:(COPD) OR abstract:(COPD)) AND (title:(pulmonary rehabilitation) OR abstract:(pulmonary rehabilitation))

Limited to publication type: systematic review

Appendix 2: Characteristics of included studies

Elliot (2004) and Lake (1999)

DESIGN	
Parallel RCT	
POPULATION	
Setting for population	Two urban hospitals in Australia.
Inclusion criteria	• Moderate to severe COPD (FEV1 34–70%) • Stable breathlessness on exertion
Exclusion criteria	• Significant cardiac or other disease • musculoskeletal problems precluding exercise • significant arterial oxygen desaturation during exercise (SaO2 £ 85%) • psychiatric or cognitive problems, or difficulty with communication • recent respiratory infections.
Total number randomised	43 (30 in hospital group; 13 in community group)
INTERVENTIONS	
GROUP A	
Total no participants	30
Setting of intervention	Hospital-based: Outpatient
Description of intervention	• Education • Exercise components: ➢ warm-up and stretch ➢ circuit strength training (upper and lower limb exercises, and abdominal strengthening exercises) ➢ aerobic training (treadmill and corridor walking, and cycling) ➢ cool-down and stretch, with.
Duration + frequency of intervention	• 1.5h sessions • 2x/week • Duration: 3 months
GROUP B	
Total no participants	13
Setting of intervention	Community-based
Description of intervention	• Education • Exercise components: ➢ warm-up and stretch ➢ walking ➢ general exercises or low-intensity circuit routines with weights (exercises focussed on function and mobility) ➢ cool-down and stretch.
Duration + frequency of intervention	• 1.5hrs sessions • 2x/week • Duration: 3 months • One patient attended one of each type of class each week.
OUTCOMES	
CRQ, 6MWD	

Guell 2008 and Guell 2006

DESIGN	
Parallel RCT	
POPULATION	
Setting for population	4 Spanish hospitals for pulmonary rehabilitation in Barcelona, Bilbao, Madrid and Seville.
Inclusion criteria	• Severe or very severe COPD (according to GOLD guideline classification) • Age between 50-75 years • Classification as an ex-smoker or smoker intending to quit • FEV1 between 30-50% of reference • Stable condition, free of exacerbations in the last 4 weeks
Exclusion criteria	• Significant response to bronchodilator (>15% increase in FEV1 from baseline after inhalation of 200 microgram of salbutamol • Severe hypoxemia (PaO2 < 60 mm Hg) • Diagnosis of asthma • Severe coronary artery disease • Orthopaedic disease limiting mobility
Total number randomised	57 (29 in hospital group, 28 in home-based group)
INTERVENTIONS	
GROUP A	
Total no participants	29
Setting of intervention	Hospital-based: Outpatient
Description of intervention	Week 1 (before randomization): • 2 informative sessions about COPD (including video) + discussion • 4 session of outpatient respiratory physical therapy sessions (supervised by physiotherapist): breathing retraining with threshold, arm exercises with weights Components (from week 2-9): • Respiratory muscle training (2 sessions of 15 min) with threshold device • Arm training: 30 min of weight lifting (start at 0.5 kg; add 1kg/week if tolerated) • Leg training: 30 min on cycle ergometer (beginning at 60% of maximum reached on the progressive stress test; then raised by increments of 10W if tolerated)
Duration + frequency of intervention	• 1.5hrs sessions • 3x/week • Duration: 9 weeks
GROUP B	
Total no participants	28
Setting of intervention	Home-based

Description of intervention	Week 1 (before randomization): • 2 informative sessions about COPD (including video) + discussion • 4 session of outpatient respiratory physical therapy sessions (supervised by physiotherapist): breathing retraining with threshold, arm exercises with weights Components (from week 2): • Respiratory muscle training (2 sessions of 15 min) with threshold device • Arm training: 30 min of weight lifting (start at 0.5 kg; add 1kg/week if tolerated) • Leg training: unsupervised street walking daily at a pace of 4 km/hr marked by podometer (15 min/day in 1st week, 30 min 2-4 week, 45 min 5-9 week) + up and down stairs for 5 min before each walk
Duration + frequency of intervention	Walk daily, but frequency of other exercises not specified (probably same as group A i.e. 3x/week)
OUTCOMES	
CRQ, 6MWD	

Holland 2013, La Trobe 2011, Holland 2016a, Holland 2016b

DESIGN	
Parallel RCT	
POPULATION	
Setting for population	Respiratory medicine clinics at the Austin or Alfred Hospitals.
Inclusion criteria	• greater than 40 years of age • a diagnosis of COPD based on an FEV1/FVC ratio of < 70% • a smoking history (current or former) of a minimum of 10 packet years
Exclusion criteria	• diagnosis of asthma • attended a pulmonary rehabilitation program within the last 2 years • experienced an exacerbation of COPD within the last four weeks • have other comorbidities which will prevent participation in an exercise training program
Total number randomised	166 (86 in hospital group; 80 in home group)
INTERVENTIONS	
GROUP A	
Total no participants	86
Setting of intervention	Hospital-based: Outpatient
Description of intervention	• Exercise Components: ➢ 30 minutes of aerobic exercise: walking or cycling ➢ Upper and lower limb strength training: functional tasks and free weight training. ➢ Resistance training used functional activities such as stair training and sit to stand from a chair.
Duration + frequency of intervention	• 2x/week • Duration: 8 week. • Participants were also be encouraged to exercise at a moderate intensity at home an additional three times per week.
GROUP B	
Total no participants	80
Setting of intervention	Home-based
Description of intervention	• Exercise components: ➢ Aerobic training: speed walked using a pedometer. Participants will be encouraged to exercise for 30 minutes, five times per week. ➢ Resistance training for the arms and legs using daily activities and equipment that is readily available in the home environment.
Duration + frequency of intervention	Aerobic training 5x/week; resistance training daily for 8 weeks.
OUTCOMES	
CRQ, 6MWD, cost/session, QALYs	

Laval 2005, Maltais 2005 and Maltais 2008

DESIGN	
Parallel RCT	
POPULATION	
Setting for population	10 academic and community medical centres in Canada
Inclusion criteria	• Stable COPD meaning no change in medication and symptoms (dyspnea, volume, or color of sputum) for at least 4 weeks before the study • 40 years or older • current or former smokers of at least 10 pack-years (20 cigarettes per pack) • FEV1 less than 70% of the predicted value and FEV1–FVC ratio less than 0.70 • a Medical Research Council dyspnea score of at least 2 • No participants had previously been involved in pulmonary rehabilitation or had lived in a long-term care facility. • Everyone understood, read, and wrote French or English.
Exclusion criteria	• a previous diagnosis of asthma, congestive left heart failure as the primary disease, a terminal disease, dementia, or an uncontrolled psychiatric illness. • We sought to study a broad COPD population and did not exclude patients with oxygen dependence or other comorbid conditions.
Total number randomised	252 (114 in hospital group; 119 in home group)
INTERVENTIONS	
GROUP A	
Total no participants	114
Setting of intervention	Hospital-based: Outpatient
Description of intervention	• Educational intervention 8 lectures (2x/week for 4 weeks) before programme • Exercises components: ➢ Aerobic: Stationary leg cycling for 25 to 30 minutes in each session. ➢ Strength exercises: 30 minutes
Duration + frequency of intervention	• 3x/ week • Duration: 8 weeks
GROUP B	
Total no participants	119
Setting of intervention	Home-based
Description of intervention	• Educational intervention 8 lectures (2x/week for 4 weeks) before programme • Components: ➢ Aerobic training with portable ergocycles; 40 minutes ➢ The strengthening exercises were the same as in the outpatient program
Duration + frequency of intervention	• 3x/ week • Duration: 8 weeks
OUTCOMES	
CRQ, SGRQ, 6MWD, incremental cycle exercise test	

Mendes de Oliveira 2010 and Oliveira 2011

DESIGN	
Parallel RCT	
POPULATION	
Setting for population	Cascavel (Southern Brazil) (private clinic)
Inclusion criteria	• COPD based on the GOLD classification • clinical stability in the eight weeks prior to the study (no reports of worsening of dyspnea, increased phlegm production or phlegm purulence)
Exclusion criteria	• hospitalization • COPD instability • presence of neuromuscular disease, associated respiratory disease, orthopedic or neurological disease that affected gait; recent impairment due to comorbidities, such as myocardial infarction, heart failure, stroke or neoplasm; • prior pneumonectomy or other thoracic surgery
Total number randomised	117 (46 in hospital group; 42 in home group)
INTERVENTIONS	
GROUP A	
Total no participants	46
Setting of intervention	Hospital based: Outpatient (private clinic)
Description of intervention	Exercise Components: • Active warm-up exercises • Strengthening of limbs: with ankle and hand weights • Aerobic exercises: walking on a tread mill for 30 minutes • Stretching
Duration + frequency of intervention	• 3x/week • Duration: 3 months
GROUP B	
Total no participants	42
Setting of intervention	Home-based
Description of intervention	• Strengthening of limbs: using ankle and hand weights • Aerobic exercise: walks on flat ground
Duration + frequency of intervention	• 3x/week • Duration: 3 months
OUTCOMES	
CRQ, SGRQ, 6MWD, incremental cycle exercise test	

Nygren Bonnier 2002

DESIGN	
Parallel RCT	
POPULATION	
Setting for population	Sweden
Inclusion criteria	• COPD • median forced expiratory volume in one second (FEV1) 41.5% of predicted value
Exclusion criteria	Not stated.
Total number randomised	24
INTERVENTIONS	
GROUP A	
Total no participants	Not stated but most likely 12
Setting of intervention	Hospital-based: Outpatient
Description of intervention	'attended a 60 minutes outpatient training session in the hospital twice a week….performed two to three sets of 10-15 repetitions of eleven strength exercises, 60- 70% of RM'
Duration + frequency of intervention	Duration: 12 weeks
GROUP B	
Total no participants	Not stated but most likely 12
Setting of intervention	Home-based
Description of intervention	'practising a home-based training program during 45 minutes each session, three times a week….. performed two to three sets of 10-15 repetitions of eleven strength exercises, 60- 70% of RM'
Duration + frequency of intervention	Duration: 12 weeks
OUTCOMES	
CRQ, Shuttle walking test	

Puente Maestu 1996, Puente Maestu 2000a and Puente Maestu 2000b

DESIGN	
Parallel RCT	
POPULATION	
Setting for population	Spain
Inclusion criteria	• age <75 years • severe COPD (history of having smoked at least 10 packs-year, post bronchodilator forced expiratory volume in one second (FEV1) <50% of predicted and FEV1/forced vital capacity (FVC) <0.7) without significant reversibility (<15% of the initial value, 15 min after the inhalation of 200 mg of salbutamol); • declared smoking cessation at least 6 month before enrolling and arterial blood carboxyhaemoglobin <3% • stable phase of their COPD, meaning no exacerbation, for at least 2 months, of acute dyspnoea needing medical assistance, changes in volume or characteristics of sputum, increase in lung sounds (wheezing or ronchi) or increases in the needs of lung medication • grade 2 or more of dyspnoea sensation measured by the a modification of the Medical Research Council scale [13] that scores dyspnoea form 0 (none) to 4 (resting dyspnoea) in ascending categories related to walking function
Exclusion criteria	• Evidence of asthma, bronchiectasis, obliterating bronchiolitis, scarring affecting >20% of one hemithorax in the chest radiography, thoracic deformities, fibrothorax, severe cardiomyopathies, ischaemic cardiopathy, severe arrhythmia, type I diabetes mellitus, neuromuscular disorders, severe hepatic or renal diseases • Physical or psychological impairment impeding exercise testing or training.showed poor collaboration or skipped >1 week of training and did not want to restart the whole training programme.
Total number randomised	49
INTERVENTIONS	
GROUP A	
Total no participants	21 (had complete data; not stated how many of the 49 were originally randomised into this group)
Setting of intervention	Hospital-based: Outpatient
Description of intervention	• Trained on a treadmill (60 minutes), supervised by a physiotherapist
Duration + frequency of intervention	• 4x/week • Duration: 8 weeks
GROUP B	
Total no participants	20 (had complete data; not stated how many of the 49 were originally randomised into this group)
Setting of intervention	Home-based
Description of intervention	• With a pedometer and asked to walk 3 or 4 km

Duration + frequency of intervention	• 4x/week • Duration: 8 weeks
OUTCOMES	
CRQ, Incremental exercise test	

Strijbos 1996a, Strijbos 1996b and Strijbos 1999

DESIGN	
Parallel RCT	
POPULATION	
Setting for population	Asthma centrum Breatrix-oord, the Netherlands.
Inclusion criteria	• 40-70 years • Severe COPD with dyspnoea as main symptom that restricts daily activities • FEV_1 after administration of bronchodilators had to be between 600-1800ml, and had to be less than 65% of the predicted FEV_1
Exclusion criteria	• Ischemic heart disease, musculoskeletal disorders, or other disabling diseases that could restrict their rehabilitation therapy. • Hypercapnia in rest ($PaCO_2$ > 6.5 kPa) • And/or hypoxia in rest (PaO_2 < 7.5 kPa)
Total number randomised	50 in total (but includes control group which we are excluding from the review). Intervention hospital 18 Intervention home 17 Control 15
INTERVENTIONS	
GROUP A	
Total no participants	18 (15 completed at 3 months)
Setting of intervention	Hospital-based: Outpatient
Description of intervention	• Patient education • Exercise components (adapted to the individuals): ➢ Breathing exercises ➢ Relax/stretch exercises ➢ General muscle strengthening exercises ➢ Aerobic exercises ➢ Education about medication use Patients were instructed partake in daily exercise individualy for at least 15min (for example, walking and stair climbing).
Duration + frequency of intervention	• 1 hr sessions • 2x/week • Duration: 12 weeks
GROUP B	
Total no participants	17 (15 completed)
Setting of intervention	Community-based

Description of intervention	• Exercise individually at least 30min on exercise days and at least 15min on other days • Visited three times by the local home-care nurse, who checked the use of medication, daily peak flow values, and motivated the patient to continue the exercises at home. • All patients visited their general practitioner on three occasions during the 12 weeks of rehabilitation. • Same exercise protocols (adapted to the individuals) as hospital-based group (these were initially thought to the involved practitioners by the researcher) ➢ Breathing exercises ➢ Relax/stretch exercises ➢ General muscle strengthening exercises ➢ Aerobic exercises ➢ Education about medication use
Duration + frequency of intervention	• 2x/week • Duration: 12 weeks
OUTCOMES	
4 minute walking distance Cycling test (ECG test at 20Watt with 10Watt per minute increase until the patient indicated that could not increase it more (Wmax). $Sa0_2$ was constantly measured and the BORG scale was used.)	

Waterhouse 2010

DESIGN	
Parallel RCT	
POPULATION	
Setting for population	Sheffield Teaching Hospitals NHS Foundation Trust, UK.
Inclusion criteria	• Diagnosis of COPD by respiratory physician, using GOLD guidelines • Medical Research Council (MRC) grade 3 or worse dyspnoea despite optimal medical care. • Clinically stable at least 4 weeks before commencing rehabilitation.
Exclusion criteria	• Inability to hear or understand educational talks (despite use of interpreters and/or hearing aids where appropriate). • Prognosis under 2 years from any disease. • Long-term oxygen therapy or absolute requirement for oxygen therapy on exercise (defined as oxygen saturation in arterial blood falling below 80% during initial ISWT). • Unstable and/or uncontrolled cardiac disease. • Lack of informed consent. • Musculoskeletal problems precluding exercise training • No access to home telephone.
Total number randomised	326 (164 to hospital, 162 community)
INTERVENTIONS	
GROUP A	
Total no participants	164
Setting of intervention	Hospital-based: Outpatient
Description of intervention	• 1 hour for review, warm-up, exercise and cool-down • 1 hour for education, with the participants being encouraged to exercise between formal classes. • The component comprised 11 workstations, with alternating upper and lower limb exercises for strength, endurance and core stability. These stations were: • thoracic rotations (using medicine ball) • step-ups • shoulder punches • knee lifts • snow angels • sit to stand • bicep curls • walking • sweeping • knee extensions • lifting and pegging washing
Duration + frequency of intervention	• 2x/week • Duration: 6 weeks
GROUP B	
Total no participants	162
Setting of intervention	Community-based
Description of intervention	• 1 hour for review, warm-up, exercise and cool-down • 1 hour for education, with the participants being encouraged to exercise between formal classes. • This component comprised 11 workstations, with alternating upper and lower limb exercises for strength, endurance and core stability. These stations were: • thoracic rotations (using medicine ball) • step-ups • shoulder punches • knee lifts • snow angels • sit to stand • bicep curls • walking • sweeping • knee extensions • lifting and pegging washing

Duration + frequency of intervention	• 2x/week • Duration: 6 weeks
OUTCOMES	
CRQ, ESWT use of health-care resources, EQ5D	

Appendix 3: Studies excluded at full text selection

Study	Reason for exclusion
Altenburg 2014	Exclusion reason: Duplicate citation (identical to a citation previously included)
Macklem 2003	Exclusion reason: Has an exercise component but is NOT aerobically demanding
Aveiro 2014	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
Lum 2007	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
UniversityofCalifornia 2013	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
Ren 2011	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
Horton 2014	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
Horton 2013	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
Swerts 1990	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
LopezVarela 2006	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
LopezVarela 2003	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
Afolabi 2004	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
Altenburg 2015	Exclusion reason: No direct pairwise comparison(s) between pulmonary rehabilitation in different settings
O'Brien 2004	Exclusion reason: Not a programme, or programme does NOT contain any exercise component
Stickland 2011	Exclusion reason: Not a Randomised Controlled Trial
Laukandt 1998	Exclusion reason: Not a Randomised Controlled Trial
Varga 2006	Exclusion reason: Not a Randomised Controlled Trial
Varga 2007	Exclusion reason: Not a Randomised Controlled Trial
Dushianthan 2009	Exclusion reason: Only a discussion Paper
Alison 2009	Exclusion reason: Only a discussion Paper
Nct 2015	Exclusion reason: PR programme has different exercise components in both groups but both performed in same setting
Puente-Maestu 2003	Exclusion reason: This citation linked to main study paper already being screened

Appendix 4: Risk of bias of included studies

Elliot (2004) and Lake (1999)

Domain	Risk of bias	Support for judgement (Location)
Random sequence generation (Selection bias)	Unclear	"Patients were randomly assigned to one of three rehabilitation groups" (No clear statement.) (pp346)
Allocation concealment (Selection bias)	Unclear	No clear statement. (pp346)
Blinding of participants and personnel *(performance bias)*	High	Blinding not possible for these interventions.(pp346)
Blinding of outcome assessment *(detection bias)*	Unclear	No clear statement. (pp347)
Incomplete outcome data *(attrition bias)*	Low	"Twenty-two of the 30 patients (73%) in the Hospital group and nine of the 13 patients (69%) in the Community group completed the 3-month programme." (pp348)
Selective outcome reporting? *(reporting bias)*	Low	All pre-specified outcomes reported. (pp348 (Table 2))
Other bias	Low	None noted

Guell 2008 and Guell 2006

Domain	Risk of bias	Support for judgement (Location)
Random sequence generation (Selection bias)	Unclear	No clear statement. (pp513)
Allocation concealment (Selection bias)	Low	"The patients were randomized to receive hospital- or home-based pulmonary rehabilitation on the basis of assignments received in sealed envelopes." (pp513)
Blinding of participants and personnel *(performance bias)*	High	Blinding not possible for these interventions. (pp513)
Blinding of outcome assessment *(detection bias)*	Low	"The personnel who carried out the tests were blinded as to group assignment." (pp513)
Incomplete outcome data *(attrition bias)*	Low	"Six of 57 withdrew from the study" No. of complete outcomes reported in tables; balanced over groups. (513-515, table 3 and 4)
Selective outcome reporting? *(reporting bias)*	Low	All pre-specified outcomes reported. (pp514-515)
Other bias	Low	None noted

Holland 2013, La Trobe 2011, Holland 2016a, Holland 2016b

Domain	Risk of bias	Support for judgement (Location)
Random sequence generation (Selection bias)	Low	"Participants will be randomised to the hospital or the home based group using stratified block randomisation, with stratification for site (Austin or Alfred) and disease severity (FEV1 < 50% predicted versus FEV1 > 50% predicted). Randomisation will be undertaken using a computer generated sequence…" (Holland 2013: pp3)
Allocation concealment (Selection bias)	Low	"Randomisation will be undertaken using a computer generated sequence and allocation will be concealed using sealed, opaque envelopes." (Holland 2013: pp3)
Blinding of participants and personnel *(performance bias)*	High	Blinding is not possible for these interventions.
Blinding of outcome assessment *(detection bias)*	Low	"An independent assessor, blinded to group allocation, will undertake the following measurements at each time point following the intervention period." "At the end of the trial, the assessors correctly identified group allocation for 52% of participants (kappa = 0.26), demonstrating the success of blinding." (Holland 2013: pp4)
Incomplete outcome data *(attrition bias)*	Low	At the end of the trial data were available for the primary outcome in 90% of the home group and 88% of the centre based group.
Selective outcome reporting? *(reporting bias)*	Low	Most pre-specified outcomes reported. Protocol available. Indirect costs and QALY's not reported but stated that these will be published in a later publication. (Holland 2016b: pp11)
Other bias	Low	None noted

Laval 2005, Maltais 2005 and Maltais 2008

Domain	Risk of bias	Support for judgement (Location)
Random sequence generation (Selection bias)	Low	"We used a centrally administered, computer-generated permuted block randomization scheme using blocks of 2, stratified according to sex and participating site." (pp871)
Allocation concealment (Selection bias)	Low	"We communicated assignments by e-mail to research staff who were not otherwise involved in the trial. The case manager subsequently informed patients of their group allocation. Study personnel were unaware of the permuted block size." (pp871)
Blinding of participants and personnel *(performance bias)*	High	Not possible for these interventions.
Blinding of outcome assessment	Low	"An independent research assistant, unaware of the patient's group assignment, conducted a standardized telephone interview every 4 weeks to

(detection bias)		identify adverse events. To minimize bias, we asked patients not to discuss their group assignment with the research assistant." (pp871)
Incomplete outcome data *(attrition bias)*	Low	Each group had 126 participants at baseline. At 3 months 114 were evaluated in the hospital group and 119 in home group. Reasons provided. (Figure 1, pp 872)
Selective outcome reporting? *(reporting bias)*	Low	All pre-specified outcomes reported. (874-875 table 2-3)
Other bias	Low	None noted

Mendes de Oliveira 2010 and Oliveira 2011

Domain	Risk of bias	Support for judgement (Location)
Random sequence generation (Selection bias)	Low	"The patients were randomized electronically by a computer into three groups as follows" (pp402)
Allocation concealment (Selection bias)	Unclear	No clear statement.
Blinding of participants and personnel *(performance bias)*	High	Blinding is not possible for these interventions.
Blinding of outcome assessment *(detection bias)*	Unclear	"Two duly trained health care professionals were responsible for the evaluations, which were performed by the same evaluators for all patients." "The PR program lasted 12 weeks, after which the individuals were evaluated a second time." "Telephone contact was made each month by a blind evaluator, who inquired about the general health status of the individuals, adverse effects and the continuity of the physical activities." (Even though the telephone contact was done blinded; there is no statement that the assessments were blinded.) (pp402-403)
Incomplete outcome data *(attrition bias)*	High	Of the 42, 29 and 46 in the home, control and outpatient programme, 33, 29 and 23 had complete data at 12 weeks (attrition 50% on outpatient group) (Figure 1; pp403)
Selective outcome reporting? *(reporting bias)*	Low	All pre-specified outcomes reported. (pp405-406)
Other bias	Low	Baseline characteristics in all groups comparable.

Nygren Bonnier 2002

Domain	Risk of bias	Support for judgement (Location)
Random sequence generation (Selection bias)	Unclear	"twenty four patients were randomly assigned"
Allocation concealment (Selection bias)	Unclear	No clear statement.
Blinding of participants and personnel *(performance bias)*	High	Blinding not possible for these interventions.
Blinding of outcome assessment *(detection bias)*	Unclear	No clear statement.
Incomplete outcome data *(attrition bias)*	Unclear	No clear statement.
Selective outcome reporting? *(reporting bias)*	High	Not all prespecified outcomes reported in the results of the abstract (e.g., shuttle walk)
Other bias	Unclear	Limited information available in abstract.

Puente Maestu 1996, Puente Maestu 2000a and Puente Maestu 2000b

Domain	Risk of bias	Support for judgement (Location)
Random sequence generation (Selection bias)	Unclear	"The randomization method used involved blocks of four patients and was established before the first patient was included." (pp518)
Allocation concealment (Selection bias)	Unclear	"The physicians who sent the patients for rehabilitation were unaware of the randomization sequence." "Patients were referred to the authors' rehabilitation programme by their pneumologists, who decided on other therapies during the study." ⇨ No clear statement of how they were allocated.
Blinding of participants and personnel *(performance bias)*	High	No blinding possible for these interventions.
Blinding of outcome assessment *(detection bias)*	Unclear	No clear statement.
Incomplete outcome data *(attrition bias)*	Low	Of the 49 participants, complete data was obtained for 41. (pp518)
Selective outcome reporting? *(reporting bias)*	Low	All pre-specified outcomes reported. (pp520-521)
Other bias	Low	Baseline characteristics are comparable between

		groups. (pp520)

Strijbos 1996a, Strijbos 1996b and Strijbos 1999

Domain	Risk of bias	Support for judgement (Location)
Random sequence generation (Selection bias)	Low	"People were allocated to one of the groups using a 'lottery procedure' (pp106)
Allocation concealment (Selection bias)	Unclear	No clear statement.
Blinding of participants and personnel *(performance bias)*	High	No blinding possible for these interventions.
Blinding of outcome assessment *(detection bias)*	Low	Letter received from author to Y. Lacasse notes that investigators performing outcome assessment were blinded
Incomplete outcome data *(attrition bias)*	Low	3 dropped out of hospital group and 1 out of primary care. Reasons provided. (pp106)
Selective outcome reporting? *(reporting bias)*	Low	All pre-specified outcomes reported. (pp107-108)
Other bias	Low	Baseline characteristics comparable between groups. (pp107)

Waterhouse 2010

Domain	Risk of bias	Support for judgement (Location)
Random sequence generation (Selection bias)	Low	"The trial statistician, SJW, generated the random allocation sequence using the RALLOC procedure in stata 8 (StataCorp, College Station, Texas, USA)16 using the 2 × 2 factorial design option, with variable block sizes and stratified by site (north or south). Each site had one possible hospital or two community options." (pp4)
Allocation concealment (Selection bias)	Low	"People were then contacted and invited to attend hospital for assessment, without knowing the venue for their rehabilitation." (pp5)
Blinding of participants and personnel *(performance bias)*	High	In view of the nature of pulmonary rehabilitation it is not possible to blind research participants or assessors. Several stratagems were adopted in an effort to ensure that objectivity was maintained as rigorously as possible: • Participants were unaware of their site of rehabilitation until they had completed all of their pre-rehabilitation assessment. • The individuals carrying out the assessments were not part of the treatment teams. • Research participants were asked not to divulge information regarding the site of rehabilitation in

		conversation during follow-up assessments. (pp5)
Blinding of outcome assessment *(detection bias)*	Low	"Research participants were asked not to divulge information regarding the site of rehabilitation in conversation during follow-up assessments. " "All personnel involved in testing were trained by the study co-ordinator (JCW) to administer the instruments, and were independent of provision of pulmonary rehabilitation." (pp8-9)
Incomplete outcome data *(attrition bias)*	High	Hospital: Of 164, 129 completed pre-rehab assessment, and 86 post-rehab assessment (52% attrition) Community: Of 162, 111 completed pre-rehab assessment, and 76 post-rehab assessment (47% attrition) Reasons provided. (pp18)
Selective outcome reporting? *(reporting bias)*	Low	All pre-specified outcomes reported or explained why not. (Chapter 4 and 5)
Other bias	Low	Baseline characteristics comparable between groups. (pp19)

Appendix 5: GRADE evidence profiles

a. Outpatient versus home-based PR

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outpatient hospital-based PR	Home-based PR	Relative (95% CI)	Absolute (95% CI)		
Change in HRQoL - CRQ (dyspnoea)												
4	randomised trials	serious [1]	not serious	not serious	not serious	none	239	234	-	MD **-0.09 lower** (-0.28 lower to 0.1 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Change in HRQoL - CRQ (fatigue)												
4	randomised trials	serious [1]	not serious	not serious	not serious	none	239	234	-	MD **-0.0** (-0.18 lower to 0.17 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Change in HRQoL - CRQ (emotional)												
4	randomised trials	serious [1]	not serious	not serious	not serious	none	239	234	-	MD **0.1 higher** (-0.24 lower to 0.45 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Change in HRQoL - CRQ (mastery)												
4	randomised trials	serious [1]	not serious	not serious	not serious	none	239	234	-	MD **-0.02 lower** (-0.28 lower to 0.25 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Change in SGRQ total (units)												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	none	114	119	-	MD **1.4 higher** (-1.5 lower to 4.3 higher)	⊕⊕◯◯ LOW	IMPORTANT
Change in Incremental Cycle Ergometry Distance (m)												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	none	114	119	-	MD **-9 lower** (-109.8 lower to 91.8 higher)	⊕⊕◯◯ LOW	IMPORTANT

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Outpatient hospital-based PR**	**Home-based PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
Chang 6MWD (m)												
4	randomised trials	serious [1]	not serious	not serious	serious [2]	none	241	247	-	MD -**0.39 lower** (-16.61 lower to 15.83 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

1. Blinding not performed in 4 out of 4 RCTs included in analysis. This is an inherent problem due to the nature of the intervention in PR
2. Wide CI that includes appreciable benefit and harm

b. Outpatient versus Community-based PR

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outpatient hospital-based PR	Community-based PR	Relative (95% CI)	Absolute (95% CI)		
HRQoL - CRQ (dyspnoea)												
2	randomised trials	serious [1]	not serious	not serious	not serious	none	111	84	-	MD **0.29 higher** (-0.05 lower to 0.62 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
HRQoL - CRQ (fatigue)												
2	randomised trials	serious [1]	not serious	not serious	serious [2]	none	115	85	-	MD **-0.02 lower** (-1.09 lower to 1.05 higher)	⨁⨁◯◯ LOW	IMPORTANT
HRQoL - CRQ (emotional)												
2	randomised trials	serious [1]	not serious	not serious	not serious	none	114	84	-	MD **0.1 higher** (-0.4 lower to 0.59 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
HRQoL - CRQ (mastery)												
2	randomised trials	serious [1]	not serious	not serious	not serious	none	113	85	-	MD **-0.08 lower** (-0.45 lower to 0.28 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Change in 6MWD (m)												
1	randomised trials	serious [1]	not serious	not serious	serious[3]	none	22	9	-	MD **66.9 higher** (-0.4 lower to 134.2 higher)	⨁⨁◯◯ LOW	IMPORTANT
Change in ESWD (m)												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	none	164	162	-	MD **67.3 higher** (-40.8 lower to 175.4 higher)	⨁⨁◯◯ LOW	IMPORTANT

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Outpatient hospital-based PR**	**Community-based PR**	**Relative (95% CI)**	**Absolute (95% CI)**		
Incremental cycle ergometry												
1	randomised trials	serious [1]	not serious	not serious	serious [3]	none	15	15	-	MD **4 higher** (-11 lower to 19 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

1. Blinding not performed in 2 out of 2 RCTs included in analysis. This is an inherent problem due to the nature of the intervention in PR
2. Wide CI that includes appreciable benefit and harm
3. Small number of participants and wide confidence interval

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