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[Prototype Review]

Tailored or adapted interventions for adults with chronic obstructive pulmonary disease and at least one other long-term condition: a mixed methods review

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition characterised by shortness of breath, cough and recurrent exacerbations. People with COPD often live with one or more co-existing long-term health conditions (comorbidities). People with more severe COPD often have a higher number of comorbidities, putting them at greater risk of morbidity and mortality.

Objectives

To assess the effectiveness of any single intervention for COPD adapted or tailored to their comorbidity(s) compared to any other intervention for people with COPD and one or more common comorbidities (quantitative data, RCTs) in terms of the following outcomes: Quality of life, exacerbations, functional status, all-cause and respiratory-related hospital admissions, mortality, pain, and depression and anxiety.

To assess the effectiveness of an adapted or tailored single COPD intervention (simple or complex) that is aimed at changing the management of people with COPD and one or more common comorbidities (quantitative data, RCTs) compared to usual care in terms of the following outcomes: Quality of life, exacerbations, functional status, all-cause and respiratory-related hospital admissions, mortality, pain, and depression and anxiety.

To identify emerging themes that describe the views and experiences of patients, carers and healthcare professionals when receiving or providing care to manage multimorbidities (qualitative data).

Search methods

We searched multiple databases including the Cochrane Airways Trials Register, CENTRAL, MEDLINE, Embase, and CINAHL, to identify relevant randomised and qualitative studies. We also searched trial registries and conducted citation searches. The latest search was conducted in January 2021.

Selection criteria

Eligible randomised controlled trials (RCTs) compared a) any single intervention for COPD adapted or tailored to their comorbidity(s) compared to any other intervention, or b) any adapted or tailored single COPD intervention (simple or complex) that is aimed at changing

the management of people with COPD and one or more comorbidities, compared to usual care. We included qualitative studies or mixed-methods studies to identify themes.

Data collection and analysis

We used standard Cochrane methods for analysis of the RCTs. We used Cochrane's risk of bias tool for the RCTs and the CASP checklist for the qualitative studies. We planned to use the Mixed Methods Appraisal tool (MMAT) to assess the risk of bias in mixed-methods studies, but we found none. We used GRADE and CERQual to assess the quality of the quantitative and qualitative evidence respectively. The primary outcome measures for this review were quality of life and exacerbations.

Main results

Quantitative studies

We included seven studies (1197 participants) in the quantitative analyses, with interventions including telemonitoring, pulmonary rehabilitation, treatment optimisation, water-based exercise training and case management. Interventions were either compared with usual care or with an active comparator (such as land-based exercise training). Duration of trials ranged from 4 to 52 weeks. Mean age of participants ranged from 64 to 72 years and COPD severity ranged from mild to very severe. Trials included either people with COPD and a specific comorbidity (including cardiovascular disease, metabolic syndrome, lung cancer, head or neck cancer, and musculoskeletal conditions), or with one or more comorbidities of any type.

Overall, we judged the evidence presented to be of moderate to very low certainty (GRADE), mainly due to the methodological quality of included trials and imprecision of effect estimates.

Intervention versus usual care

Quality of life as measured by the St George's Respiratory Questionnaire (SGRQ) total score may improve with tailored pulmonary rehabilitation compared to usual care at 52 weeks (mean difference (MD) −10.85, 95% confidence interval (CI) −12.66 to −9.04; 1 study, 70 participants; low-certainty evidence). Tailored pulmonary rehabilitation is likely to improve COPD assessment test (CAT) scores compared with usual care at 52 weeks (MD −8.02, 95% CI −9.44 to −6.60; 1 study, 70 participants, moderate-certainty evidence) and with a multicomponent telehealth intervention at 52 weeks (MD −6.90, 95% CI −9.56 to −4.24; moderate-certainty evidence). Evidence is uncertain about effects of pharmacotherapy optimisation or telemonitoring interventions on CAT improvement compared with usual care.

There may be little to no difference in the number of people experiencing exacerbations, or mean exacerbations with case management compared with usual care (OR 1.09, 95% CI 0.75 to 1.57; 1 study, 470 participants; very low-certainty evidence).

For secondary outcomes, six-minute walk distance (6MWD) may improve with pulmonary rehabilitation, water-based exercise or multicomponent interventions at 38 to 52 weeks (low-certainty evidence). A multicomponent intervention may result in fewer people being admitted to hospital at 17 weeks, although there may be little to no difference in a telemonitoring intervention. There may be little to no difference between intervention and usual care for mortality.

Intervention versus active comparator

We included one study comparing water-based and land-based exercise (30 participants). We found no evidence for quality of life or exacerbations.

There may be little to no difference between water- and land-based exercise for 6MWD (MD 5 metres, 95% CI −22 to 32; 38 participants; very low-certainty evidence).

Qualitative studies

One nested qualitative study (21 participants) explored perceptions and experiences of people with COPD and long-term conditions, and of researchers and health professionals who were involved in an RCT of telemonitoring equipment.

Several themes were identified, including health status, beliefs and concerns, reliability of equipment, self-efficacy, perceived ease of use, factors affecting usefulness and perceived usefulness, attitudes and intention, self-management and changes in healthcare use. We judged the qualitative evidence presented as of very low certainty overall.

Authors' conclusions

Owing to a paucity of eligible trials, as well as diversity in the intervention type, comorbidities and the outcome measures reported, we were unable to provide a robust synthesis of data. Pulmonary rehabilitation or multicomponent interventions may improve quality of life and functional status (6MWD), but the evidence is too limited to draw a robust conclusion. The key take-home message from this review is the lack of data from RCTs on treatments for people living with COPD and comorbidities.

Given the variation in number and type of comorbidity(s) an individual may have, and severity of COPD, larger studies reporting individual patient data are required to determine these effects.

PLAIN LANGUAGE SUMMARY

Approaches to help people with COPD who have one or more long-term conditions

What is COPD and comorbidity?

COPD is a common condition caused mainly by smoking and can lead to long-term breathing problems. Symptoms include shortness of breath, and cough with sputum production due to airways and lung damage. People with COPD may have one or more other long-term conditions (comorbidities) such as heart disease, hypertension, diabetes, asthma and lung cancer which can lead to poor health. People living with two or more comorbidities can also be known as living with multimorbidity.

Why did we do this review?

Because many people with COPD live with multimorbidity, naturally people in clinical trials will have multimorbidities. However, the results of those trials are usually not reported broken down by multimorbidity. People with comorbidities may need to adapt interventions to take account of their comorbidity — for example taking exercise in water instead of on land so that their bodies are better supported. Historically, Cochrane Airways Reviews have not taken into account people's comorbidities, and this review is a first step to addressing this. We decided to complete a review that centres on people with COPD and comorbidities following a meeting with our COPD patient group, who highlighted concerns over comorbidities. After some deliberation, we decided to include the following two sorts of trials.

1. Any single intervention for COPD delivered to people with COPD adapted to or targeting their comorbidity compared to routine care or any other intervention.

2. Any intervention aimed at changing the management of people with COPD and comorbidities, which could be simple (e.g. scheduling COPD and heart clinics on the same day) or more complex (e.g. developing a new care package for management of people with COPD across a local health service), compared to routine care.

We wanted to know which treatments improve quality of life and reduce exacerbations for people living with COPD and one or more comorbidities.

We also wanted to find out about how people with COPD, carers and health professionals felt about those treatments.

What information did we find?

We carried out a search for studies in January 2021. We found seven eligible randomised controlled trials (RCTs) including 1197 people, and one qualitative study which was part of one of the randomised trials and provided information about people's opinions and experiences of using telehealth equipment. People included in the trials were aged between 64 and 72 years, and their COPD severity ranged from mild to very severe. The trials either included people with COPD and a specific comorbidity such as cardiovascular disease or lung cancer, or they included people with COPD and one or more other conditions of any sort.

Results and conclusions

There is not enough evidence on people with COPD and other comorbidities to draw firm conclusions about interventions aimed at COPD that are adapted for the comorbidity. The available evidence indicated the following:

- Quality of life as measured by the St George's Respiratory Questionnaire (SGRQ) total score may improve with tailored pulmonary rehabilitation compared to usual care (note that there is a strong evidence base for pulmonary rehabilitation in people with COPD).

- Pulmonary rehabilitation is likely to improve quality of life as measured by the COPD assessment test (CAT) scores compared with usual care at 52 weeks and with a multicomponent telehealth intervention.

- Evidence is uncertain about the effects of pharmacotherapy optimisation or telemonitoring interventions on CAT improvement compared with usual care.

- There may be little to no difference in the number of people experiencing exacerbations, or mean exacerbations with case management compared with usual care.

- For secondary outcomes, the distance walked by participants in six minutes may improve with pulmonary rehabilitation, water-based exercise or multicomponent interventions. A multicomponent intervention may result in fewer people being admitted to hospital, although there may be little to no difference in a telemonitoring intervention.

- There may be little to no difference between intervention and usual care for deaths across several studies.

- One study compared water-based exercise with land-based exercise. We found no evidence for quality of life or exacerbations. There may be little to no difference between water- and land-based exercise on the distance walked by participants in six minutes.

- One qualitative study explored perceptions and experiences of people with COPD and long-term conditions, and of researchers and health professionals who were involved in an RCT of telemonitoring equipment. Several themes were identified, including health status, beliefs and concerns, reliability of equipment, self-efficacy, perceived ease of use, factors affecting usefulness and perceived usefulness, attitudes and intention, self-management and changes in healthcare use.

Larger studies with more people with COPD and comorbidities could help to find out if targeted approaches can improve health.

Certainty of the information

Overall there were very few studies and most studies were small. This means the results are based on a small amount of information. Trials with different interventions and different or more people may give a different result.

SUMMARY OF FINDINGS

Summary of findings 1. Intervention compared to usual care for COPD and at least one other long-term condition

Intervention compared to usual care for COPD and at least one other long-term condition

Patient or population: COPD and at least one other long-term condition
Setting: community teaching hospital (1), hospital outpatient clinic (1), university hospital (1), tertiary public hospital (1), multi-centre (3), single hospital (1)
Intervention: Intervention (rehabilitation, organisation of care, pharmacotherapy, multicomponent intervention)
Comparison: Usual care

Outcome domain	Intervention group (follow-up)	Anticipated absolute effects* (95% CI)		Relative effect	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with usual care	Risk with intervention				
Quality of life - SGRQ total Scale from: 0 to 100 (lower scores better)	**Rehabilitation (pulmonary rehab)** (follow-up 52 weeks)	The mean SGRQ total score was 70	MD 10.85 lower (12.66 lower to 9.04 lower)	—	70 (1 RCT)	(95% CI) ⊕⊝⊝ LOW[a,b]	MCID for SGRQ is a change of 4 points (Jones 2005)
Quality of life - CAT total Scale from 0 to 40 (lower scores better)	**Pharmacotherapy (optimised COPD treatment)** (follow-up 52 weeks)	The mean CAT total score was 0.4	MD 0.00 (3.40 lower to 3.40 higher)	—	77 (1 RCT)	⊕⊕⊝⊝ LOW[a,c,d]	MCID for CAT total is 2 points (Kon 2014)
	Rehabilitation (pulmonary rehab) (follow-up 52 weeks)	The mean CAT total score was 24.34	MD 8.02 lower (9.44 lower to 6.6 lower)	—	70 (1 RCT)	⊕⊕⊕⊝ MODERATE[a,b]	
	Organisation of care (telemonitoring) (follow-up 39 weeks)	The mean CAT total score was 17.17	MD 0.41 lower (2.19 lower to 1.37 higher)	—	312 (1 RCT)	⊕⊕⊝⊝ LOW[c,d]	
	Multicomponent intervention (follow-up 52 weeks)	The mean CAT total score was 1.6	MD 6.9 lower (9.56 lower to 4.24 lower)	—	80 (1 RCT)	⊕⊕⊕⊝ MODERATE[a,c]	
Exacerbations - number of people experi-	**Rehabilitation (case management)** (follow-up 52 weeks)	573 per 1000	594 per 1000 (501 to 678)	OR 1.09 (0.75 to 1.57)	470 (1 RCT)	⊕⊝⊝⊝ VERY LOW[e,f]	-

encing one or more							
Functional status-6MWD (metres)	**Rehabilitation (pulmonary rehab and water-based exercise)** (follow-up 38.8 weeks**)	The mean distance walked in 6 minutes was 344 metres	MD 60.4 metres higher (44.26 higher to 76.54 higher)	—	100 (2 RCTs)	⊕⊕⊖⊖ LOW[a,c]	MCID for the 6MWT is 25 to 35 metres (Holland 2013)
	Multicomponent intervention (follow-up 52 weeks)	The mean distance walked in six minutes was -15	MD 75 higher (28.06 higher to 121.94 higher)	—	80 (1 RCT)	⊕⊕⊖⊖ LOW[a,c]	
All-cause hospital admissions - people experiencing one or more	**Organisation of care (telemonitoring)** (follow-up 39 weeks)	292 per 1000	273 per 1000 (185 to 382)	OR 0.91 (0.55 to 1.50)	312 (1 RCT)	⊕⊕⊖⊖ LOW[c]	-
	Multicomponent intervention (follow-up 17 weeks)	732 per 1000	459 per 1000 (277 to 647)	OR 0.31 (0.14 to 0.67)	112 (1 RCT)	⊕⊕⊖⊖ LOW[a,c]	-
All-cause mortality (deaths)	**Pharmacotherapy (optimised COPD treatment)** (follow-up 17.6 weeks**)	170 per 1000	102 per 1000 (45 to 217)	OR 0.55 (0.23 to 1.35)	177 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[a,e,g]	-
	Organisation of care (case management and telemonitoring) (follow-up 46.7 weeks**)	102 per 1000	60 per 1000 (36 to 98)	OR 0.56 (0.33 to 0.96)	782 (2 RCTs)	⊕⊕⊖⊖ LOW[e]	-
	Multicomponent intervention (follow-up 52 weeks)	18 per 1000	18 per 1000 (1 to 230)	OR 1.00 (0.06 to 16.39)	112 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,c,h]	-

*__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).

**Weighted mean duration of follow-up

6MWD: 6-minute walk distance; **CAT:** COPD assessment test; **CI:** Confidence interval; **COPD:** chronic obstructive pulmonary disease; **GIV:** generic inverse variance; **HADS**: Hospital Anxiety and Depression Scale; **MD**: mean difference; **MCID:** minimally clinically important difference; **OR:** Odds ratio; **RCT:** randomised controlled trial;**RR:** Risk ratio; **SGRQ:** St George's Respiratory Questionnaire.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]The evidence was downgraded by 1 for imprecision due to the optimal information size of less than 200 participants.
[b]The evidence was downgraded by 1 for risk of performance bias.
[c]The evidence was downgraded by 1 for risk of performance and attrition bias.
[d]The evidence was downgraded by 1 for imprecision due to wide confidence intervals.
[e]The evidence was downgraded by 2 for risk of performance and detection bias.
[f]The evidence was downgraded by 1 for imprecision as the lower confidence interval crossed the line of no effect.
[g]The evidence was downgraded by 1 for risk of attrition due to high dropout rate in the study.
[h]The evidence for this outcome was downgraded by 2 for imprecision due to very wide confidence intervals.

Summary of findings 2. Intervention compared to active comparison for COPD and at least one other long-term condition

Intervention compared to active comparison for COPD and at least one other long-term condition

Patient or population: COPD and at least one other long-term condition
Setting: outpatient respiratory departments from 5 hospitals (multicentre), hospital outpatient clinic (1), tertiary public hospital (1)
Intervention: Intervention (rehabilitation water-based versus land-based exercise programme)
Comparison: active comparison

Outcome domain	Intervention group (follow-up)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with active comparison	Risk with Intervention				
Quality of life - SGRQ total	Not reported	-	-	-	-	-	-
Quality of life - CAT total	Not reported	-	-	-	-	-	-
Exacerbations	Not reported	-	-	-	-	-	-
Functional status - 6MWD (metres)	Rehabilitation (follow-up 8 weeks)	The mean distance walked in 6 minutes was 43 metres	MD 5 metres higher	-	30 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c]	The MCID for 6MWT is 25 to 35 me-

			(22.21 lower to 32.21 higher)				tres (Holland 2013)
All-cause hospital admissions	Not reported	-	-	-	-	-	-
All-cause mortality	Not reported	-	-	-	-	-	-

*__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).

6MWD: 6-minute walk distance; **CAT:** COPD assessment test; **CI:** Confidence interval; **COPD:** chronic obstructive pulmonary disease; **MD**: mean difference; **MCID:** minimally clinically important difference; **RCT:** randomised controlled trial;**SGRQ:** St George's Respiratory Questionnaire.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]The evidence was downgraded by 1 for imprecision due to the lower confidence interval crossing 1.0.
[b]The evidence was downgraded by 1 for imprecision as the optimal information size was less than 200 participants.
[c]The evidence was downgraded by 2 for risk of performance and attrition bias.

Summary of findings 3. Summary of findings table for qualitative GRADE CERqual assessment

Theme	Methodological limitations	Coherence	Adequacy of data	Relevance	Dissemination bias	Overall assessment	Explanation of CERQual assessment	Studies contributing to the review finding
Health status, beliefs and concerns							**The findings were graded as very low confidence because of minor concerns regarding**	Middlemass 2017
Unchanging nature of condition	Some concerns[a]	Major concerns[b]	Major concerns[b]	Some Concerns[c]	No concerns	Very low[c]		
Withdrawal of face to face communication	Some concerns[a]	Major concerns[b]	Major concerns[b]	Some Concerns[c]	No concerns	Very low[c]		

Reminder of illness and anxiety	Some concerns[a]	Major concerns[b]	Major concerns[b]	Some Concerns[c]	No concerns	Very low[c]	**methodological limitations and relevance. There were major concerns regarding coherence and adequacy of data**
Information							
Subjective norms	Some concerns[a]	Major concerns[b]	Major concerns[b]	Some Concerns[c]	No concerns	Very low[c]	
Technology							
Unreliable technology	Some concerns[a]	Major concerns[b]	Major concerns[b]	Some Concerns[c]	No concerns	Very low[c]	
HIT Self-efficacy	Some concerns[a]	Major concerns[b]	Major concerns[b]	Some Concerns[c]	No concerns	Very low[c]	
Perceived usefulness							
Daily monitoring of conditions	Some concerns[a]	Major concerns[b]	Major concerns[b]	Some Concerns[c]	No concerns	Very low[c]	
Factors affecting usefulness							
Lack of feedback	Some concerns[a]	Major concerns[b]	Major concerns[b]	Some Concerns[c]	No concerns	Very low[c]	
Behaviour							
Self-management and healthcare utilisation	Some concerns[a]	Major concerns[b]	No concerns	No concerns	No concerns	Very low[c]	

Criteria for assessment (https://www.cerqual.org/publications/)

Methodological limitations: risk to rigour see Table 1.

Coherence: how clear and cogent the fit is between the data from the primary studies and the review finding that synthesises that data. 'Findings' are 'transformations' of the underlying data into descriptions, interpretations and /or explanations of the phenomenon of interest. Findings are developed by identifying patterns in the data across primary studies

Adequacy: overall determination of the degree of richness as well as the quantity of data supporting the review finding i.e., extent to which information that the study authors provide is detailed enough to interpret the meaning and context of what is being researched.

Relevance: refers to the extent to which the body of data from primary studies supports the review finding in terms of applicability to the review question.

Dissemination bias: a systematic distortion of the phenomenon of interest due to selective dissemination of qualitative studies or the findings of qualitative studies

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[a]There were some concerns about the research design, and recruitment strategy to address the aims. It was not clear how the data was collected.
[b]The evidence mainly because the evidence is based on one study. Due to the limited number of studies, we cannot be certain that there are any issues about whether the data fit the finding of the review. Findings do not support quantitative data.
[c]The findings from the study did not answer all aspects of context specified in the review question.

BACKGROUND

Description of condition

It is estimated that the global population of people aged 60 and over will triple to 2.1 billion by 2050, with an increase of 32% in more developed countries, and 10% to 19% in less developed countries (United Nations 2013). As more people live longer, the number of chronic physical conditions that they may have are likely to increase (Academy of Medical Sciences Report 2018; Garin 2016).

The term 'multimorbidity' is defined as the co-existence of two or more chronic conditions, neither (or none) of which are considered to be an index condition (Academy of Medical Sciences Report 2018). Multimorbidity is associated with increasingly poor health outcomes (including reduced quality of life; impaired functional status; weakened physical and mental health; increased risk of re-admission to hospital; and mortality) (Barnett 2012; Holland 2016; NICE 2018).

Prevalence of multimorbidity on a global level may be difficult to determine, as access to health care and diagnosis of chronic conditions vary from country to country (Academy of Medical Sciences Report 2018). However, one cross-sectional study has recently shown that the prevalence of multimorbidity increases from over 40% to 70% in those aged 60 to 69 years across several low-, middle- and high-income countries (China, Finland, Ghana, India, Mexico, Poland, Russia, South Africa and Spain) (Garin 2016). It is estimated that approximately one in four people in the UK live with two or more long-term conditions, rising to two-thirds in people aged 65 and over (Barnett 2012; NHS England 2018; Salisbury 2018).

Chronic obstructive pulmonary disease (COPD) is the name for a group of lung diseases, including bronchitis and emphysema. COPD occurs in adults (aged 35 years and over), and is characterised by chronic airflow obstruction that interferes with normal breathing and is not fully reversible (World Health Organization 2018). Chronic airflow obstruction is defined by spirometry in which "the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC), and the volume of air exhaled during the first second (forced expiratory volume in one second, FEV_1)" are measured. A FEV_1/FVC ratio of less than 0.70 is an indicator for airway obstruction (GOLD 2021). Diagnosis of COPD is considered in people experiencing day-to-day symptoms such as coughing, breathlessness (dyspnoea), wheezing, frequent chest infections and is confirmed with spirometry - a post-bronchodilator FEV1/FVC ratio below 70% indicates airflow limitation (GOLD 2021). People may also experience periodic exacerbations (flare-ups) that punctuate the disease course. Risk factors for COPD include smoking and environmental exposures leading to abnormalities of the airways and alveoli (World Health Organization 2018; GOLD 2021).

Comorbidity is defined as any distinct clinical entity that may occur during the clinical course of a patient with the index disease under study. The focus of this review is COPD as the index disease. COPD is associated with a high prevalence of comorbidities (Smith 2014), and it is common for people with COPD to have more than one co-existing long-term health condition that can vary in nature and severity (Cavailles 2013; Holland 2016). People with more severe COPD (GOLD stage D) are likely to have a higher number of comorbidities (Raherison 2018), which puts them at a higher risk of mortality compared to people with mild or moderate COPD, or those without COPD and co-existing long-term health conditions (Divo 2012; Hanlon 2018; Mannino 2008).

Common long-term conditions that co-exist with COPD are cardiovascular disease, hypertension, diabetes, asthma, and lung cancer (Hillas 2015). People may also live with long-term condition system complexes such as frailty and chronic pain (Andenes 2018; Holland 2016). In this review we will treat pain as an outcome, rather than a condition. These long-term conditions may or may not be related to COPD.

In this review, we focus on people with COPD living with one or more long-term physical conditions (also referred to as comorbidities of COPD) (Holland 2016; Smith 2016). We did not plan to include people with conditions caused by COPD treatments, such as pneumonia, or ongoing conditions such as learning disability, sensory impairment such as sight or hearing loss, and alcohol and substance misuse.

Description of interventions

Interventions (treatments) for people with COPD are either aimed at helping them to manage the symptoms of COPD in day-to-day life, or are treatment of exacerbations (flare-ups). For treating the symptoms, there are drugs including inhaled therapies (such as long-acting beta$_2$-agonists, long-acting muscarinic antagonists, and inhaled corticosteroids), phosphodiesterases and antibiotics, as well as physical interventions such as pulmonary rehabilitation, physical therapy (e.g. exercise), ventilation (e.g. non-invasive ventilation (NIV)). For treating exacerbations, there are inhaled therapies, antibiotics and ventilation.

In this review we looked at COPD interventions which target the comorbidity, and interventions for the overall management of people with COPD and one or more comorbidities.

We created a framework from the GOLD 2021 guidelines and the Cochrane Airways subtopic list, from which we intend to create an evidence (gap) map and use it as a basis for the analysis (Table 2).

How will the intervention work?

Long-term conditions other than COPD may interfere with the delivery of the COPD intervention. An example of people with comorbid COPD engaging with an intervention differently from those with COPD alone is seen in pulmonary rehabilitation, one of the more effective treatments for people with COPD (McCarthy 2015). Researchers have shown that people with comorbid COPD are more likely than people with COPD alone to either decline to enrol for treatment or, once enrolled, to drop out of the programme or not attend sessions regularly (Fischer 2009; Hayton 2013; Keating 2011). People are more likely to drop out of pulmonary rehabilitation programmes as a result of symptoms of other comorbidities (Blackstock 2018). Furthermore, researchers have evaluated the impact of co-existing conditions on outcomes of a pulmonary rehabilitation intervention for people with COPD which showed that, depending on the co-existing condition, pulmonary rehabilitation outcomes can be positive or negative (Carreiro 2013; Crisafulli 2008; Holland 2016; Walsh 2013). Targeted interventions can help people take part in pulmonary rehabilitation programmes: a targeted water-based exercise component of a pulmonary rehabilitation programme was shown to be more effective than land-based exercise (McNamara 2013a). We therefore

intend to summarise evidence from randomised controlled trials (RCTs) which target a COPD intervention to take account of another comorbidity.

People with multimorbidities may be taking multiple drugs for each individual condition; for example, prescribed drugs, over-the-counter treatments, herbal remedies or dietary supplements. This is called polypharmacy and 16.4% of people over the age of 65 years are estimated to be taking 10 or more treatments each day (Duerden 2013; Guthrie 2012). This can lead to unfavourable drug interactions and practical issues with remembering to take so many medications in a day. We will include interventions which help people adapt to taking multiple medications; we will not, however, be looking at polypharmacy interventions which aim to optimise a person's drugs and reduce harmful drug interactions.

People with multimorbidities may also have to see many healthcare professionals (HCPs) to help them with various different elements of their different long-term conditions. We will include trials which aim to streamline (or simplify) this care in some way, to make it easier or better for the patient. These might include, for example, putting a patient under the care of one particular consultant who works across several hospital departments, thereby providing a holistic package of care. It may include a hospital putting together an integrated disease management programme — a map of a patient's journey for managing their condition in a particular location. We will also consider simpler interventions such as running COPD and cardiovascular clinics on the same day to reduce the number of attendances at hospital.

Anxiety and depression are common in people with COPD. Pharmacological and psychological interventions aimed at treating the anxiety and depression are explored in a suite of Cochrane Reviews (Pollok 2018; Pollok 2019; Usmani 2011; Usmani 2017). Because the interventions are treating the comorbidity rather than the COPD, we do not include them in this review. We will also not include studies of people with COPD who have symptoms of depression or anxiety as the sole comorbidity.

We have been unable to update a draft logic model that we presented in the protocol for this review (Figure 1, Janjua 2019), due to limited evidence found. As a result, we were unable to take this forward to our Cochrane Airways Patient Advisory Group and Programme Grant Steering Group for their consideration.

Figure 1. Study flow diagram for randomised controlled trials

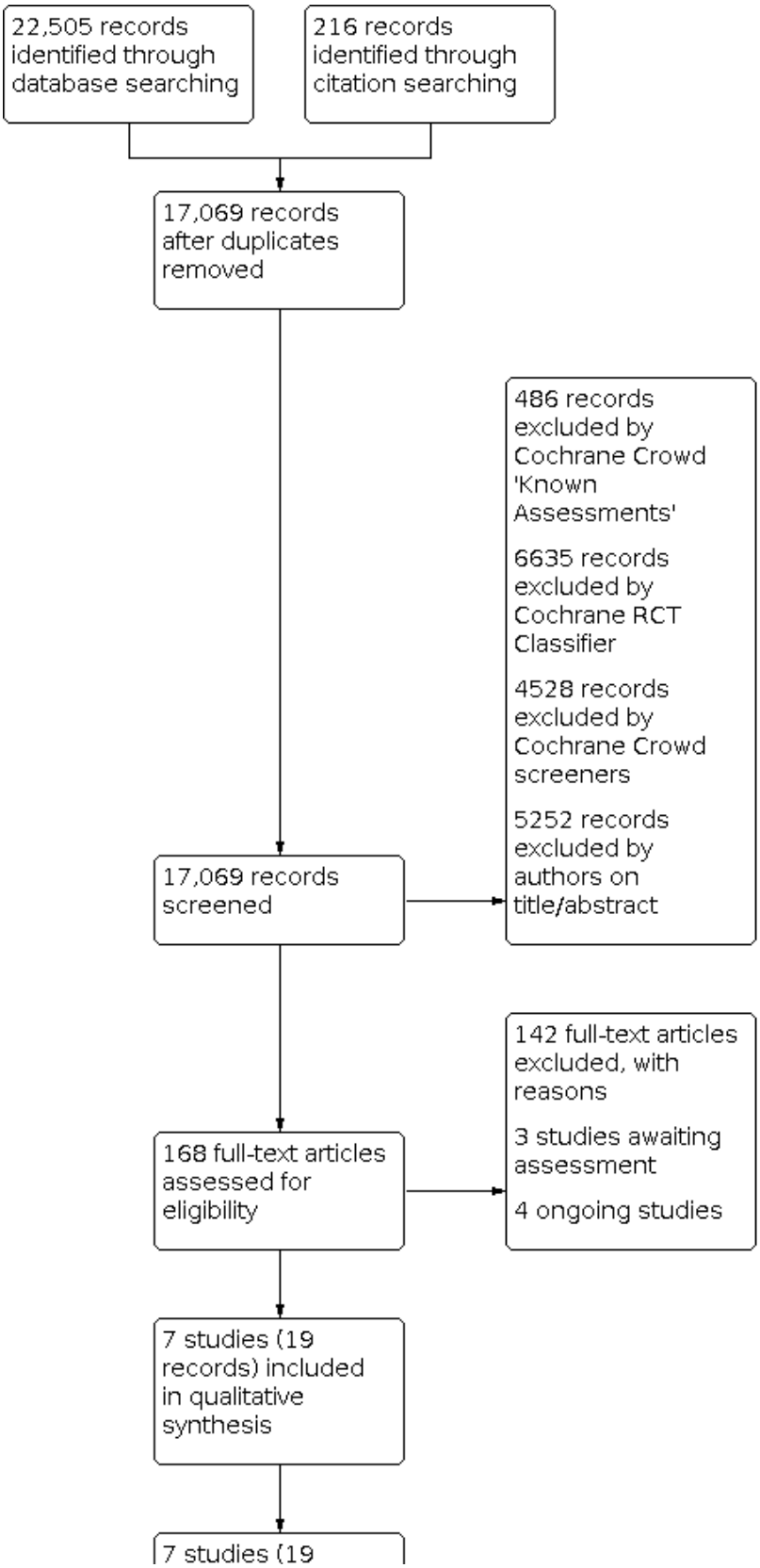
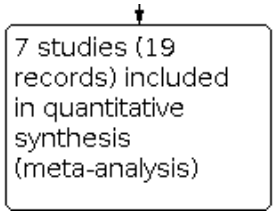


Figure 1. (Continued)



Why is it important to do this review?

Most clinical trials are designed to involve people with one condition, and exclude people with multimorbidities — which may represent well over half of people who live with COPD. Systematic reviews, including Cochrane Reviews, have therefore also traditionally focused on these patients, rather than including a sample representing the true population. This means that most studies may not be applicable to people with more than one chronic condition: for example, trials may only enrol people with COPD and may exclude people with asthma or heart disease. This means that we cannot be confident about applying the results of the trial to people with COPD and asthma, or people with COPD and heart disease.

There is a substantial health burden for people living with COPD and multimorbidities, with associated cost implications due to an increased need for hospital utilisation compared to those who only have one condition (Chen 2017). People living with multimorbidity may also have to manage several symptoms, to adhere to multiple drug regimens and various lifestyle recommendations, all while attending appointments with different HCPs (Smith 2016). Healthcare services experience higher demands as people with multimorbidities require more frequent complex care (Barnett 2012; Rijken 2018), and these services can be fragmented (Smith 2016).

Policy-makers are increasingly aware that overall care for people with multimorbidities needs to be patient-centred (i.e. care that takes a person's needs into account, either via individual preference, or by involving the person in making decisions about their care) and integrated (i.e. organisations and staff working together to provide seamless care through processes that are flexible and continuous) (Rijken 2016).

In addition, guidance for managing multimorbidities is limited because of the potential exclusion from clinical trials of people living with multimorbidity. The systematic failure of clinical trials to include people living with multimorbidity leads to care strategies that may not be suitable or helpful for most people with COPD (Wyatt 2014). For example, multiple prescriptions (polypharmacy) can lead to potential interactions between conditions and medication resulting in inadequate and complex choices of treatment in terms of benefit and harm (Sinnot 2013; Muth 2018), or fragmented and poorly co-ordinated care packages can lead to complications such as over-hospitalisation when managing patients with multimorbidities (Sinnot 2013; Rijken 2016).

We have decided to undertake this review because the Cochrane Airways Patient Advisory Group and Programme Grant Steering Group considered this to be an important topic to be reviewed for a programme of Cochrane Airways Reviews funded by the National Institute for Health Research. The patients and HCPs agreed that the systematic review should report information about the clinical effectiveness of interventions, and the views and experiences of those involved in managing multimorbidities and COPD, and identify gaps in the evidence. The review will address issues that are important for people with COPD who have co-existing conditions, as well as for HCPs and policy-makers. A scoping search of quantitative and qualitative evidence conducted prior to initiation of the protocol showed potentially eligible studies.

In comparison with a previous Cochrane Review (Smith 2016), we decided to take a mixed-methods approach to evaluate the evidence that exists for people living with COPD and at least one other chronic condition in this review, because of concerns that interventions begun with the best intentions may not always be helpful for patients. Combining both quantitative and qualitative data can provide a better understanding of why some interventions are successful and why others less so. This approach helps to add richness and depth to quantitative findings, which is not methodologically possible to do when interpreting quantitative data alone. It can identify areas where quantitative research may be lacking but appears to be important to patients, carers or health professionals (as identified from qualitative research). We identified studies conducted in a community or hospital setting and combined both quantitative data (numerical data from clinical trials), and qualitative data (non-numerical data from, for example, semi-structured interviews, focus group discussions and patient, carer or health professional observations). To illustrate: we are aware of a local example where people with COPD and heart disease have been put under a co-ordinated care regimen, but the patients have said they prefer separate appointments because they are shorter, and they like having a reason to get out of the house.

We deliberately left the types of intervention very broad (compared to Smith 2016), to reflect the reality of people living with COPD and other long-term health conditions in trying to make sense of a sparse literature, who nonetheless need to make decisions about how to manage their own symptoms and daily life. The interventions aimed to address COPD rather than the full extent of multimorbidity.

OBJECTIVES

- To assess the effectiveness of any single intervention for COPD adapted or tailored to their comorbidity(s) compared to any other intervention for people with COPD and one or more common comorbidities (quantitative data, RCTs) in terms of the following outcomes: Quality of life, exacerbations, functional status, all-cause and respiratory-related hospital admissions, mortality, pain, and depression and anxiety.
- To assess the effectiveness of an adapted or tailored single COPD intervention (simple or complex) that is aimed at changing the management of people with COPD and one or more

common comorbidities (quantitative data, RCTs) compared to usual care in terms of the following outcomes: Quality of life, exacerbations, functional status, all-cause and respiratory-related hospital admissions, mortality, pain, and depression and anxiety.
- To identify emerging themes that describe the views and experiences of patients, carers and healthcare professionals when receiving or providing care to manage comorbidities (qualitative data).
- To use a mixed-methods approach to combine quantitative and qualitative data resulting from the first three objectives, provided that we find relevant data. If we find that we are unable to combine quantitative data and qualitative textual themes, we will present the data and themes separately.

METHODS

Types of studies

We included the following study designs to address the objectives of this review.

- Randomised controlled trials (RCTs) to assess effectiveness of interventions (quantitative data).
- Qualitative studies of any design, including in-depth interviews, semi-structured interviews, focus group discussion, observations, and surveys that explore views, opinions and experiences of people with comorbid COPD, their carers and health professionals involved in provision of care.
- Mixed-methods studies (RCTs that also include a qualitative study as part of their investigations).

Types of participants

We included adults with a primary diagnosis of COPD of any severity (e.g. Global Initiative for Chronic Obstructive Lung Disease (GOLD), or American Thoracic Society (ATS) criteria), with at least one other long-term condition (e.g. asthma, coronary heart disease, diabetes, atrial fibrillation, heart failure, hypertension, stroke/transient Ischaemic attack, lung cancer or osteoporosis (Barnett 2012)).

We included people with COPD who also had anxiety or depression or both, but this was not permitted to be the only comorbidity.

We included studies involving carers and healthcare professionals (HCPs) when receiving or providing care to manage comorbidities.

Types of interventions

We included the following interventions for quantitative studies.

- Any single intervention for COPD delivered to people with COPD adapted to or targeting their comorbidity (or comorbidities) (e.g. participants receiving a pulmonary rehabilitation programme tailored to take account of their comorbidities by delivering the exercise component in water rather than out of water (McNamara 2013a)) compared to any other intervention. We envisage these interventions being broken into the following categories of interventions.
  * Pulmonary rehabilitation.
  * Self-management.
  * Exercise or other physical therapy.
  * Ventilation.
  * Pharmacotherapy (e.g. change of inhaler).
- Any intervention aimed at changing the management of people with COPD and one (or more) co-existing long-term condition(s), which could be simple (e.g. scheduling COPD and heart clinics on the same day) or more complex (e.g. developing an integrated care package for management of people with COPD in a particular hospital and providing training to staff to deliver it), compared to routine care (or usual care, control, or no intervention). We envisage these interventions being broken into the following categories of interventions.
  * Organisation-wide interventions (such as introducing a new care pathway).
  * Simple changes within the organisation (such as scheduling relevant clinics on the same day).
  * Interventions across a wider area (such as integration between GP, hospital and pharmacy).

We included interventions delivered in primary (community) or secondary (hospital) care.

We excluded studies of interventions for the comorbidity (e.g. heart surgery).

We excluded studies of pharmacological or psychological interventions that targeted anxiety or depression or both rather than COPD (previous Cochrane Reviews have, for example, included COPD patients with either anxiety (Usmani 2017), depression (Pollok 2018; Pollok 2019), or both anxiety and depression (Usmani 2011)).

We excluded interventions that were designed to reduce the number of prescribed medicines or interactions between them (polypharmacy), but we planned to include interventions that aim to help people to manage polypharmacy.

We excluded interventions delivered to HCPs.

We included qualitative studies that explored the experiences of participants, carers and HCPs, taking part in the above interventions.

Types of outcome measures

We included the following outcomes for quantitative analysis.

Primary outcomes

- Quality of life (e.g. St. George's Respiratory Questionnaire (SGRQ), COPD assessment test (CAT))
- Exacerbations (as defined by trialists, depending on the data available, we extracted either number of participants experiencing one or more exacerbation, or the exacerbation rate, or both)

Secondary outcomes

- Functional status (6-minute walk distance (6MWD)/incremental shuttle walk test (ISWT))
- All-cause hospital admissions (also as a proxy for use of services, e.g. reduction of use)
- Respiratory hospital admissions
- Mortality (all causes)

- Pain (as reported in trials)
- Anxiety symptoms (measured by e.g. Hospital Anxiety and Depression Scale (HADS))
- Depression symptoms (measured by e.g. HADS)

For the planned qualitative synthesis, our outcomes were themes arising from the data.

We included studies regardless of whether they report our predefined outcomes.

There was no minimum duration for the interventions, and we used data reported for the last follow-up point.

Search methods for identification of studies

Electronic searches

We searched for studies in June 2019, February 2020, and January 2021 in the following databases and trials registries:

- Cochrane Airways Register of Trials through the CRS, from inception onwards;
- Cochrane Central Register of Controlled Trials (CENTRAL, in the Cochrane Library) through the Cochrane Register of Studies (CRS), from inception onwards;
- MEDLINE Ovid SP from 1946 onwards;
- Embase Ovid from 1974 onwards;
- PsycINFO Ovid Sp from 1974 onwards;
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) from 1937 onwards;
- Web of Science Core Collection from 1970 onwards;
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov;
- World Health Organization International Clinical Trials Registry Platform (ICTRP).

Searches for qualitative and quantitative studies were run separately using appropriate study design filters. We combined search terms for the target population with the Cochrane Highly Sensitive Search Strategy to identify reports of RCTs (Lefebvre 2021), and terms from the search strategies developed and tested by DeJean 2016 to find reports of qualitative studies. The search was developed in MEDLINE by ES, with input from the other authors, and was peer-reviewed by another Information Specialist using the PRESS checklist (McGowan 2016). The MEDLINE search strategy was adapted appropriately for use in the other databases. We did not apply any language limits, and we did not limit the search strategy by population characteristics such as age, gender, or race. Details of the database search strategies, search dates, and the number of results retrieved are presented in Appendix 1.

We initially searched all databases from their inception to June 2019. We updated the searches in February 2020 and January 2021 in a reduced number of databases (Appendix 2) following an analysis of the individual database yield of eligible study references.

Searching other resources

We conducted a forwards and backwards citation search in Web of Science for each included study on 15 May 2020 (RCTs) and 5 June 2020 (qualitative studies).

We checked the reference lists of related review articles for additional references. We used the Epistemonikos database to search for relevant systematic reviews (www.epistemonikos.org).

We searched for errata or retractions from included studies published in full text on PubMed on 4 December 2020.

Data collection and analysis

Selection of studies

We retrieved many search results, and we therefore used Cochrane's 'Screen4Me' workflow to help assess the results of our search for RCTs. Screen4Me comprises three components: known assessments — a service that matches records in the search results to records that have already been screened in Cochrane Crowd and have been labelled as 'RCT' or as 'Not an RCT'; the RCT classifier — a machine-learning model that distinguishes RCTs from non-RCTs (Marshall 2018); and if appropriate, Cochrane Crowd — Cochrane's citizen science platform where 'the crowd' help to identify and describe health evidence (Noel-Storr 2020).

Following use of the Screen4Me workflow, two of three review authors (SJ, ES and ED) screened each title and abstract of the remaining search results independently and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports of all potentially eligible studies and two of three review authors (SJ, ES and ED) independently screened each full text for inclusion, and recorded the reasons for exclusion of ineligible studies.

We resolved any disagreement through discussion or, if required, we consulted a third review author (SH). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009).

Data extraction and management

Three authors (SJ, ED, ES) screened citations in Covidence. One review author (SJ) piloted the data extraction form on at least one quantitative and one qualitative study before we extracted data from the rest of the included studies. We extracted data into a Microsoft Excel spreadsheet.

Quantitative studies

Three review authors extracted the following study characteristics from included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
- Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected (e.g. confidence intervals, P values, measurement scales used), and time points reported. Definitions used to diagnose an exacerbation were sought and recorded.

- Notes: funding for studies and notable conflicts of interest of trial authors.

Three review authors (SJ, ES and ED) independently extracted outcome data from included studies. We planned to note in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third person/review author (SH). One review author (ED) transferred quantitative data into the Review Manager 5 (RevMan 5) file (Review Manager 2020). We double-checked that data are entered correctly by comparing the data presented in the review with the study reports. A second review author (SJ) spot-checked study characteristics for accuracy against the study report, and results were also checked by the Cochrane Airways Group statistician.

Qualitative studies

In order to capture context, two review authors (from SJ, ES, ED) extracted the following study characteristics from included studies.

- Study details: country, study type (e.g. focus group, semi-structured interviews, structured interviews, surveys), dates, source of funding, objectives.
- Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
- Methods: sampling, setting (e.g. community or hospital), data collection (e.g. how the authors conducted the study, length of interviews, whether interviews were recorded, use of interview guide, data collected until achievement of thematic saturation), data analysis (e.g. method of analysis of transcripts, framework used, coding, thematic map).
- Results: authors' interpretations, quotes from participants provided by authors.

Assessment of risk of bias

Quantitative studies

Three review authors (SJ, ES and ED) assessed risks of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another author (SH). We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other potential bias.

We judged each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from a patient-reported quality-of-life scale). We planned to note where information on risk of bias was from unpublished data or correspondence with a trialist, but we decided not to contact trial authors for clarification or unpublished data. When considering treatment effects, we took into account the risk of bias for the studies that contribute to that outcome via GRADE assessment of the certainty of the evidence (see below).

We presented a risk of bias table for all studies.

Qualitative studies

Two review authors (SJ, SH) assessed risk of bias independently for each study using the criteria outlined by the Cochrane Quality and Intervention Methods Group (Hannes 2011). We resolved any disagreements by discussion or by involving another review author (AH). We assessed the risk of bias according to the following criteria.

- Quality of reporting (explicitness in reporting of all study aspects).
- Methodological rigour (validity and reliability of study design and process).
- Conceptual depth and breadth (are reported aims, rationale or theory reflected in the study design, process and findings?).

We used the Critical Appraisal Skills Programme (CASP) checklist (Critical Appraisal Skills Programme 2018) to assess risk of bias. We present risk of bias of studies in a table.

We assessed the risk of bias after the identification of relevant data to help us make judgements about the relative strength of messages in the included research.

Mixed-methods studies

We planned to use the Mixed Methods Appraisal Tool (MMAT) to assess risk of bias (Hong 2018; Pluye 2011). Two review authors (SJ and ED) would have assessed risk of bias independently for each study using the criteria outlined by the MMAT. We planned to resolve any disagreements by discussion or by involving another author (SH). We planned to assess the risk of bias according to the following criteria.

- Is there an adequate rationale for using a mixed-methods design to address the research question?
- Are the different components of the study effectively integrated to answer the research question?
- Are the outputs of the integration of qualitative and quantitative components adequately addressed?
- Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?
- Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?

Measurement of treatment effect

Quantitative treatment effects

We analysed dichotomous data as an odds ratios (OR) and continuous data as the mean difference (MD) or standardised mean difference (SMD). Where data from rating scales were combined in a meta-analysis, we ensured they were entered with a consistent direction of effect (e.g. lower scores always indicate improvement). We undertook meta-analyses only where this was meaningful: that is, if the treatments, participants and the underlying clinical

question were similar enough for pooling to make sense. Where we encountered substantial statistical or clinical heterogeneity, we presented data in graphs, but did not pool them. We described skewed data narratively (for example, as medians and interquartile ranges for each group).

Where multiple trial arms were reported in a single study, we included only the relevant arms for either comparison. Where two comparisons (e.g. intervention A versus intervention B) were combined in the same meta-analysis, we planned to either combine the active arms or halve the control group to avoid double-counting, but this was not necessary. If adjusted analyses were available (ANOVA or ANCOVA), we used these as a preference in our meta-analyses. If both change from baseline and endpoint scores were available for continuous data, we used change from baseline unless there was low correlation between measurements in individuals. Where studies reported outcomes at multiple time points, we used endpoint data. We used intention-to-treat (ITT) or 'full analysis set' analyses where they were reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per protocol analyses.

Unit of analysis issues

Quantitative analysis

For dichotomous outcomes, we used participants, rather than events, as the unit of analysis. Where rate ratios were reported in a study, we planned to analyse them on this basis. We planned to meta-analyse data from cluster-RCTs where data had been adjusted (or could be adjusted by us), to account for the clustering.

Dealing with missing data

We planned to contact investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data (e.g. when a study is identified as an abstract only), however when conducting the review, we decided not to contact authors for missing data.

Assessment of certainty of evidence

Quantitative data

We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence as it relates to the following outcomes: Quality of life (SGRQ and CAT), exacerbations, functional status (6MWD), all-cause hospital admissions, all-cause mortality, anxiety and depression (unfortunately we did not specify these a priori). We used the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), using GRADEpro GDT software (GRADEpro GDT; Guyatt 2008). We justified all decisions to downgrade the quality of studies in the footnotes of the table, and made comments to aid the reader's understanding of the results where necessary. We presented GRADE findings in a summary of findings table.

Qualitative data

We used the GRADE Confidence in the Evidence from Reviews of Qualitative Research (CERQual) approach to assess our confidence in the evidence of effectiveness arising from studies evaluating interventions (Lewin 2015). One review author (SJ) did this independently and Jane Noyes (from the Cochrane Qualitative and Implementation methods group) checked the completed assessment separately. This assessment allowed us to make judgements on the following four domains.

- Methodological limitations of included studies.
- Relevance of contributing studies to the research question.
- Coherence of study findings.
- Adequacy of data supporting the study findings.

We used the methods and recommendations described in Chapter 21 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We summarised findings of the four domains for each outcome in a CERQual Qualitative Evidence Profile (Lewin 2015). We rated the overall assessment of confidence of evidence as high, moderate, low or very low. We presented CERQual findings in a summary of findings table (Glenton 2020). We justified all decisions to downgrade the quality of studies in the footnotes of the table, and we made comments to aid the reader's understanding of the review where necessary.

Assessment of heterogeneity

Quantitative data

We used the I^2 statistic to measure heterogeneity among the studies in each analysis where possible. We conducted a meta-analysis using a random-effects model, as the interventions were varied. We explored possible causes of heterogeneity.

We considered the following I^2 ranges in the analyses (Deeks 2021).

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

We checked all data where we encountered substantial statistical heterogeneity. We did not pool data where there was substantial heterogeneity.

Assessment of reporting bias

Quantitative data

If we had been able to pool more than 10 studies, we planned to create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

Quantitative data

We used RevMan 5 and RevManWeb to perform quantitative data syntheses (meta-analyses) (Review Manager 2020); and where data for population or interventions were similar, we pooled such data. Where we felt it was not appropriate to pool data, we present the data in forest plots to show the range of effect sizes where possible. Where we found clinical heterogeneity within the studies we identified, we grouped studies according to interventions and outcomes, and used the random-effects model in the analyses (Ioannidis 2008). Where it was not possible to perform a meta-analysis, we considered presenting data graphically and narratively using recommendations in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Qualitative data

Where studies were similar in design we planned to synthesise their data using a thematic analysis (Thomas 2008). This method would have allowed us to identify important or recurrent themes that arise from studies and summarise them under thematic headings. We planned to tabulate information, allowing identification of prominent themes and offer structured ways of dealing with the data in each theme. This type of synthesis would have helped us to identify emerging themes that described the experiences of participants, carers and HCPs when receiving or providing care to manage comorbid COPD.

We planned to initially analyse carer and HCP data separately to identify, for example, conflicting views or experiences. If we had found that the views and experiences had been similar, we planned to combine the two subgroups in subsequent syntheses.

Combining quantitative and qualitative data

We planned to use the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions,* and methods outlined by the Cochrane Qualitative and Implementation Methods Group (Higgins 2021 and Harden 2018, respectively). There are two main approaches to integrating qualitative and quantitative data: sequential and convergent. The sequential approach involves synthesising qualitative and quantitative analyses separately, followed by using common frameworks to integrate the findings across syntheses. We planned to use the sequential approach to integrate qualitative data to explain quantitative findings. We planned to analyse quantitative data at the first stage, followed by synthesis of qualitative data in the second stage.

Integrating the qualitative syntheses with the quantitative analyses can be achieved by using a 'matrix' to compare and contrast findings across both types of evidence. The matrix will help to identify gaps in the evidence. This approach can help us to understand why heterogeneity exists that we may find in the quantitative analyses. Other approaches include the development of a 'logic model' by providing a common framework within which both quantitative and qualitative evidence can contribute (Harden 2018). We acknowledge that the methods for integration are dependent on the quantity of studies and extracted evidence available, and quality of description within included studies (e.g. intervention content, context, and study findings). For divergent data (qualitative data that does not match the quantitative data), we aimed to resolve divergence (deviation of the qualitative data from the quantitative data, or vice versa (Erzberger 1997)) where possible by providing a narrative explanation according to research and knowledge of the topic area.

Subgroup and investigation of heterogeneity

We investigated clinical heterogeneity in the quantitative studies. We planned to perform subgroup analyses using the following prespecified groups, but we used the subgroup function in RevMan to present data by intervention type, and did not complete the following subgroup analysis due to lack of a sufficient number of studies.

- Number of comorbidities in addition to COPD (≤ 2 conditions versus ≥ 3 conditions).
- Duration of intervention (< 3 months versus ≥ 3 months).

We planned to use the following outcomes in the subgroup analyses.

- Quality of life.
- Functional status.
- Hospital admissions.
- Exacerbations.

We planned to use the formal test for subgroup interactions in Review Manager 5 (Review Manager 2020).

Sensitivity analysis

We planed to carry out sensitivity analyses excluding studies in which one or more risk of bias domains is judged to be at high risk of bias.

Assessment of bias conducting the systematic review

We conducted the review according to our published protocol and justified any deviations from it in the 'Differences between protocol and review' section.

Review author reflexivity

We maintained a reflexive stance throughout the stages of the review process, from study selection to data syntheses. Progress was discussed regularly among the team and decisions made were discussed critically. As a review author team, our expertise has been listed in Contributions of authors. Based on our collective and individual experiences as clinicians, academics and researchers, we anticipated that the findings of our review would identify a combination of organisational, professional and individual factors influencing the implementation of targeted interventions and approaches to care for people with COPD to manage comorbidities. ED has overseen progress of the review, a process that has allowed her to document and reflect on any decisions made.

RESULTS

Description of studies

Results of the search

Quantitative studies

The literature search run on 8 January 2021 for reports of RCTs identified a total of 17,069 search results after duplicates were removed. We used Cochrane's Screen4Me workflow to help identify potential reports of randomised trials: 486 records were excluded by Cochrane Crowd Known Assessments, 6635 records were excluded by the Cochrane RCT Classifier, and 4528 records were excluded by Cochrane Crowd screeners After this initial assessment, we screened the remaining 5420 records and excluded 5252 records after reading the titles and abstracts. We obtained 168 articles for full-text review, excluded 142 of these with reasons (see Characteristics of excluded studies), and identified three studies that require further assessment (Characteristics of studies awaiting classification).

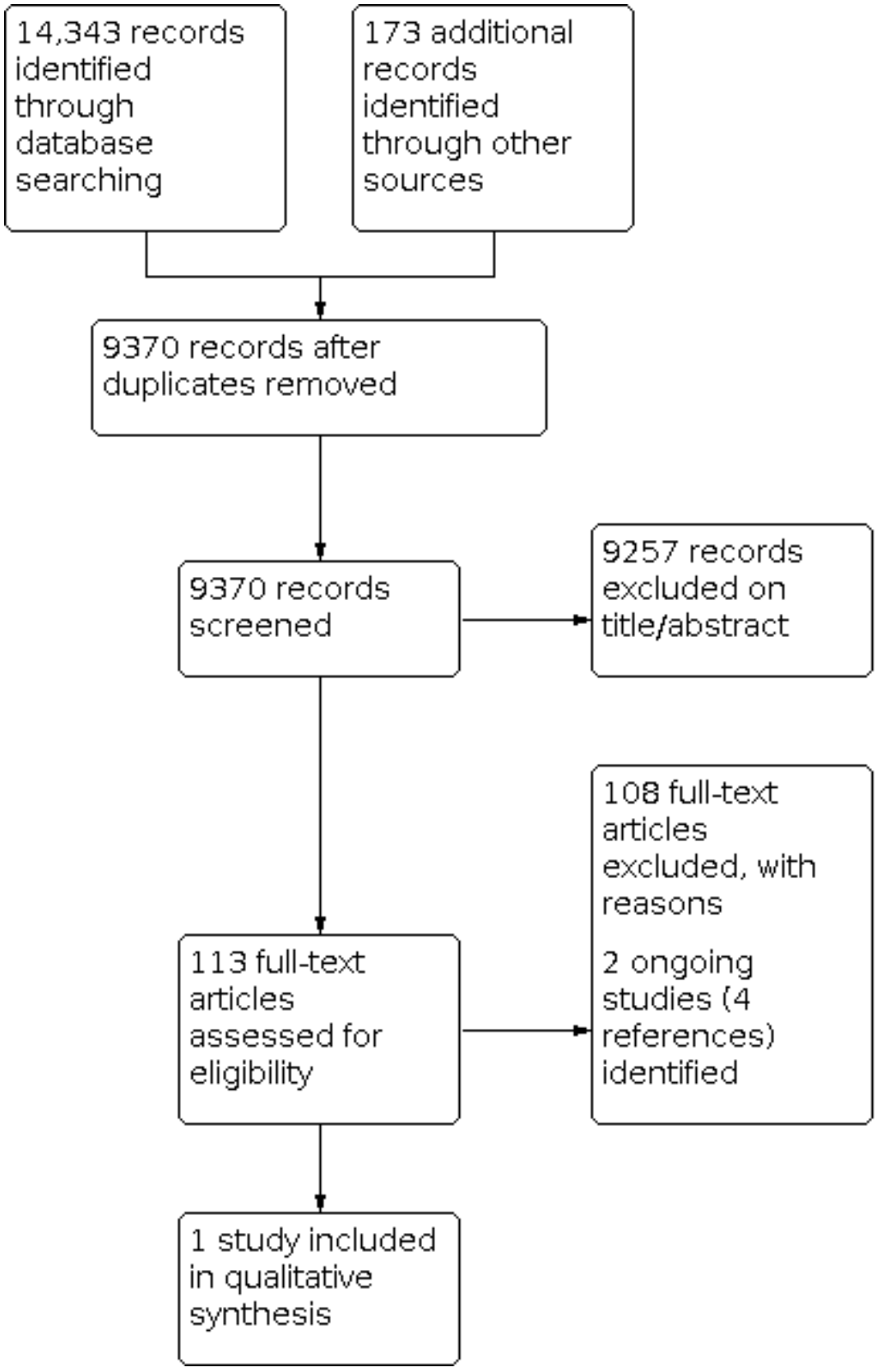
We included seven studies (19 references) and found a further four ongoing studies (Characteristics of ongoing studies). See Figure 1 for an overview of the study selection process.

Qualitative studies

The search for qualitative studies, run on 8 January 2021, identified a total of 9370 search results after duplicates were removed. We excluded 9257 records after reading the titles and abstracts, and obtained 113 articles for full-text assessment. We excluded 108 records with reasons (Characteristics of excluded studies) and identified two ongoing studies (four references), one of which is an ongoing RCT with a planned qualitative element (Characteristics of ongoing studies).

We included one study in the qualitative synthesis. See Figure 2 for an overview of the study selection process for qualitative studies.

Figure 2. Study flow diagram for qualitative studies



Included studies

Quantitative

We included seven studies in the quantitative synthesis. An overview of the study characteristics is given in Table 3.

Participants

Participants in included studies had COPD that ranged from mild to very severe. The studies involved people with a range of comorbidities. Three studies accepted people with COPD plus one or more of a range of specified comorbidities (McNamara 2013b; Rose 2018; Walker 2018). The participants in McNamara 2013b had either musculoskeletal or neurological comorbidities, or obesity. Participants in Rose 2018 had two or more comorbidities. The most common comorbid conditions were cardiovascular disease, diabetes, osteopenia/osteoporosis, and depression. Walker 2018 included participants with one or more comorbid conditions including hyperlipidaemia, diabetes, congestive heart failure and/or ischaemic heart disease, sleep-disordered breathing and osteoporosis. The other four studies included people with COPD plus one specific comorbidity: lung cancer (EUCTR2010-021412-42-GB); lung cancer, or head and neck cancer (Gottlieb 2020); cardiovascular disease (Bernocchi 2018), and metabolic syndrome (Budnevskiy 2015). See Table 4 for more information.

The proportion of men in the studies ranged from 28% to 88%. Mean age ranged from 67 to 72 year. Ethnicity was not reported in the studies.

Interventions

Two studies delivered pharmacological interventions. EUCTR2010-021412-42-GB compared inhaler optimisation plus usual care, with usual care alone. EUCTR2010-021412-42-GB tailored the intervention by considering the poor prognosis of participants with co-existing lung cancer, and the intervention group was given the maximum inhaled therapy. Gottlieb 2020 optimised the COPD treatment for the intervention group while the control group received usual care; the tailoring element was that the therapy was re-considered at each six-monthly visit.

Two studies delivered a rehabilitation intervention. Budnevskiy 2015 compared a pulmonary rehabilitation programme, where the exercises took into account metabolic syndrome comorbidity, and included education, physical training and nutritional recommendations, versus usual care. McNamara 2013b compared water-based exercise training with land-based exercise training or usual care. The tailoring element was that the exercises were carried out in water, which provides more support to people's bodies, and participants were able to choose the most comfortable level of water immersion. We used both comparisons in the review in separate comparisons (water- vs land-based training and water-based training versus usual care).

Two studies were categorised under organisation of care. Rose 2018 assigned case-managers to deliver case management and this group was compared to usual care. Case-managers tailored the intervention to the individual by providing an individualised action plan. Walker 2018 compared telemonitoring with usual care. Participants in the treatment arm were given a wearable device and used the CHROMED monitoring platform, and there was a nested qualitative study that collected feedback from participants, researchers and HCPs in the study (Middlemass 2017).

All participants in Bernocchi 2018 received inpatient rehabilitation, then people were randomised to a package of care (including personalised discharge, nurse telephone support and telemonitoring, physiotherapist-personalised maintenance rehabilitation) or usual care.

Setting

Four of the seven studies were conduced in single-centre hospital-based settings from Australia (McNamara 2013b), Denmark (Gottlieb 2020), Russia (Budnevskiy 2015), and United Kingdom (EUCTR2010-021412-42-GB). Three were multicentre studies, one based in two community teaching hospitals in Canada (Rose 2018), one based in three centres (respiratory, cardiology and telemedicine) in Italy (Bernocchi 2018), and one in multiple centres in Estonia, Slovenia, Spain, Sweden and United Kingdom (Walker 2018).

Study design

Six of the studies were parallel RCTs, plus one RCT (Walker 2018), which included a nested qualitative study of a subset of the participants and people involved in running the study (Middlemass 2017).

Trial duration

The duration of the trials ranged from 4 to 52 weeks (Table 5). We used the data from the latest endpoint in those studies that reported multiple time points during the intervention duration (Bernocchi 2018; EUCTR2010-021412-42-GB; Gottlieb 2020; Rose 2018). The remaining studies reported outcome data at the end of the intervention (Budnevskiy 2015; McNamara 2013b; Walker 2018). None of the studies reported follow-up data after the intervention was stopped.

Outcomes

The studies reported a range of outcomes, summarised in Table 5. Briefly, measures of all-cause hospitalisations were reported by Bernocchi 2018, Rose 2018 and Walker 2018. Two studies reported functional status (Bernocchi 2018; McNamara 2013b). All seven studies reported one or more measures of quality of life (Bernocchi 2018; Budnevskiy 2015; EUCTR2010-021412-42-GB; Gottlieb 2020; McNamara 2013b; Rose 2018; Walker 2018) (Table 5).

Qualitative

We included one study in the qualitative synthesis. An overview of the study characteristics is given in Characteristics of included studies table.

Participants

Twenty-one participants with severe COPD aged between 60 and 99 years and their partners or relatives if available, from the pilot study and a subset of the main intervention group in Walker 2018 were included in Middlemass 2017. Middlemass 2017 did not report the participants' comorbidities. However, the CHROMED RCT linked to this publication included people with COPD who had one or more comorbidities (congestive heart failure and/or ischaemic heart disease hypertension, sleep-related disordered breathing, osteoporosis, or hyperlipidaemia) (Walker 2018).

Interventions

Middlemass 2017 explored participants' perceptions of using telehealth equipment at home (those who were assigned to the intervention arm of Walker 2018).

Setting

Middlemass 2017 was a nested qualitative study linked to Walker 2018, and was based in participants' homes in Estonia, Italy, Norway, Slovenia, Spain, Sweden and United Kingdom (two sites).

Study design

Middlemass 2017 was an instrumental, collective study design that used qualitative interviews. They conducted a framework thematic analysis, using the Health Information Technology Acceptance Model (HITAM) as a guide.

Duration of study

Qualitative interviews were conducted once, shortly after the equipment was installed, and at the end of the study at 39 weeks.

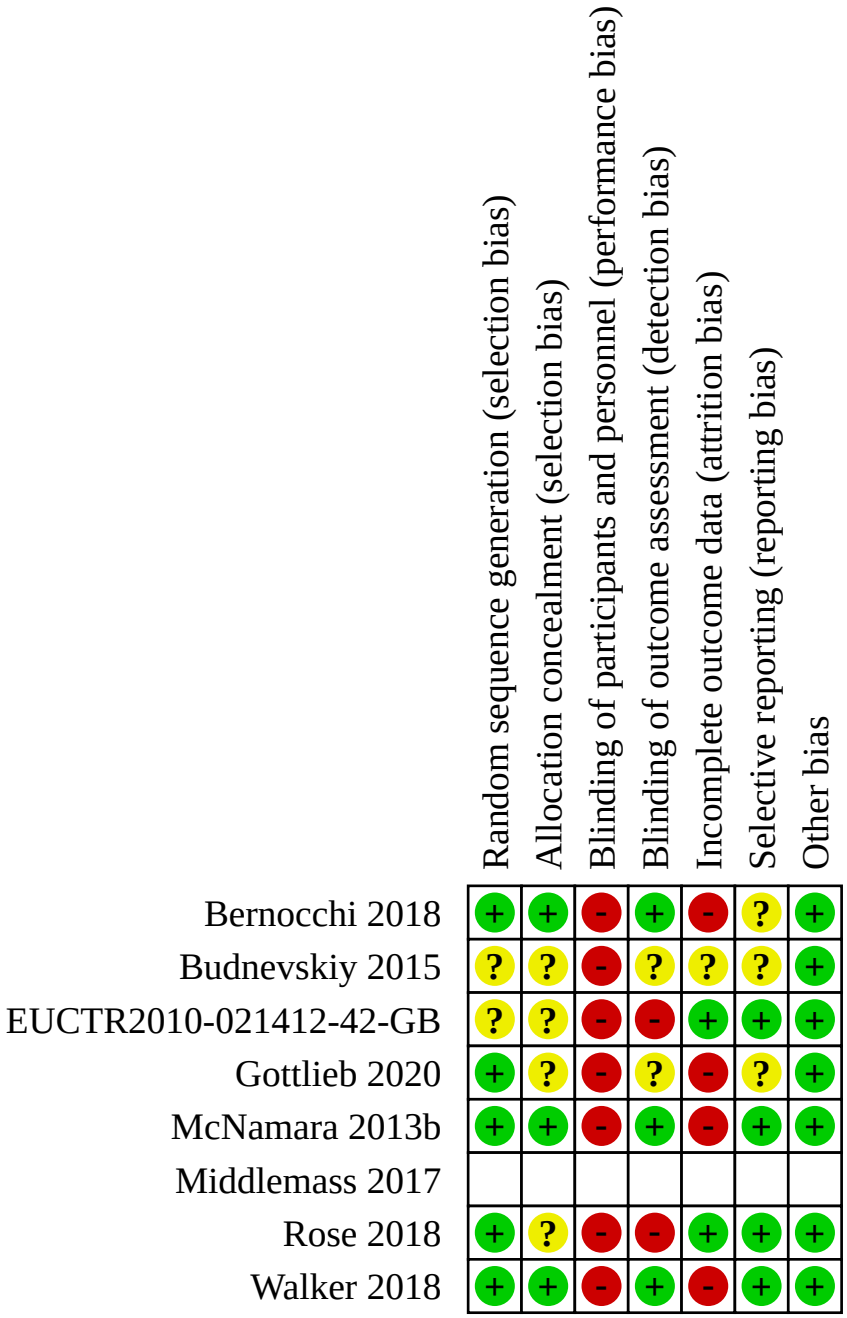
Themes

A range of themes are summarised in Table 6.

Risk of bias in included studies — quantitative

See Figure 3 for a summary of the risk of bias judgments.

Figure 3. Risk of bias summary



Allocation

We judged five studies to be at low risk of bias for random sequence generation (Bernocchi 2018; Gottlieb 2020; McNamara 2013b; Rose 2018; Walker 2018), while two were unclear (Budnevskiy 2015; EUCTR2010-021412-42-GB). We judged three studies to be at low risk of bias for allocation concealment (Bernocchi 2018; McNamara 2013b; Walker 2018), while four were judged to be at unclear risk of bias (Budnevskiy 2015; EUCTR2010-021412-42-GB; Gottlieb 2020; Rose 2018).

Blinding

Where the interventions involved a complex intervention such as pulmonary rehabilitation, case management or telemonitoring, it was not possible to blind participants or personnel because they would know whether they were receiving the intervention or not and were therefore judged to be at high risk of bias. This applied to most of the studies. The two studies that involved optimisation of medication (EUCTR2010-021412-42-GB; Gottlieb 2020), were run as open-label studies and so were also judged to be at high risk of bias.

Blinding of outcome assessors only protects studies if the participants are also blinded, or if outcomes are objective or not self-reported or both. So while we have awarded some low risk of bias, they may not be protected. Three studies explained that they blinded outcome assessors, earning them a low risk of bias assessment for this domain (Bernocchi 2018; McNamara 2013b; Walker 2018). While the reporting was not clear enough to make a judgement for two studies (Budnevskiy 2015; Gottlieb 2020), two studies did not blind the outcome assessors so they were judged to be at high risk of bias (EUCTR2010-021412-42-GB; Rose 2018).

Incomplete outcomes data

Incomplete outcome data relates to attrition or withdrawal from the study. Two studies had zero to low levels of dropouts (EUCTR2010-021412-42-GB; Rose 2018) and were judged at low risk of bias for this domain. One study did not provide any information on dropouts or how many people completed the study, so we judged the domain as unclear risk (Budnevskiy 2015). The remaining four studies were at high risk of bias for the following reasons; Bernocchi 2018 reported more dropouts in the control group compared to the intervention group (37.5% versus 19.6%); Gottlieb 2020 had a high loss to follow-up in both intervention and control groups (28% and 33% respectively), and McNamara 2013b reported more dropouts (25%) in the land-based training group because of exacerbation of comorbidity or loss of interest in the study. Sixteen per cent of participants in the water-based training group dropped out due to skin tear or general fatigue. Walker 2018 had high and unbalanced dropout rates and 5% withdrew as they could not use the equipment. Rose 2018 reported that missing data were problematic for their secondary outcomes measured at 52 weeks.

Selective reporting

Four studies were at low risk of bias because protocols were available and outcomes specified were reported in the full text (EUCTR2010-021412-42-GB; McNamara 2013b; Rose 2018; Walker 2018). One study was at unclear risk of bias because there was no published protocol (Gottlieb 2020) and two studies were at unclear risk because they did not report a standard deviation (SD) to accompany a mean for some outcomes (Budnevskiy 2015; Bernocchi 2018). We did not contact the authors because we did not think that clarifying this information would change the outcome of the review.

Other bias

We did not observe any other risks of bias.

Risk of bias in included studies — Qualitative

See Table 1 for critical appraisal of qualitative studies.

Overall, there were some concerns about risk of bias in Middlemass 2017. We could not be sure if the study design was justified in addressing the aims of the study. Similarly, methods for collecting the data may not have addressed the research question because it was not clear if the interviews were in-depth or semi-structured. There was no justification provided for using interviews rather than focus groups. Authors did not provide details on data saturation. The researcher and participant relationship was not considered, as the role of the interviewer was not examined. We did not have any concerns with ethical issues as they had been taken into consideration. The data analysis was rigorous and the process was well described. There was a clear statement of findings which were explicit and well organised.

Effects of the interventions - quantitative

For an overall summary, see Summary of findings 1 and Summary of findings 2.

Intervention versus usual care

For this comparison we included seven studies with 1177 participants.

Quality of life (primary outcome)

Quality of life was reported in several studies using a range of measures: St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), Chronic Respiratory Disease Questionnaire (CRQ), Minnesota Living with Heart Failure Questionnaire (MLHFQ) and EuroQuol-5D VAS (EQ-5D).

In this comparison, we used water-based versus usual care for McNamara 2013b.

SGRQ

Two studies reported the SGRQ total (Budnevskiy 2015; Rose 2018). Budnevskiy 2015, a rehabilitation study of 70 participants, reported SGRQ total scores at 52 weeks follow-up. Uncertain evidence suggests that pulmonary rehabilitation may result in a decrease (improvement) in SGRQ score compared to usual care (mean difference (MD) −10.85, 95% confidence interval (CI) −12.66 to −9.04; low-certainty evidence; Analysis 1.1; Summary of findings 1).

The second study (Rose 2018) provided outpatient case management and reported on the SGRQ total score at 52 weeks follow-up. The mean difference of 4 was reported with a very tight confidence interval This is likely to overestimate the benefit of the intervention. There were also some discrepancies between the published and supplemental data. We therefore decided not to present the results graphically.

CAT

Four studies from four different categories of intervention reported the CAT total score; these were not pooled because the interventions were too diverse (Analysis 1.2).

One rehabilitation study (Budnevskiy 2015) showed that pulmonary rehabilitation probably improves quality CAT score at 52 weeks follow-up (MD −8.02, 95% CI −9.44 to −6.60; moderate-certainty evidence; Analysis 1.2; Summary of findings 1). The multicomponent telehealth intervention trialled in Bernocchi 2018 probably improves CAT score at 17 weeks follow-up (MD −6.90, 95% CI −9.56 to −4.24; moderate-certainty evidence; Analysis 1.2;

Summary of findings 1). Evidence is uncertain about effects of pharmacotherapy optimisation or telemonitoring interventions on quality of life as there is little to no difference in effect compared to usual care at 25 weeks (MD 0.00, 95% CI −3.40 to 3.40) or at 39 weeks follow-up (MD −0.41, 95% CI −2.19 to 1.37) respectively (Walker 2018; Gottlieb 2020) (low-certainty evidence; Analysis 1.2; Summary of findings 1).

CRQ domains (dyspnoea, fatigue, emotion, mastery)

One study reported results from the CRQ which was presented as the four subdomains rather than an overall domain (McNamara 2013b; Analysis 1.3). Water-based exercise training may offer a slight improvement in quality of life, as measured by CRQ dyspnoea (MD 3.25, 95% CI 0.90 to 5.60; 1 study, 33 participants), fatigue (MD 4.70, 95% CI 2.40 to 7.00), and emotion (MD 3.10, 95% CI 0.10 to 6.10) domains, compared with usual care at eight weeks follow-up. There may be little of no difference in the mastery domain (MD 1.90, 95% CI −0.20 to 4.00).

MLHFQ

One study (Bernocchi 2018) reported on the MLHFQ and showed that a targeted multicomponent intervention may result in a small but clinically insignificant improvement in this outcome at 17 weeks follow-up (MD −10.06, 95% CI −16.27 to −3.85; 92 participants; Analysis 1.4). The minimal clinically important difference (MCID) is 45 (Behlouli 2009).

EQ-5D

One study reported on the EQ-5D, but reported two scores, the VAS and the utility domain (Walker 2018). For both scores on the standardised mean difference (SMD) scale, there is little to no difference in the effect of targeted interventions on VAS (SMD −0.02, 95% CI −0.24 to 0.20; 303 participants; Analysis 1.5) or utility scores (MD −0.01, 95% CI −0.23 to 0.21; 303 participants) at 39 weeks follow-up.

Exacerbations (primary outcome)

One study reported exacerbations as the number of people experiencing one or more exacerbations resulting in an emergency department (ED) visit (Rose 2018). Case management may result in little to no difference in the number of people experiencing exacerbations at 52 weeks follow-up compared to usual care, with the evidence very uncertain (OR 1.09, 95% 0.75 to 1.57; 470 participants; very low-certainty evidence; Analysis 1.6; Summary of findings 1). Rose 2018 also reported mean exacerbations per person, which showed case management may result in little to no difference in effect at 52 weeks follow-up, regardless of the issue of missing data reported (Analysis 1.7).

Functional status (secondary outcome)

Three rehabilitation studies reported at least one outcome relating to functional status (Bernocchi 2018; Budnevskiy 2015; McNamara 2013b). The specific outcomes reported were the six-minute walk distance (6MWD), incremental shuffle walk test (ISWT), and endurance shuttle walk test (ESWT).

6MWD

Data from two studies reported that tailored rehabilitation interventions (pulmonary rehabilitation and water-based exercise) are likely to result in a large increase in 6MWD at mean 38.8 weeks follow-up (MD 60.40 metres, 95% CI 44.26 to 76.54; I^2 = 0%; 2 studies, 100 participants; low-certainty evidence; Analysis 1.8; Summary of findings 1). One study reported that a multicomponent intervention is likely to result in a large increase in 6MWD at 52 weeks follow-up, with evidence uncertain (MD 75.00 metres, 95% CI 28.06 to 121.94; 80 participants; low-certainty evidence; Analysis 1.8; Summary of findings 1). The MCID for the 6MWT is 25 to 35 meters (Holland 2013).

ISWT

One study (McNamara 2013b) with 30 participants reported that a water-based exercise may improve ISWT compared to usual care at eight weeks follow-up (MD 50 metres, 95% CI 20 to 80; Analysis 1.9). However, with the small number of participants, we were uncertain about the results.

ESWT

One study with 30 participants reported ESWT at eight weeks follow-up (McNamara 2013b). The results favoured the water-based exercise group compared to usual care (MD 371 metres, 95% CI 120 to 622; Analysis 1.10), although with so few participants and a wide confidence interval, we are uncertain about the results.

All-cause hospital admissions (secondary outcome)

Number of people experiencing one or more hospitalisations (all-cause)

Two studies reported the number of people experiencing one or more hospitalisations for any cause (Bernocchi 2018; Walker 2018). We did not pool the data owing to variations in the interventions. The evidence is very uncertain about the effects of telemonitoring compared to usual care at 39 weeks (OR 0.91, 95% CI 0.55 to 1.50; 312 participants; low-certainty evidence; Analysis 1.11; Summary of findings 1). A multicomponent intervention may reduce the number of people experiencing hospitalisations at 17 weeks, but evidence is uncertain (OR 0.31, 95% CI 0.14 to 0.67; 112 participants; low-certainty evidence; Analysis 1.11; Summary of findings 1). Although the sample size is small, the trial was sufficiently powered (80% with a P value < 0.05), which was reported in the publication methods (Bernocchi 2018). The study is at risk of bias and should be interpreted with caution.

Mean hospitalisations per person

One study reported the mean number of hospitalisations per person (Rose 2018). There may be little to no difference in case management on mean hospitalisations compared to usual care at 52 weeks (MD −0.10, 95% CI −0.40 to 0.20; 470 participants; Analysis 1.12).

Respiratory hospital admissions (secondary outcome)

One study reported the number people with respiratory-related hospital admissions (Bernocchi 2018). There may be little to no difference in a multicomponent intervention on respiratory hospital admissions compared to usual care at 17 weeks (OR 0.49, 95% CI 0.17 to 1.44; 112 participants; Analysis 1.13).

Mortality — all-cause (secondary outcome)

Five studies reported the number of deaths during the trial (Bernocchi 2018; EUCTR2010-021412-42-GB; Gottlieb 2020; Rose 2018; Walker 2018). Overall there were 90 deaths in a total of 1071 participants (8.4%).

Evidence from two pharmacotherapy studies showed that optimising pharmacotherapy may result in little to no difference in mortality, with a pooled OR of 0.55 (95% CI 0.23 to 1.35; I^2 = 0%; 2 studies, 177 participants; very low-certainty evidence; Analysis 1.14; Summary of findings 1).

Evidence from two studies showed that effects of organisation-of-care interventions (case-management and telemonitoring) may result in fewer deaths compared to usual care at mean 46.7 weeks follow-up (OR 0.56, 95% CI 0.33 to 0.96; ; I^2 = 0%; 2 studies, 782 participants; low-certainty evidence; Analysis 1.14; Summary of findings 1).

Evidence from one multicomponent intervention study (Bernocchi 2018) was very uncertain (OR 1.00, 95% CI 0.06 to 16.39; 112 participants; very low-certainty evidence; Analysis 1.14; Summary of findings 1). Two studies did not report mortality as an outcome.

Pain (secondary outcome)

None of the studies reported on pain.

Anxiety (secondary outcome)

Two studies reported results from the HADS-anxiety questionnaire. Water-based exercise may have little or no effect on anxiety at eight weeks follow-up compared to no exercise, and we are uncertain about the evidence (MD −1.00, 95% CI −3.50 to 1.50; 1 study, 33 participants; Analysis 1.15). A case-management intervention may have an effect on anxiety at 52 weeks, (Rose 2018) but we are very uncertain about the evidence due to risk of bias. The confidence interval was very tight, and there were discrepancies between the results in the main text and supplementary information. We have therefore decided not to present the results.

Depression (secondary outcome)

Two studies reported results from the HADS-depression questionnaire (McNamara 2013b; Rose 2018). Water-based exercise may have little to no effect on the HADS-Depression score at eight weeks follow-up compared with usual care (Analysis 1.16). Again there were discrepancies in the reporting of results in Rose 2018, so data are not presented here.

Intervention versus active comparator

In this comparison, we used water-based exercises versus land-based exercises for the McNamara 2013b study (30 participants).

Quality of life (primary outcome)

CRQ domains (dyspnoea, fatigue, emotion, mastery)

One study reported results from the four domains of the CRQ (McNamara 2013b). Water-based exercise training may result in little to no difference in the dyspnoea domain, compared with land-based exercise training (MD 1.70, 95% CI −0.65 to 4.05; 1 study, 38 participants, Analysis 2.1), emotion domain (MD 2.90, 95% CI −0.10 to 5.90), and the mastery domain (MD 1.10, 95% CI −0.90 to 3.10). A possible small difference in the fatigue domain was reported (MD 3.10, 95% CI 0.80 to 5.40).

Exacerbations (primary outcome)

None of the studies reported on exacerbations.

Functional status (secondary outcome)

One rehabilitation study reported 6MWD, ISWT and ESWT as change from baseline to eight weeks (McNamara 2013b).

6MWD

One study reported the 6MWD as change from baseline (McNamara 2013b). The evidence is very uncertain about the effect of water-based exercise compared with land-based exercise. The interventions may result in little to no difference in 6MWD (MD 5.00 meters, 95% CI −22.21 to 32.21; very low-certainty evidence, Analysis 2.2; Summary of findings 2).

ESWT

McNamara 2013b reported ESWT as change from baseline within group. McNamara 2013b indicated a potentially large difference favouring water-based exercise, but there is a wide confidence interval around the effect estimate, including the possibility of no effect (MD 2.04 meters, 95% CI −7.16 to 415.16; Analysis 2.3).

ISWT

McNamara 2013b reported ISWT as change from baseline within the group. The results favoured water-based exercise compared to land-based exercise and the confidence interval is wide (MD 36.00, 95% CI 1.46 to 70.54; Analysis 2.4).

All-cause hospital admissions (secondary outcome)

None of the studies reported on hospitalisations.

Respiratory hospital admissions (secondary outcome)

None of the studies reported on hospitalisations.

Mortality — all-cause (secondary outcome)

None of the studies reported on mortality.

Pain (secondary outcome)

No studies reported this outcome.

Anxiety (secondary outcome)

One study reported results from the HADS-anxiety questionnaire at eight weeks (McNamara 2013b). Water-based exercise may have little or no effect on anxiety compared to land-based exercise (Analysis 2.5). The number of cases of anxiety were not reported in the studies.

Depression (secondary outcome)

One study reported results from the HADS-depression questionnaire at eight weeks (McNamara 2013b). Water-based exercise may have little or no effect on depression compared to land-based exercise (Analysis 2.6). The number of cases of depression was not reported in the studies.

Effects of interventions — qualitative

One study (Middlemass 2017) reported qualitative data from interviews of a subset of participants (n = 21) in a telemonitoring trial (Walker 2018). We present the results, including quotes from participants and personnel and judgements from the trial authors from Middlemass 2017 in Table 6. Because there was only one

qualitative study, we were unable to draw out themes across several studies.

Some participants said they were able to accept their condition, aging and inevitable death. While some people expressed that the telemonitoring machine was a daily reminder of their condition and got them into negative thinking, others felt positive about their data being sent to their HCP, having the sense that people were looking after them from afar, and others reported that their friends and relatives were happy that their condition was being monitored. Some technical issues were identified by participants, including issues with WiFi, and some people would have liked to have seen the screen with the readings while they were using the machine. The results were sent straight to the HCP, and some participants would have liked access to their own data so they could monitor themselves and give themselves the confidence to do things when their health was better. Some people went to the GP more often after getting the health information technology (HIT) device, and others felt that they were going to the GP less often because they were able to "sort everything out". For quotes and author and systematic review interpretations see Table 6.

The certainty of thematic evidence identified from Middlemass 2017 was rated as very low, with some concerns about study methodology and relevance, and major concerns about coherence, adequacy of data and dissemination (Table 1; Summary of findings 3). As we only found one qualitative study, we were not able to synthesise findings and examine emerging common themes.

Integration of qualitative and quantitative data

As we only identified one eligible qualitative study (Middlemass 2017), it was not possible to carry out an integrated synthesis of qualitative and quantitative data. This study has given us some insight into the barriers and facilitators to participating in the CHROMED telemonitoring intervention, as described above.

DISCUSSION

Summary of main results

Owing to a paucity of studies, as well as the diversity in the intervention type, comorbidities and reported outcome measures, we were unable to provide a robust synthesis of data. Instead the review pulls together the disparate data available for this population in a series of tables and forest plots. There is insufficient evidence from high-quality studies to clearly determine benefits of these interventions. The key take-home message from this review is the lack of data from RCTs on treatments for people living with comorbid COPD.

We planned to update a preliminary logic model that we developed in the protocol for this review (Janjua 2019), intended to explain how the interventions affected people with COPD. However, due to the paucity of the evidence, we were unable to update the logic model in collaboration with our COPD patient steering group.

Overall completeness and applicability of evidence

This review aimed to look at trials involving people living with COPD and one or more comorbidities that investigated COPD interventions specifically tailored to the comorbidity. We were interested in the tailoring aspect of the interventions, but unfortunately were unable to locate many studies addressing this group. An alternative way of looking at people with COPD and comorbidities would be to search for trials aimed at treating people with COPD and a specific comorbidity, such as coronary heart disease. This may lead to more trials being included and perhaps this would be of more help to certain users (e.g. if the tailoring aspect is of less interest).

This review, or trials eligible for it, may not be the best way to consider the evidence for interventions for this population. Given the high prevalence of multimorbidity in this patient population (GOLD 2021; Hillas 2015), many, if not all, COPD trials include people with comorbidities. It might be better for RCTs to report individual patient data together with more information about the individual's comorbidities, which would allow for analysis of outcomes in trials based on an individual patient's health.

We took data from the last reported time point in the trials, so none of the data relate to the impact of trials after the intervention has finished.

We chose to exclude studies where the only comorbidity was depression, anxiety, or both. This may have meant that people with depression and anxiety are underrepresented in the review. The implications of this are discussed below.

None of the studies evaluated impact on pain. Pain is emerging as an important symptom to consider in people with COPD, and targeted rehabilitation interventions are often rationalised by the presence of pain - for example, exercises done with the support of water rather than on land, where impact can cause pain. Sixty-six per cent of older people with COPD live with pain compared to 25% of the general population, and pain is cited as a common reason for dropping out of pulmonary rehabilitation programmes (Harrison 2017).

We were surprised by the apparent lack of qualitative studies. However, our inclusion criteria for qualitative studies focused very specifically on participants who had taken part in a tailored intervention, and their experiences of it. A broader inclusion criterion of qualitative studies investigating the experiences of people living with comorbid COPD, their carers, and HCPs more generally may have yielded more studies, and given some important information on the challenges of living with comorbid COPD and what the most important issues are for patients, carers and healthcare professionals. This in turn may help to inform the design of future interventions and evidence syntheses.

Certainty of the evidence

Quantitative - intervention versus usual care

The certainty of evidence in this comparison ranged from very low to moderate (Summary of findings 1). SGRQ evidence was rated as low certainty due to imprecision (small sample size) and risk of bias due to lack of blinding. Evidence for the CAT total score was rated as moderate certainty for rehabilitation and multicomponent interventions, but low certainty for pharmacotherapy and organisation-of-care interventions. Exacerbations were rated as very low certainty, due to lack of blinding, as well as imprecision (confidence intervals crossing the line of no effect). Functional status as measured by the six-minute walk distance, was rated as low certainty due to imprecision (small sample size) and risk of bias (lack of blinding). Evidence for all-cause hospital admissions was rated as low certainty, regardless of the intervention, mainly due to

imprecision (small sample size) and risk of bias (lack of blinding). Both HADS-A and HADS-D were rated as very low to low, due to imprecision (confidence intervals crossing the line of no effect), and risk of bias (lack of blinding).

Quantitative - intervention versus active control

The certainty of evidence in this comparison ranged from very low to low (Summary of findings 2). Functional status, 6MWD, was rated as very low certainty due to imprecision (small sample size and a confidence interval crossing the line of no effect) and risk of bias (lack of blinding and attrition). HADS-A evidence was rated as low certainty due to imprecision (small sample size) and lack of blinding of participants and those providing the intervention. Similarly, evidence for HADS-D was rated as very low certainty due to imprecision (small sample size and a confidence interval crossing the line of no effect) and risk of bias (lack of blinding of participants and personnel).

Qualitative

The certainty of the qualitative evidence was assessed as very low (Summary of findings 3). There were some concerns with methodological limitations for all outcomes because of the research design, recruitment strategy, and how the data were collected. Coherence and adequacy of data were of major concern as the evidence was based on one study, and we could not be certain of any issues about the qualitative data fitting the findings of the review. The relevance of the findings from the evidence was of some concern, because the study did not answer all aspects of the context specified in the review question.

Potential biases in the review process

This review was based on a published protocol (Janjua 2019). The terminology used to describe comorbidity and multimorbidity varies across studies and the terms are sometimes used synonymously (Smith 2016). We therefore included both terms and their variants in our search strategy and conducted a broad search across multiple databases. Despite this, it is possible that we could have missed relevant studies that did not describe the population with our included search terms. To try and mitigate this, we conducted supplementary forward-and-backward citation searches of our included studies.

This multimorbidity review is the first of its kind in Cochrane Airways. We wanted to conduct a review to explore multimorbid COPD, and there are a number of ways that this could have been done. Mindful of taking on too large a project for the time and money we had available, we decided to focus on interventions for COPD that were tailored to take account of the multimorbidity. We also decided to exclude populations where anxiety or depression were the sole comorbidity, and also because of potential overlap with other Cochrane Reviews on depression and anxiety in people with COPD. This decision may have been misguided, owing to the high prevalence of clinically relevant anxiety and depression in people with COPD — 40% compared to less than 10% in the general population (Atlantis 2013). Furthermore, as explained by Atlantis 2013 "Depression or anxiety comorbidity in patients with COPD predicts poor adherence to pulmonary rehabilitation and COPD-related medication; decreased exercise capacity and health-related quality of life; lost productivity; and increased health resource use, functional disability, and risk of exacerbation and mortality." Furthermore, there is a complex relationship between smoking, COPD and depression and anxiety — smoking is a risk factor for COPD, and depression predicts smoking initiation and deceases physical activity (Atlantis 2013). This limitation may have meant we missed studies that provided COPD interventions tailored to take account of people's depression and anxiety that would benefit 40% of the COPD population. Furthermore, because of these exclusions is possible that the level of anxiety and depression in the study populations may be lower than in the general COPD population and therefore the scope for improvement in these outcomes may have decreased.

We decided not to contact the authors of included studies for further information. This was a pragmatic decision, as we felt that the future information requested would not ultimately allow us to draw a firmer conclusion, even if greater accuracy was achieved.

Agreements and disagreements with other studies or reviews

A review by Kastner 2018 investigated interventions aimed at managing multiple chronic diseases in older people. They included studies of patients who had the same combination of chronic diseases, rather than studies where all the participants had an index condition with any comorbidity. The interventions were mainly co-ordinated care or health technology involving multiple components. They found that co-ordinated care interventions had the greatest potential for improving outcomes in older adults. They highlighted a general lack of evidence around interventions aimed at managing multimorbidity.

A Cochrane Review of interventions for people with multimorbidity in primary care or community settings (Smith 2016) included a mix of studies in which participants either had the same combination of chronic diseases or a broad range of conditions. The included interventions were mainly organisation of care, or self-management, and again involved multiple components. They found mixed evidence on the effectiveness of interventions, with no clear improvements seen in clinical outcomes, healthcare use, medication adherence, patient or healthcare professional behaviour or cost. However, they observed an improvement in mental health and functional outcomes.

The population included in this review differs from the above reviews, in that we included participants with an index condition (COPD) and one or more comorbidities. However, we found a similar paucity of evidence on interventions for managing patients with comorbidities. Because the number of included studies was small, it is difficult to draw direct comparisons between the efficacy of interventions in people with COPD and multimorbidity and those without multimorbidity. However limited evidence indicates the effects of pulmonary rehabilitation interventions were similar to or better than those seen in previous COPD trials.

AUTHORS' CONCLUSIONS

Implications for practice

Owing to a paucity of eligible trials, as well as diversity in the intervention type, comorbidities and the outcome measures reported, we were unable to provide a robust synthesis of data. Rehabilitation or pharmacological management may improve quality of life, but evidence is based on single studies and should be interpreted with caution. We could not determine a benefit or

harm of interventions on other outcomes, including exacerbations. The key take-home message from this review and a potential area of investigation is the lack of data from RCTs on treatments for people living with COPD and comorbidities.

Implications for research

Future COPD comorbidity studies should evaluate the impact of interventions on pain. Researchers should consider adding a qualitative element to their RCT, or running a qualitative study alongside it to help understand the experiences of care for people with complex chronic conditions which may not be captured by quantitative measurement tools that are often disease-specific. This information is important in understanding decision-making processes about acceptance and their ability to process the information provided. It can inform the delivery of the intervention and the individuals most likely to benefit. Qualitative studies should explore the experiences of participants, carers and HCPs who take part in trials of these interventions.

It is important that the inclusion criteria for COPD trials allow the participation of people with comorbidity, to ensure their results can be applied to people with COPD living with multiple long-term conditions. Trials should make full individual patient data (IPD) available so that the impact of interventions on outcomes in people with comorbid COPD can be assessed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bernocchi 2018

Study characteristics	
Methods	**Intervention assignment**: randomised **Study design**: parallel **Blinding**: open-label **Trial duration**: 17 weeks **Recruitment setting:** 3 centres in Lumezzane, Italy (Respiratory unit, cardiology unit, telemedicine service)
Participants	**Population**: 112 people with COPD and cardiovascular disease randomised (telerehabilitation = 56; usual care =56) **Baseline characteristics:** • **Age (mean):** Telerehabilitation = 71 (SD 9), usual care = 70 (SD 9.5) • **% male:** telerehabilitation = 88, usual care =75 • **COPD severity:** mild to very severe • **Ethnicity**: not reported in either treatment group • **Pack years**: not reported in either treatment group • **Current smoker**: not reported in either treatment group • **% anxiety**: not reported in either treatment group • **% depression**: not reported in either treatment group • **Dyspnoea (mean):** telerehabilitation = 2.8 (SD 0.98); usual care= 2.7 (SD 0.98) • **6MWT (mean):** telerehabilitation group = 329 (SD 115), usual care group = 308 (SD 105) • **% withdrawal:** telerehabilitation group = 19.6, usual care group = 37.5

Bernocchi 2018 *(Continued)*

- **Medications**: telerehabilitation = SABA 10%; LAMA 28%; LABA + LAMA 7%; LABA + ICS 14%; LAMA + LABA + ICS 41%; usual care = SABA 8%; LAMA 23%; LABA + LAMA 12%; LABA + ICS 23%; LAMA + LABA + ICS 35%

Inclusion criteria: 18 + years, COPD GOLD classification B, C, D, spirometry in the last 12 months, and/or sys/diastol CHF defined by ECG in a clinical stability. II, III, and IV NY Heart association class, optimised drug therapy

Exclusion criteria: Limited physical activity due to non-cardiac or non pulmonary problems, limited life expectancy, severe cognitive impairments

Interventions	**Intervention detail:** • **Telerehabilitation** with education, monitoring and personalised and supported exercise programme • **Setting:** participants' home • **Provider**: nurse tutor and physiotherapist tutor • **Materials/method:** physiotherapist tutor designed a personalised exercise programme and each person provided with mini-ergometer, pedometer and diary. Participants provided with a pulse oximeter, and a portable 1-lead ECG for real-time telemonitoring of vital signs • **Mode of delivery:** physiotherapist tutor instructed patients and their caregivers on how to perform the exercises correctly. Weekly structured phone call (nurse tutor) to collect information and provide advice on diet, lifestyle, and medication; weekly phone call (physiotherapist tutor) to verify training level, plan rehabilitation targets, and reinforce diet and lifestyle advice • **Schedule:** exercises 3 - 7 days per week • **Tailoring:** the programme was targeted to reach a moderate or high level of dyspnoea and/or muscle fatigue according to the Borg scale. Based on this assessment, the physiotherapist tutor could decide to increase or maintain the workload **Comparator detail:** • **usual care** • **Setting**: participants' home • **Provider:** Visits from the GP, and in-hospital check-ups on demand • **Materials/method:** medications and oxygen prescription. Participants were instructed in an educational session about the desirability of maintaining a healthy lifestyle and were invited to practice daily physical activity as preferred • **Mode of delivery:** at enrolment • **Schedule:** NA • **Tailoring:** NA
Outcomes	**Primary outcomes measured**: Exercise tolerance improvement (6MWT, primary) **Secondary outcomes measured:** Reduction of hospitalisations (cardiovascular and/or respiratory), reduction of hospitalisations (all cause), improvement of QoL (MLHFQ, CAT), reduction in impairment/disability (Barthel Index), reduction in dyspnoea (MRC), reduction in dyspnoea and fatigue at rest (Borg), improvement of physical activity profile (PASE questionnaire and daily steps reported by participant), improvement of oxygenation (PaO_2/FiO_2)
Notes	**Funding:** Minestero della Salute Italian Ministry of Health

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Yes	A computer-generated table to allocate participants in fixed blocks of 4

Bernocchi 2018 *(Continued)*

Allocation concealment (selection bias)	Yes	The allocation sequence was concealed from the investigators enrolling and assessing patients, in sequentially-numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias)	No	Due to the nature of the intervention, neither the participants nor the physicians were blinded to participants' group allocation
Blinding of outcome assessment (detection bias)	Yes	Outcome assessors and data analysts were blinded, but this is still at risk of bias especially for self-reported outcomes such as risk of bias, because the participants are not blinded
Incomplete outcome data (attrition bias)	No	Attrition higher in the control group compared to the intervention group (37.5% versus 19.6%); if the reason for withdrawal was related to the (lack of) treatment, then this could mean that the difference between groups was underestimated
Selective reporting (reporting bias)	Unclear	Hospitalisation outcome was unclear. Not sure if mean only or total numbers and no SD/CI/SE reported. Time to first hospitalisation/death was not separate. All other outcomes reported as planned, and the flow diagram was reported in a supplementary document with the publication. (Note that we did not contact the authors to request this information)
Other bias	Yes	None noted

Budnevskiy 2015

Study characteristics	
Methods	**Intervention assignment**: randomised **Study design**: parallel **Blinding**: open-label **Trial duration**: 52 weeks **Recruitment setting:** Russia
Participants	**Population**: 70 people with COPD and metabolic syndrome randomised (pulmonary rehabilitation = 35; usual care = 35) **Baseline characteristics:** • **Age (mean):** 48.3 (SD 0.6) • **% male:** pulmonary rehabilitation = 66, usual care = 71 • **COPD severity:** moderate • **Ethnicity**: not reported in either treatment group • **Pack years**: not reported in either treatment group • **Current smoker**: not reported in either treatment group • **% anxiety**: not reported in either treatment group • **% depression**: not reported in either treatment group • **Dyspnoea (mean):** pulmonary rehabilitation = 1.74 (SD 0.56), usual care = 1.66 (SD 0.59) • **6MWT (mean):** not reported in either treatment group • **% withdrawal:** not reported in either treatment group

Budnevskiy 2015 *(Continued)*

- **Medications**: All participants with COPD received standard treatment according to the GOLD recommendations (2013 revision): long-acting inhaled anticholinergics (tiotropium bromide 18 µg/day), LABA (formoterol 24 µg/day) and combined short-acting drugs (berodual) taken as needed

Inclusion criteria: Moderate COPD according to GOLD; metabolic syndrome; COPD in remission in combination with MS. Diagnosis of COPD made on basis of complaints, medical history, objective status, spirometry data in accordance with GOLD (2013 revision). MS diagnosed in accordance with clinical guidelines for patients with MS of the Ministry of Health of the Russian Federation (2013)

Exclusion criteria: Mild and severe COPD, COPD in exacerbation period, diagnosed with diabetes mellitus, diseases of the musculoskeletal system with functional disorders and severe concomitant diseases and their complications

Interventions	**Intervention detail:** • **Pulmonary rehabilitation** patient education, smoking cessation, physical training, nutritional recommendations. • **Setting:** not reported • **Provider**: not reported • **Materials/method:** Education consisted of a series of seminars covering aetiology, pathogenesis, clinical presentation, treatment and prevention of COPD and MS. Physical training included therapeutic exercises taking into account concomitant MS • **Mode of delivery:** Seminars delivered in groups of 4 - 5 people lasting 1 hour 30 minutes • **Schedule:** 5 lessons per week. An additional seminar on tobacco dependence and modern methods of its treatment for smokers. Physical training daily for 30 days • **Tailoring:** exercises took into account concomitant MS **Comparator detail:** • **Usual care,** standard COPD therapy • **Setting**: not reported • **Provider:** not reported • **Materials/method:** standard treatment according to the GOLD recommendations (2013 revision) • **Mode of delivery:** NA • **Schedule:** NA • **Tailoring:** NA
Outcomes	**Outcomes measured**: Waist circumference, BMI, systolic and diastolic arterial pressure, level fasting blood glucose and 2 hours after an oral glucose load (oral glucose tolerance test - PTTG), cholesterol HDL and LDL, triglycerides Dov (TG); assessment of the severity of COPD using the computer programme "Management system for medical and diagnostic stastic process in patients with bronchial asthma and COPD (Pulmosys) (using the number of exacerbations, emergency medical calls, and hospitalisations during the last 12 months), FVC (% predicted), VC (% predicted) FEV1 (% predicted), FEV1/FVC (% predicted), peak volumetric velocity - PIC (% predicted), the maximum space velocity measured after exhalation of the first 75, 50 and 25% FVC 75, 50 and 25 (% predicted), post-bronchodilator FEV1, mMRC Dyspnoea questionnaire; CCQ; CAT; SGRQ; 6MWD
Notes	**Funding:** not reported

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Quote: "Using random numbers"
Allocation concealment (selection bias)	Unclear	no information

Budnevskiy 2015 *(Continued)*

Blinding of participants and personnel (performance bias)	No	Unblinded
Blinding of outcome assessment (detection bias)	Unclear	No information
Incomplete outcome data (attrition bias)	Unclear	No information. It was not clear from the translation how many people completed the study
Selective reporting (reporting bias)	Unclear	For hospitalisations and ED visits, only the mean for the intervention group was reported. Spirometry was stated as no significant difference only. (Note that we did not contact the authors to request this information)
Other bias	Yes	None noted

EUCTR2010-021412-42-GB

Study characteristics	
Methods	**Intervention assignment**: randomised **Study design**: parallel **Blinding**: open-label **Trial duration**: 4 weeks **Recruitment setting:** 1 hospital in London, UK
Participants	**Population**: 63 people with COPD and lung cancer randomised (inhaler optimisation = 32 ; active control = 31) **Baseline characteristics:** • **Age (median, range):** inhaler optimisation = 68 (59 to 75), usual care = 67 (61 to 71) • **% male:** inhaler optimisation = 34, active control = 38 • **COPD severity:** not reported in either treatment group • **Ethnicity**: not reported in either treatment group • **Pack years**: not reported in either treatment group • **Current smoker (n)**: inhaler optimisation = 4/32, active control = 8/31 • **% anxiety**: not reported in either treatment group • **% depression**: not reported in either treatment group • **Dyspnoea (median, range):** inhaler optimisation EORTC QLQ-C30: 38.9 (33.3 to 44.4), active control = EORTC QLQ-C30: 33.3 (22.2 to 55.6) • **6MWT (median, range):** inhaler optimisation = 375 (325 to 450); active control = 396.5 (333 to 450) • **% withdrawal:** 0 in both groups • **Medications**: not reported in either treatment group **Inclusion criteria**: Men or women aged > 35 years; diagnosis of lung cancer (Non-small cell lung cancer, small cell lung cancer and mesothelioma) and COPD; subjective dyspnoea (breathlessness) of VAS score ≥ 4 **Exclusion criteria**: Involvement in any other studies of breathlessness; reversible causes of breathlessness; patients receiving radiotherapy, chemotherapy, biological therapy or surgery. Or with a plan to begin these treatments within 4 weeks; current use of bronchodilators either inhaled or oral (aminophylline, methylxanthines) except for short-acting bronchodilators; recent change to OCS therapy

EUCTR2010-021412-42-GB *(Continued)*

	dose (within 1 week of randomisation); current use of beta-blockers for any reason; current use of anti-cholinergic-containing drugs; current use of potent CYP30 inhibitors (ritonavir, ketoconazole, itraconazole); patients with the following conditions: asthma, severe cardiovascular disorders (myocardial infarction within 6 week), heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia, glaucoma, prostate problems, patients with difficulty passing urine, renal failure, TB (current or previous); pregnancy; patients with hypersensitivity to any of the study drugs, lactose allergy
Interventions	**Intervention detail:** • **Inhaler optimisation** and best supportive care • **Setting:** outpatient • **Provider**: • **Materials/method:** Evohaler 100 µg, Spiriva 18 mg via Handihaler, fluticasone propionate 500 µg • **Mode of delivery:** inhaler • **Schedule:** Evohaler 2 puffs 4 times a day, Spiriva once daily, fluticasone propionate 2 times a day • **Tailoring:** The study design took into account the possible poor prognosis of people with lung cancer. Therefore it was decided a priori that the intervention group would be treated with maximum inhaled therapy rather than the stepwise approach suggested by the British Thoracic Society and similar organisations **Comparator detail:** • **Active control,** best supportive care (i.e. usual care) • **Setting**: outpatient • **Provider:** • **Materials/method:** standard COPD management according to local guidelines, appropriate treatment decided by clinician, oramorph to be used if pharma measures required • **Mode of delivery:** inhaler • **Schedule:** Opiate-naïve participants 10 mg/5 mL solution to take 2.5 mg as required every 4 hours, participants on regular opioids prescribed 10 mg/5 mL every 4 hours • **Tailoring:** Participants will have no alterations to their current COPD management or no intervention if previously not diagnosed with COPD
Outcomes	**Primary outcomes measured**: VAS for dyspnoea **Secondary outcomes measured:** 6MWT, FEV1, QoL, physical activity (questionnaire)
Notes	**Funding:** The Royal Marsden NHS Foundation trust

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	No further information
Allocation concealment (selection bias)	Unclear	No further information
Blinding of participants and personnel (performance bias)	No	Open-label study
Blinding of outcome assessment (detection bias)	No	Open-label study

EUCTR2010-021412-42-GB *(Continued)*

Incomplete outcome data (attrition bias)	Yes	No participants withdrew from the study treatment
Selective reporting (reporting bias)	Yes	Study protocol was found on the European trials registry, but no publication found
Other bias	Yes	None noted

Gottlieb 2020

Study characteristics	
Methods	**Intervention assignment**: randomised **Study design**: parallel **Blinding**: open-label **Trial duration**: 25 weeks **Recruitment setting:** 1 large University Hospital in the capital region of Denmark
Participants	**Population**: 114 people with COPD and lung or head/neck cancer randomised (management = 57 ; usual care = 57) **Baseline characteristics:** • **Age (mean):** management = 67.8 (SD 8.3), usual care = 67.2 (SD 8.1) • **% male:** management = 58, usual care = 69 • **COPD severity:** Mild to severe • **Ethnicity**: not reported in either treatment group • **Pack years**: management = 42, usual care =43 • **Current smoker (n)**: management = 16; usual care = 11 • **% anxiety**: management = anxiety/depressions 3.5, usual care = anxiety/depressions 3.5 • **% depression**: management = anxiety/depressions 3.5, usual care = anxiety/depressions 3.5 • **Dyspnoea (mean):** management = 37.5 (SD 29.9), usual care = 27.5 (SD 29.0) • **6MWT (mean):** not reported in either treatment group • **% withdrawal:** management = 28.1, usual care = 33.3 • **Medications**: not reported in either treatment group **Inclusion criteria**: newly-diagnosed patients with lung and head/neck cancer; diagnosed with COPD at screening **Exclusion criteria**: Patients who were planned to have short treatment duration (less than 1 month)
Interventions	**Intervention detail:** • **management,** optimising COPD treatment • **Setting:** outpatient clinic, oncological department • **Provider**: pulmonary physician • **Materials/method:** 2 visits at 12 and 24 weeks in an outpatient clinic established at the oncological department and staffed with a pulmonary physician, where the adjustment of COPD treatment was considered • **Mode of delivery:** dialogue with the participants - any need for changes in the COPD medication was assessed by the physician and discussed with the participant • **Schedule:** 2 visits at 12 and 24 weeks

Gottlieb 2020 *(Continued)*

- **Tailoring:** adjustment of COPD treatment was considered at each visit

Comparator detail:

- **usual care**
- **Setting**: NA
- **Provider:** NA
- **Materials/method:** Continued current, if any, COPD treatment and follow-up
- **Mode of delivery:** NA
- **Schedule:** NA
- **Tailoring:** NA

Outcomes	**Primary outcomes measured**: CAT-score **Secondary outcomes measured:** QoL (EORTC, CAT), mortality
Notes	**Funding:** Boehringer-Ingelheim Danmark A/S [071-SOP-059-00481_RD01]

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Yes	Quote: "Randomization was stratified to ensure equal distribution of sex, age, LC and HNC between the control group and the intervention group."
Allocation concealment (selection bias)	Unclear	ARRACT software used
Blinding of participants and personnel (performance bias)	No	open-label
Blinding of outcome assessment (detection bias)	Unclear	No information
Incomplete outcome data (attrition bias)	No	Quote: "The relatively large loss to follow-up is also of concern in the control group compared to the intervention group (33% versus 28% respectively), since this can possibly introduce an information bias, meaning that those who are most ill (or most well) are also most likely not to return the schedules or show up for an appointment"
Selective reporting (reporting bias)	Unclear	No study protocol available
Other bias	Yes	None noted

McNamara 2013b

Study characteristics	
Methods	**Intervention assignment**: randomised **Study design**: parallel **Blinding**: Single-blind **Trial duration**: 8 weeks

McNamara 2013b *(Continued)*

Recruitment setting: 1 Australian tertiary public hospital

Participants	**Population**: 53 people with COPD and 1 or more physical comorbidities randomised (water-based exercise training = 18 ; land-based exercise training = 20, usual care = 15) **Baseline characteristics:** • **Age (mean):** water-based exercise training = 72 (SD 10); land-based exercise training = 73 (SD 7), usual care =70 (SD 9) • **% male:** water-based exercise training = 28; land-based exercise training = 50, usual care = 47 • **COPD severity:** not reported • **Ethnicity**: not reported in either treatment group • **Pack years**: not reported in either treatment group • **Current smoker (n)**: Water-based exercise training = 3 ; Land-based exercise training = 1, usual care = 2 • **% anxiety**: not reported in either treatment group • **% depression**: not reported in either treatment group • **Dyspnoea (mean):** not reported in either treatment group • **6MWT (mean):** not reported in either treatment group • **% withdrawal:** Water-based exercise training = 16.7; Land-based exercise training = 25.0, usual care = 0 • **Medications**: not reported in either treatment group **Inclusion criteria**: Confirmed diagnosis of COPD according to GOLD criteria (FEV1/FVC < 70%) that was in a stable phase and the presence of 1or more physical comorbidities (including musculoskeletal conditions affecting lumbar spine or lower limbs, 1 or more lower limb joint replacement restricting mobility and/or range of motion, or peripheral vascular disease, neurological conditions such as a stroke or obesity with BMI ≥ 32 kg/m^2). Diagnosis of the physical comorbidity was based on medical referral, patient history and physical examination. People using supplemental oxygen were included **Exclusion criteria**: Unstable cardiac disease, contraindications to water-based therapy, such as uncontrollable incontinence or open wounds, had completed pulmonary rehabilitation in the past 12 months or were currently attending an exercise programme, had cognitive decline or were unable to understand oral and written English
Interventions	**Intervention detail:** • **Water-based exercise training** • **Setting:** hospital hydrotherapy pool • **Provider**: physiotherapist • **Materials/method:** Exercise in hydrotherapy pool (depth graduating from 1.1 m to 1.6 m; length 18 m; width 6 m) with water temperature of 34 °C, air temperature of 30 °C and relative air humidity of 30%. Exercise routine included warm-up, lower limb endurance, upper limb endurance, and cool down • **Mode of delivery:** Supervised exercise led by experienced physiotherapist • **Schedule:** 3 x 60-min sessions a week • **Tailoring:** Participants encouraged to exercise at an intensity rating of 3 to 5 on the modified Borg scale for dyspnoea and perceived exertion. Training intensity was measured 3 times during each exercise session and the mean value recorded. If the intensity reported was below 3, participants were encouraged to increase their intensity. Participants were able to choose the most comfortable level of water immersion in the standing position to perform most of the exercises **Intervention detail:** • **Land-based exercise training** • **Setting:** hospital gymnasium • **Provider**: physiotherapist • **Materials/method:** Exercise in a temperature-controlled hospital gymnasium. Exercise routine included warm-up, lower limb endurance, upper limb endurance, and cool down • **Mode of delivery:** Supervised exercise led by experienced physiotherapist

McNamara 2013b *(Continued)*

- **Schedule:** 3 x 60-min sessions a week
- **Tailoring:** Participants encouraged to exercise at an intensity rating of 3 to 5 on the modified Borg scale for dyspnoea and perceived exertion. Training intensity was measured 3 times during each exercise session and the mean value recorded. If the intensity reported was below 3, participants were encouraged to increase their intensity

Comparator detail:

- **Usual care**
- **Setting**: NA
- **Provider:** NA
- **Materials/method:** Usual medical care and no exercise training. They were asked not to alter their exercise level over the study period
- **Mode of delivery:** NA
- **Schedule:** NA
- **Tailoring:** NA

Outcomes	**Primary outcomes measured**: Endurance exercise capacity measured by ESWT **Secondary outcomes measured:** FEV1 and FVC, DLCO, static lung volumes by body plethysmography, MIP and MEP, self-paced 6MWT, ISWT, CRDQ, HADS
Notes	**Funding:** Physiotherapy Research Foundation (grant number S07-011)

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Yes	Randomised by an investigator external to the study using a web-based computer-generated sequence (www.randomization.com). Randomisation was stratified according to the limiting factor in the 6MWT (that is, breathlessness or physical comorbidity) and BMI (≥ 32 kg/m^2)
Allocation concealment (selection bias)	Yes	Concealed allocation was achieved using opaque envelopes
Blinding of participants and personnel (performance bias)	No	Due to the nature of the exercise interventions, it was not possible to blind the therapist or participants to their allocation
Blinding of outcome assessment (detection bias)	Yes	This study was a prospective randomised controlled trial with assessor blinding. However this is still at risk of bias especially for self-reported outcomes such as risk of bias, because the participants are not blinded
Incomplete outcome data (attrition bias)	No	25% dropped out of the land-based exercise, and 16% from the water-based exercise
Selective reporting (reporting bias)	Yes	Protocol available on registry website. Outcomes reported as planned
Other bias	Yes	Compliance with exercise group attendance was high, with participants allocated to the water-based exercise training group attending a mean of 21 (SD 2) sessions out of a total of 24 sessions and participants in the land-based exercise training group attending 19 (SD 4) out of 24 sessions, with no statistical difference in attendance between groups

Middlemass 2017

Study characteristics	
Methods	**Study design**: nested qualitative study (linked to Walker 2018) **Method:** face-to-face interviews **Duration**: 39 weeks. This is how long the participant had the intervention **Setting:** participants' home (multi-country study: Italy, Estonia, Spain, Sweden, Norway, Slovenia and 2 UK sites)
Participants	**Population**: 21 participants with COPD **Baseline characteristics:** • **Age (range)**: 60 to 90 years • **Co-morbidities:** 3 participants had severe COPD/heart condition. No other information provided about the 21 participants **Sampling/inclusion criteria:** participant in the intervention arm of the RCT. The inclusion criteria for the RCT were: not reported, but all with COPD grade II and above with COPD exacerbations and/or hospitalisation in the previous year, comorbidity such as CHF, SDB, ≥ 10 pack years (information from clinicaltrials.gov), participated in the pilot and RCT, aged ≥ 60 years
Interventions	**Research aims:** To explore perceptions and experiences of older patients with long-term conditions using telemonitoring equipment at home; to compare the results with HITAM, and then to apply HITAM to home telemonitoring for this group of participants to see if the model could be used to help with increasing the uptake of HIT as it has not been done in this age group previously **Data collection:** Interviews were conducted after installation of equipment and then at the end of the study by 2 experienced interviewers (also the researchers). Post-installation interviews were conducted via phone, shorter (20 to 30 mins). The last interview was conducted in the participants' home (about 60 min). Interviews were audiotaped and transcribed by researchers. All information was anonymised **Analysis:** framework analysis. Nvivo 10 software was used to manage and analyse data. Three researchers read the transcripts repeatedly to become familiar with the data. Two researchers independently coded the interviews line by line using HITAM guidance. Significant and meaningful subthemes and data fragments were captured using open codes. Consensus about subthemes was reached on discussion and quotes were referenced in a table and linked to text. Synthesis, mapping and interpretation were transferred to a HITAM map, and where themes did not match, the model was amended to fit the additional theme **Theoretical framework:** HITAM **Reflexivity:** not reported
Outcomes	**Themes**: Health status, beliefs and concerns; HIT reliability; HIT self-efficacy; perceived ease of use (mediating process); perceived usefulness (mediating process); Factors affecting perceived usefulness – lack of interactivity; Factors affecting perceived usefulness - appropriateness and handling of clinical alerts; Attitude towards HIT and behavioural intention; Actual behaviour change in terms of self-management and changes in health care utilisation
Notes	**Ethical approval:** Ethical approval was obtained for the CHROMED study from East Cambridge Ethics Committee (NRES 13/EE0065) and University of Lincoln Research Ethics Committee in 2013. NHS Research Governance approvals from the health organisations involved in the study were also acquired prior to commencement. All participants recruited to the CHROMED study also gave informed written consent to take part in 2 taped interviews to ascertain their views of using the equipment should they be allocated in that arm of the study **Funding**: Funding for the CHROMED study was secured for the RCT from the EU Seventh Framework Programme. Total EU Contribution EUR2,503,340.02 across all study sites. Lead Partner TESAN in Italy

Middlemass 2017 *(Continued)*

Risk of bias: see Table 1

Rose 2018

Study characteristics	
Methods	**Intervention assignment**: randomised **Study design**: parallel **Blinding**: open-label **Trial duration**: 52 weeks **Recruitment setting:** 2 community teaching hospitals in Canada
Participants	**Population**: 475 people with COPD and ≥ 2 comorbidities randomised (case management = 237 ; usual care = 238) **Baseline characteristics:** • **Age (mean):** case management = 71 (SD 9.2), usual care = 71 (SD 9.7) • **% male:** case management = 50, usual care = 44 • **COPD severity:** Moderate to severe • **Ethnicity**: not reported in either treatment group • **Pack years**: not reported in either treatment group • **% Current smoker**: case management = 23, usual care = 26 • **% anxiety**: case management = 6, usual care = 7 • **% depression**: case management = 17, usual care = 20 • **Dyspnoea (mean, SD):** not reported in either treatment group • **6MWT (mean, SD):** not reported in either treatment group • **% withdrawal:** case management = 12.7, usual care = 197.7 • **Medications**: Most common medications were inhaled bronchodilator (95%), inhaled steroid (91%) and anti-hypertensives (65%) **Inclusion criteria**: COPD diagnosis according to GOLD criteria and published Canadian reference values confirmed by a respirologist or internist, ≥ 50 years of age, ≥ 1 ED visit or hospital admission for COPD exacerbation in previous 12 months, and ≥ 2 prognostically-important COPD-associated comorbidities (as defined by GOLD and Canadian Thoracic Society Guidelines) identified via medical record screening **Exclusion criteria**:Primary diagnosis of asthma; terminal diagnosis; dementia; uncontrolled psychiatric illness; inability to understand English; no telephone access; inability to attend follow-up; resident in a long-term care facility; enrolled in the provincial telehome monitoring programme; and no family physician
Interventions	**Intervention detail:** • **Case management,** multicomponent, case manager-led exacerbation prevention/management model (plus usual care) • **Setting:** outpatient • **Provider**: case-manager • **Materials/method:** education session based on Living Well with COPD**,** telephone consultations, ongoing communication with physician, and hospital specialist including respirologist • **Mode of delivery:** education session at enrolment**,** telephone consultations • **Schedule:** education: 1 x 40-min session; telephone consultations: 12 x weekly and then monthly for a subsequent 9 months (21 sessions)

Rose 2018 *(Continued)*

- **Tailoring:** individualised care and action plans for COPD exacerbation recognition, self-management and management of comorbidities

Comparator detail:

- **Usual care**
- **Setting**: outpatient;
- **Provider:** NA
- **Materials/method:** outpatient clinic visits, referral to a hospital rehab programme, action planning, educational materials
- **Mode of delivery:** NA
- **Schedule:** 3 x monthly clinic visits
- **Tailoring:** an individualised action plan. Smokers referred to smoking cessation resources

Outcomes	**Primary outcomes measured**: Number of ED presentations **Secondary outcomes measured:** hospital admission rates, number of hospitalised days over 1 year, time to death, COPD severity measured by the BODE index, change in HRQoL using EQ5D, SGRQ and HADS, change in COPD self-efficacy scale, patient satisfaction using the CSQ8, Caregiver Impact Scale, adherence to chronic disease management measures, smoking cessation status (if applicable), influenza and pneumonia vaccination, up-to-date documented action plan, electronic medication reconciliation
Notes	**Funding:** Building Bridges to Integrate Care (BRIDGES) program, funded by Ministry of Health and Long Term Care. CIHR New Investigator Award

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Yes	Randomisation was performed according to a centralised, computer-generated 1:1 randomisation schedule stratified by study site
Allocation concealment (selection bias)	Unclear	Only treating respirologists were not aware of the allocation. There was no report of allocation concealment, open-label study
Blinding of participants and personnel (performance bias)	No	Because of the nature of the intervention and co-location of research staff within the respiratory clinics, healthcare providers, participants and outcome assessors were not blinded, although treating respirologists were not informed of study allocation
Blinding of outcome assessment (detection bias)	No	Because of the nature of the intervention and co-location of research staff within the respiratory clinics, healthcare providers, participants and outcome assessors were not blinded, although treating respirologists were not informed of study allocation
Incomplete outcome data (attrition bias)	Yes	Premature terminations low in intervention (3%) and control (2%) groups. 3 people (1%) in the control group withdrew. Authors state missing data were an issue for secondary outcome data at 52 weeks
Selective reporting (reporting bias)	Yes	Comment: outcomes specified in NCT record were reported. Quote: "we are unable to compare the frequency of exacerbation that did not result in an emergency department visit or hospitalisation in the control arm as these participants were not contacted weekly or monthly to collect these data." Comment - the issue with the exacerbation was made transparent

Rose 2018 *(Continued)*

Other bias	Yes	None noted

Walker 2018

Study characteristics	
Methods	**Intervention assignment**: randomised **Study design**: parallel **Blinding**: open-label **Trial duration**: 39 weeks **Recruitment setting:** 6 sites in 5 countries (Spain, United Kingdom, Slovenia, Estonia, and Sweden)
Participants	**Population**: 312 people with COPD and ≥ 1 non-pulmonary comorbidities randomised (telemonitoring = 154; usual care = 158) **Baseline characteristics:** • **Age (median, interquartile range):** telemonitoring = 71 (66.0 to 75.8), usual care = 71 (65.3 to 76.0) • **% male:** telemonitoring = 66, usual care = 66 • **COPD severity:** Mild to very severe • **Ethnicity**: not reported in either treatment group • **Pack years (median)**: telemonitoring = 40, usual care = 40; • **% anxiety**: not reported in either treatment group • **% depression**: not reported in either treatment group • **Dyspnoea (mean, SD):** not reported in either treatment group • **6MWT (mean, SD):** not reported in either treatment group • **% withdrawal:** telemonitoring = 29.2, usual care = 22.8 • **Medications**: not reported in either treatment group **Inclusion criteria**: People aged 60 years or older, with a diagnosis of COPD GOLD grade II or higher, a history of acute exacerbation with or without hospitalisation in the previous 12 months, a smoking history of ≥ 10 pack-years, and 1 or more documented non-pulmonary chronic conditions including CHF, IHD, hypertension, hyperlipidaemia, and clinically significant sleep-disordered breathing. Participants were clinically stable, with at least 4 weeks elapsed since their last exacerbation **Exclusion criteria**: People with significant visual disturbance or mental health disorders that would make them unable to use the monitoring platform, a planned prolonged absence from home, living in areas not covered by a mobile data network, or unable to use the study equipment were excluded
Interventions	**Intervention detail:** • **Telemonitoring**, and phone calls • **Setting:** outpatient • **Provider**: study nurse • **Materials/method:** CHROMED monitoring platform: a device that measured within-breath respiratory mechanical impedance using FOT, touch-screen computer and mobile modem. People with CHF used a wearable device to assess blood pressure, oxygen saturation, heart rate, and body temperature (WristClinic; Medic4All) over a 4-minute period • **Mode of delivery:** wearable device • **Schedule:** NA • **Tailoring:** An algorithm-generated respiratory alerts if a trend of worsening was detected. The alert triggered contact with the study nurse to determine the participant's clinical status and whether any

Walker 2018 *(Continued)*

	intervention was required. Technical alerts were issued if no data were recorded for more than 2 days. When this occurred, the local site contacted the study patient **Comparator detail:** • **Usual care,** details • **Setting**: outpatient • **Provider:** NA • **Materials/method:** According to local practice • **Mode of delivery:** NA • **Schedule:** NA • **Tailoring:** NA
Outcomes	**Primary outcomes measured**: TTFH and change in the EQ-5D utility index score **Secondary outcomes measured:** Moderate exacerbation rate, hospitalisation, and final scores of the CAT, PHQ-9, and MLHFQ questionnaires, cost-utility analysis
Notes	**Funding:** European Commission grant (no. 306093)

Item	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Yes	Quote: " to intervention or control groups (1:1) using a concealed computer-generated randomisation sequence with a four element block design and stratified on a clinical centre basis. "
Allocation concealment (selection bias)	Yes	Quote: " to intervention or control groups (1:1) using a concealed computer-generated randomisation sequence with a four element block design and stratified on a clinical centre basis. "
Blinding of participants and personnel (performance bias)	No	Not described, but not possible
Blinding of outcome assessment (detection bias)	Yes	Data about healthcare resource use were obtained and analysed independently of the clinical study team
Incomplete outcome data (attrition bias)	No	High and unbalanced rates - 29% withdrew from intervention group and 23% withdrew from control group. 5% of participants dropped out because they could not use the equipment
Selective reporting (reporting bias)	Yes	Consistent with protocol. Hospital admissions from clinical records
Other bias	Yes	None noted

6MWT: six-minute walk test; 6MWD: six-minute walk distance; BMI: body mass index; BODE: Body-mass index, airflow Obstruction, Dyspnea, and Exercise; CAT: COPD assessment test; CCQ: Clinical COPD Questionnaire; CHF: coronary heart disease; COPD: chronic obstructive pulmonary disease; CRQ: chronic respiratory questionnaire; CSES: COPD Self-Efficacy Scale; CSQ8: Client Satisfaction Questionnaire-8; CVD: cardiovascular disease; DLCO: Diffusing Capacity Of The Lungs For Carbon Monoxide; ED: emergency department; EORCT QLQ-c30: European Organization for Research and Treatment of Cancer core quality of life questionnaire; ESWT: endurance shuttle walk test; FEV1: forced expiratory volume in one second; FFMI: fat-free mass index; FiO2: fraction of inspired oxygen; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; GP: general practitioner; HADS: Hospital Anxiety and Depression Scale; HDL: high-density lipoprotein; HITAM: Health Information Technology Acceptance Model; ICFS: Identity-Consequence Fatigue Score ; ICS: inhaled corticosteroid; ILD: interstitial lung disease; ISWT: incremental shuttle walk test; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; LDL: low-density lipoprotein; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MLHFQ:

Minnesota Living with Heart Failure Questionnaire; MMSE: mini-mental state examination; mMRC: modified Medical Research Council questionnaire; MRC: Medical Research Council questionnaire; MS: metabolic syndrome; NA: not applicable; OCS: oral corticosteroid; PaO2: partial pressure of oxygen; PASE: Physical Activity Profile; PHQ-9: Patient Health Questionnaire-9; PIC: Program of Integrated Care; PIH: Partners in Health scale; PPTG: pedunculopontine tegmental nucleus; QoL: quality of life; RCT: randomised controlled trial; SABA: short-acting beta$_2$-agonist; SDB: sleep-disordered breathing; SGRQ: St George's Respiratory questionnaire; TB: tuberculosis; UC: usual care; VAS: visual analogue scale; VC: vital capacity.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12608000348358	Wrong intervention - treating the co-morbidity
ACTRN12613000187741	Wrong population - not everyone has COPD
ACTRN12614001186640	Wrong population - not everyone has COPD
ACTRN12614001187639	Wrong population - not everyone has COPD
ACTRN12616000607471	Wrong population - not everyone has COPD
ACTRN12617001285347	Wrong population - not everyone has COPD
Ageev 2010	Wrong intervention - treating the co-morbidity
Aisanov 2004	Literature review
Ali 2018	Wrong population - not everyone has COPD
Andell 2019	Wrong population - not everyone has COPD
Ansari 2013	Wrong intervention
Apps 2017	Wrong intervention
Ashton 2017	Wrong population - not everyone has COPD
Barker 2018	Wrong population - not everyone has COPD
Barua 2012	Wrong study design
Bayliss 2016	Wrong patient population
Benzo 2011	Wrong intervention - not COPD management
Bingol 2005	Wrong intervention - not COPD management
Blanck 2018	Wrong patient population
Boeckxstaens 2012	Wrong intervention
Boeckxstaens 2016	Wrong intervention
BohingamuMudiyanselage 2018	Wrong population - not everyone has COPD
Bolieva 2014	Wrong intervention - treating the co-morbidity

Study	Reason for exclusion
Bond 2015	Wrong patient population
Bower 2012	Wrong population - not everyone has COPD
Brien 2016	Wrong intervention
Brusselle 2016	Wrong study design
Bubnova 2016	Wrong intervention - treating the co-morbidity
Burgess 2013	Wrong patient population
Butorov 1999	Wrong intervention - treating the co-morbidity
Camsari 2003	Wrong intervention - treating the co-morbidity
Carlin 2018	Not an RCT - a combined analysis of trials
Cazzola 1998	Wrong intervention - COPD intervention not adapted to the co-morbidity
Cejudo 2014	Wrong population - not everyone has COPD
Centanni 1997	Wrong population - not everyone has COPD
Centanni 2002	Lab test rather than an intervention
Chang 2016	Wrong patient population
Chaplin 2018	Wrong population - not everyone has COPD
Charbek 2018	Wrong study design
Chen 2008	Wrong patient population
Chen 2016	Wrong patient population
ChiCTR1800016955	Wrong intervention
ChiCTR INR 17012648	Wrong intervention - not COPD management
ChiCTR IOR 16007768	Wrong intervention
ChiCTR TRC 12002559	Wrong population - not everyone has COPD
ChiCTR TRC 12002889	Wrong intervention
Cittee 2015	Wrong patient population
Cochrane 2016	Wrong population - comorbidity not an inclusion criteria of the study
Cornford 2000	Wrong intervention
Coventry 2014a	Wrong patient population
Coventry 2014b	Wrong patient population

Study	Reason for exclusion
Cowie 2009	Wrong patient population
CTRI/2012/12/003223	Wrong intervention - treating the co-morbidity
Curry 2006	Wrong patient population
Dahlberg 1992	Wrong population - not everyone has COPD
Davis 2016	Wrong patient population
Davisson 2018	Wrong patient population
Dennis 2017	Wrong patient population
Desveaux 2017	Wrong patient population
Dibao-Dina 2018	Wrong patient population
Disler 2015	Wrong patient population
Disler 2019	Wrong patient population
Doos 2015	Wrong study design
Dorenkamp 2015	Wrong study design
DRKS00000476 2010	Wrong patient population
DRKS00000584	Wrong population - not everyone has COPD
DRKS00005602	Wrong population - not everyone has COPD
Ellison 2012	Wrong patient population
Elwyn 2012	Wrong patient population
Essue 2010	Wrong patient population
Etkind 2017	Wrong study design
EUCTR2004 002216 28 BE	Wrong intervention - treating the co-morbidity
EUCTR2007 007725 46 BG	Wrong intervention - treating the co-morbidity
EUCTR2010 018763 42 GB	Wrong intervention - treating the co-morbidity
EUCTR2010 020917 97 IT	Wrong intervention - treating the co-morbidity
EUCTR2011 003310 17 ES	Wrong intervention - treating the co-morbidity
EUCTR2013 001312 30 IT	Wrong intervention - treating the co-morbidity
EUCTR2017 003551 32 DK	Wrong intervention - treating the co-morbidity
Faul 2009	Wrong population - not everyone has COPD

Study	Reason for exclusion
Fors 2018	Wrong population - not everyone has COPD
Freund 2011	Wrong population - not everyone has COPD
Gale 2015	Wrong intervention
Glasser 2016	Wrong intervention
GlaxoSmithKline 2005	Lab test rather than an intervention
Goodridge 2011	Wrong patient population
Goodridge 2019	Wrong patient population
GorgasTorner 2012	Wrong population - not everyone has COPD
GrigorevaNIu 2013	Wrong intervention - COPD intervention not adapted to the co-morbidity
Grimsmo 2018	Wrong intervention
GSK115805 2012	Wrong intervention - COPD intervention not adapted to the co-morbidity
Gurgun 2013	Muscle wasting is a multisystem consequence of COPD rather than a separate disease
Hannink 2011	Lab test rather than an intervention
Hawkins 2009	Wrong intervention - treating the co-morbidity
Hawkins 2010	Wrong population - not everyone has COPD
Hesselink 2017	Wrong patient population
Hogg 2009	Wrong population - not everyone has COPD
Hohlfeld 2015	Not an RCT - a combined analysis of trials
ISRCTN62025354	Wrong population - not everyone has COPD
Jabbour 2010	Wrong intervention - treating the co-morbidity
Jensen Lise 2016	Wrong patient population
Jerant 2008	Wrong population - not everyone has COPD
Johnson 2016	Wrong intervention - COPD intervention not adapted to the co-morbidity
Jones 2019	Wrong intervention
Jowsey 2009	Wrong patient population
Jowsey 2014	Wrong patient population
Juanes 2018	Wrong population - not everyone has COPD
Kaimakamis 2019	Wrong study design

Study	Reason for exclusion
Kapella 2011	Wrong intervention - treating the co-morbidity
Kapella 2016	Wrong intervention - treating the co-morbidity
Kaptein 1993	Wrong population - not everyone has COPD
Kayyali 2014	Wrong study design
Kayyali 2016	Wrong study design
Kayyali 2016a	Wrong study design
Kenning 2013	Wrong patient population
Koul 2005	Comment article
Koziolova 2015	Wrong intervention - treating the co-morbidity
Krahnke 2015	Wrong intervention - treating the co-morbidity
Kucukcoskun 2013	Wrong intervention - treating the co-morbidity
Kukes 2003	Wrong intervention - treating the co-morbidity
Lainscak 2011	Wrong intervention - treating the co-morbidity
Lainscak 2013	Wrong intervention - treating the co-morbidity
Lamothe 2006	Wrong patient population
Lang 2019	Wrong patient population
Lanning 2017	Wrong intervention
Lanning 2019	Wrong study design
Laue 2016	Wrong intervention
Lee 2015	Wrong intervention
Lemmens 2011	Wrong patient population
Lenferink 2016	Not an RCT - a combined analysis of trials
Lenferink 2019	Some participants would have had COPD and depression or anxiety as their co-morbidity.
Levine 2018	Wrong population - not everyone has COPD
Lewis 2012	Wrong patient population
Liddy 2008	Wrong population - not everyone has COPD
Lima 2016	Wrong intervention
Lin 1996	Wrong intervention - treating the co-morbidity

Study	Reason for exclusion
Lin 2017	Wrong intervention - treating the co-morbidity
Lin 2019	Wrong intervention
Man 2016	Wrong population - not everyone has COPD
Mathar 2015	Wrong patient population
Mathar 2017	Wrong intervention
McNamara 2014	Wrong study design
McNamara 2016	Wrong patient population
Mirkovic 2016	Wrong patient population
Mirzaei 2013	Wrong patient population
Mitlehner 1992	Wrong intervention - COPD intervention not adapted to the co-morbidity
Morales-Asencio 2010	Wrong patient population
Morgan 2010	Wrong intervention - treating the co-morbidity
Naz 2019	Wrong study design
NCT00202150	Wrong population - not everyone has COPD
NCT00668408	Wrong intervention - COPD intervention not adapted to the co-morbidity
NCT00730067	Wrong intervention - treating the co-morbidity
NCT00789100	Wrong population - not everyone has COPD
NCT01055405	Wrong intervention - treating the co-morbidity
NCT01627327	Wrong intervention - COPD intervention not adapted to the co-morbidity
NCT01648621	Wrong study design
NCT01691131	Wrong patient population
NCT01862536	Wrong intervention - treating the co-morbidity
NCT01867970a	Wrong population - not everyone has COPD
NCT01867970b	Wrong study design
NCT01892566	Wrong intervention - COPD intervention not adapted to the co-morbidity
NCT01960907	Wrong population - not everyone has COPD
NCT02446769	Wrong intervention - not COPD management
NCT02522637	Wrong patient population

Study	Reason for exclusion
NCT02652559	Wrong patient population
NCT02742597a	Wrong population - not everyone has COPD
NCT02742597b	Wrong study design
NCT02789800	Wrong study design
NCT03387735	Wrong population - not everyone has COPD
NCT03810755	Wrong population - not everyone has COPD
NCT04212676	Wrong patient population
Nekrasov 2019	Wrong study design
NTR1839	Trial terminated shortly after registration
NTR4452	Wrong study design
Ogunbayo 2017	Wrong intervention
Onorati 2011	Wrong intervention - treating the co-morbidity
Orr 2019	Wrong population - not everyone has COPD
Overlack 1994	Wrong intervention - treating the co-morbidity
Paget 2010	Wrong patient population
Paleev 1989	Wrong intervention - treating the co-morbidity
Pascual 2011	Wrong population - not everyone has COPD
Patel 2016	Wrong patient population
Pinnock 2009	Wrong study design
Pommer 2012	Wrong population - not everyone has COPD
Pooler 2005	Wrong study design
Pooler 2014	Wrong study design
Porta 2002	Wrong population - not everyone has COPD
Porter 2016	Wrong patient population
Rabinowitz 1999	Wrong patient population
Ream 1997	Wrong patient population
Rijken 2016	Wrong study design
Ringe 1987	Wrong intervention - treating the co-morbidity

Study	Reason for exclusion
Ritchie 2016	Wrong population - not everyone has COPD
Røsstad 2013	Wrong study design
Salem 2014	Wrong intervention - treating the co-morbidity
Sandelowsky 2014	Wrong study design
Sandelowsky 2016	Wrong study design
Savaria 2017	Wrong study design
Schaarup 2016	Wrong study design
Schinaman 2005	Wrong intervention
Schroedl 2013	Wrong study design
Seto 2017	Wrong population - not everyone has COPD
Sevostyanova 2016	Wrong intervention
Simon 2014	Literature review
Simpson 2010	Wrong patient population
Sin 2007	Wrong intervention - COPD intervention not adapted to the co-morbidity
Smyrnova 2018	Wrong intervention - COPD intervention not adapted to the co-morbidity
Sobnath 2016	Wrong study design
Solaligue 2014	Wrong patient population
Spence 2008	Wrong study design
Stachel 2017	Wrong patient population
Statsenko 2014	Wrong intervention - treating the co-morbidity
Sugawara 2010	Wrong patient population
Summit 2016	Wrong intervention - COPD intervention not adapted to the co-morbidity
Tavazzi 2013	Wrong intervention - treating the co-morbidity
Taylor 2015	Wrong study design
Thorpe 2014	Wrong study design
Tocci 2015	Wrong study design
Toms 2002	Wrong patient population
Tsvetkova 2007	Wrong intervention - treating the co-morbidity

Study	Reason for exclusion
Uddin 2014	Wrong study design
UMIN000027228	Wrong intervention - COPD intervention not adapted to the co-morbidity
UMIN000033212	Wrong intervention
Van der Woude 2005	Wrong intervention - treating the co-morbidity
Van Eijk 2004	Wrong patient population
Van Mourik 2012	Wrong population - not everyone has COPD
Walters 2012	Wrong patient population
Weldam 2015	Wrong patient population
Weldam 2017	Wrong patient population
Wodskou 2014	Wrong patient population
Woo 2009	Wrong population - not everyone has COPD
Wortz 2012	Wrong patient population
Yen 2011	Wrong study design
Young 2011	Wrong patient population
Zakrisson 2010	Wrong patient population
Zhou 2014	Wrong intervention - treating the co-morbidity
Zujovic 2017	Wrong population - not everyone has COPD
Zulkarneev 2012	Wrong intervention - not COPD management

Characteristics of studies awaiting classification *[ordered by study ID]*

Boer 2011

Study design	Randomised, parallel, controlled trial
Population	COPD patients GOLD stage 3 - 4 and comorbid disease
Intervention	Case management care versus usual care
Outcomes	Hospital admissions, exacerbations, health status
Notes	Reported as a conference abstract only. More information required

Imanalieva 2016

Study design	Randomised, parallel, controlled trial
Population	Patients with COPD and essential hypertension
Intervention	Telephone patient education versus control
Outcomes	Hospital admissions, 6-minute walk test, quality of life
Notes	Reported as a conference abstract only. More information required

NCT04350541

Study design	-
Population	Heart failure and COPD
Intervention	-
Outcomes	quantitative outcomes (see trial registry record)
Notes	Ongoing study. More information required to assess eligibility

Characteristics of ongoing studies *[ordered by study ID]*

Ansari 2017

Study name	Ansari 2017
Starting date	2017
Contact information	Sameera Ansari, School of Public Health and Community Medicine, UNSW Medicine, Australia, Sydney, NSW 2052, Australia
Population	COPD and at least 1 other comorbidity
Interventions	Qualitative evaluation of the self-management education programme was done by interviewing PNs, general physicians (GPs) and patients
Outcomes	Qualitative evaluation
Notes	Quantitative data published. Waiting for publication of qualitative data (as at September 2020)

ISRCTN43508703

Study name	Tailored Intervention at home for patients with moderate-to-severe COPD and comorbidities by Pharmacists and Consultant Physicians (TICC PCP): a pilot randomised controlled trial
Starting date	29 October 2019

ISRCTN43508703 *(Continued)*

Contact information	Richard.lowrie@ggc.scot.nhs.uk . NHS Greater Glasgow and Clyde
Population	Chronic obstructive pulmonary disease, and other morbidities
Interventions	Pharmacist home visits every month for 6 months then every 2 months for 6 months versus usual care
Outcomes	Primary: whether the researchers should proceed to a definitive trial Qualitative: semi-structured interviews with 15 - 20 participants, and 7 - 10 health professionals
	-
Notes	Ongoing study. Quantitative and qualitative

NCT03662711

Study name	Comparison of 1-year treatment with inhaled long acting bronchodilators (LABD) plus inhaled glucocorticosteroids (ICS) versus LABD without ICS on re-hospitalizations and/or death in elderly patients with chronic obstructive pulmonary disease (COPD) recently hospitalised because of an acute exacerbation of COPD (ICS-Life Study)
Starting date	7 September 2018
Contact information	Alberto Papi, MD, Professor, Università degli Studi di Ferrara
Population	Patients with COPD and 1 or more cardiac comorbidities
Interventions	Long-acting muscarinic antagonist (LAMA) and/or Long-acting beta-agonist (LABA) plus ICS plus usual care for comorbidities versus LABA or LABA/LAMA plus usual care for comorbidities
Outcomes	Composite event of the first time to first re-hospitalisation and/or death (all-cause), COPD exacerbations, re-hospitalizations and deaths (all-cause), Quality of life, adverse events
	-
Notes	Ongoing study

TCTR20180530007

Study name	Efficiency of slow loaded breathing training on cardiovascular functions in COPD with hypertension
Starting date	1 June 2018
Contact information	Chattarin Wongsawat. Faculty of Associated Medical Science, Khon Kaen University
Population	COPD patients stage I-IV with hypertension
Interventions	Breathing training versus active comparator
Outcomes	Morning home blood pressure and heart rate, Heart rate variability and blood pressure variability, Arterial stiffness, Baroreflex sensitivity

TCTR20180530007 *(Continued)*

Notes	Ongoing study

TCTR20180601002

Study name	Effect of slow loaded breathing training on inspiratory muscle strength, exercise capacity and blood pressure in chronic obstructive pulmonary disease with co-existing hypertension
Starting date	15 June 2018
Contact information	-
Population	COPD patients stage moderate to severe with hypertension
Interventions	Breathing training versus active comparator
Outcomes	Inspiratory muscle strength, lung function, exercise endurance, dynamic hyperinflation, blood pressure and heart rate, quality of life, dyspnoea, exhaled breath temperature
	-
Notes	Ongoing study

DATA AND ANALYSES

Comparison 1. Intervention versus usual care

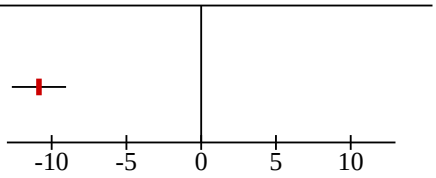
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Quality of life - SGRQ total	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2 Quality of life - CAT total	4		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2.1 Pharmacotherapy	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2.2 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2.3 Organisation of care	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.4 Multicomponent intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3 Quality of life - CRQ domains	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.1 Dyspnoea	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.2 Fatigue	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.3 Emotion	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.4 Mastery	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.4 Quality of life - MLHFQ	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.4.1 Multicomponent intervention	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.5 Quality of life - EQ-5D	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.5.1 VAS	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.5.2 EQ-5D utility domain	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.6 Exacerbations - people experiencing one or more	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.6.1 Rehabilitation	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.7 Exacerbations - mean number per person	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.7.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.8 Functional status - 6MWT	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8.1 Rehabilitation	2	100	Mean Difference (IV, Random, 95% CI)	60.40 [44.26, 76.54]
1.8.2 Multicomponent intervention	1	80	Mean Difference (IV, Random, 95% CI)	75.00 [28.06, 121.94]
1.9 Functional status - ISWT	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10 Functional status - ESWT	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11 All-cause hospital admissions - people experiencing one or more	2		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.11.1 Organisation of care	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.11.2 Multicomponent intervention	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.12 All-cause hospital admissions - mean number per person	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.12.1 Organisation of care	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.13 Respiratory-related hospital admissions	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.13.1 Multicomponent intervention	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.14 All-cause mortality (deaths)	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.14.1 Pharmacotherapy	2	177	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.23, 1.35]
1.14.2 Organisation of care	2	782	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.33, 0.96]
1.14.3 Multicomponent intervention	1	112	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.06, 16.39]
1.15 Anxiety HADS-A	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.15.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.16 Depression HADS-D	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.16.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.16.2 Organisation of care	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Intervention versus usual care, Outcome 1: Quality of life - SGRQ total

Study or Subgroup	MD	SE	Mean Difference IV, Random, 95% CI
1.1.1 Rehabilitation			
Budnevskiy 2015 (1)	-10.85	0.9251	-10.85 [-12.66 , -9.04]

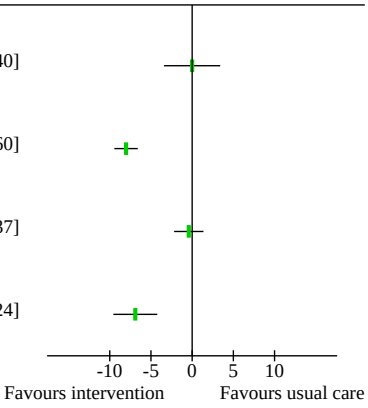


Footnotes

(1) 52 weeks follow-up

Analysis 1.2. Comparison 1: Intervention versus usual care, Outcome 2: Quality of life - CAT total

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Random, 95% CI
1.2.1 Pharmacotherapy							
Gottlieb 2020 (1)	0.4	6.8	40	0.4	8.3	37	0.00 [-3.40 , 3.40]
1.2.2 Rehabilitation							
Budnevskiy 2015 (2)	16.32	3.05	35	24.34	3.01	35	-8.02 [-9.44 , -6.60]
1.2.3 Organisation of care							
Walker 2018 (3)	16.76	7.71	154	17.17	8.33	158	-0.41 [-2.19 , 1.37]
1.2.4 Multicomponent intervention							
Bernocchi 2018 (4)	-5.3	5.51	45	1.6	6.41	35	-6.90 [-9.56 , -4.24]

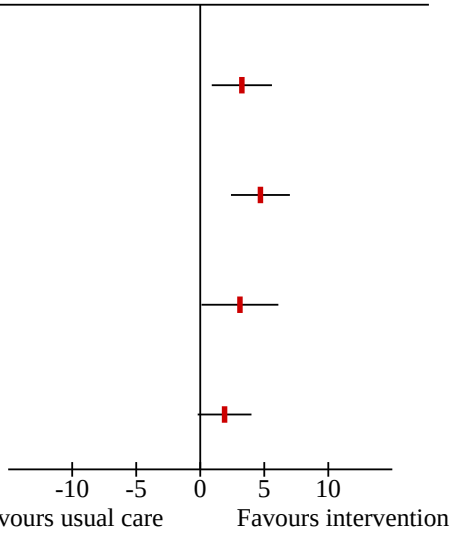


Footnotes

(1) 25 weeks follow-up
(2) 52 weeks follow-up
(3) Telemonitoring intervention, 39 weeks follow-up
(4) 17 weeks follow-up

Analysis 1.3. Comparison 1: Intervention versus usual care, Outcome 3: Quality of life - CRQ domains

Study or Subgroup	MD	SE	Mean Difference IV, Random, 95% CI
1.3.1 Dyspnoea			
McNamara 2013b (1)	3.25	1.199	3.25 [0.90 , 5.60]
1.3.2 Fatigue			
McNamara 2013b	4.7	1.1735	4.70 [2.40 , 7.00]
1.3.3 Emotion			
McNamara 2013b	3.1	1.5306	3.10 [0.10 , 6.10]
1.3.4 Mastery			
McNamara 2013b	1.9	1.0714	1.90 [-0.20 , 4.00]

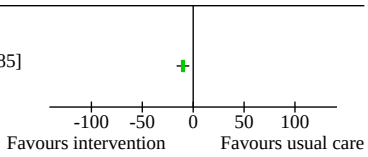


Footnotes

(1) 8 weeks follow-up

Analysis 1.4. Comparison 1: Intervention versus usual care, Outcome 4: Quality of life - MLHFQ

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Random, 95% CI
1.4.1 Multicomponent intervention							
Bernocchi 2018 (1)	-10.5	12.1699	45	-0.44	15.3597	35	-10.06 [-16.27 , -3.85]

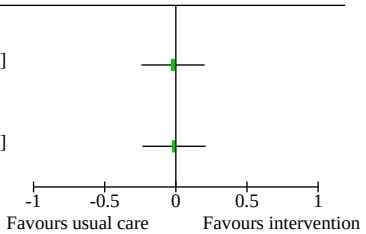


Footnotes

(1) 17 weeks follow-up

Analysis 1.5. Comparison 1: Intervention versus usual care, Outcome 5: Quality of life - EQ-5D

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Std. Mean Difference IV, Random, 95% CI
1.5.1 VAS							
Walker 2018 (1)	55.35	18.46	154	55.75	21.17	158	-0.02 [-0.24 , 0.20]
1.5.2 EQ-5D utility domain							
Walker 2018 (1)	0.637	0.225	154	0.64	0.248	158	-0.01 [-0.23 , 0.21]

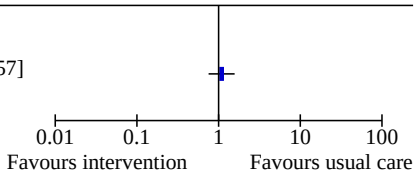


Footnotes

(1) 39 weeks follow-up

Analysis 1.6. Comparison 1: Intervention versus usual care, Outcome 6: Exacerbations - people experiencing one or more

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Odds Ratio M-H, Random, 95% CI
1.6.1 Rehabilitation					
Rose 2018 (1)	140	236	134	234	1.09 [0.75 , 1.57]

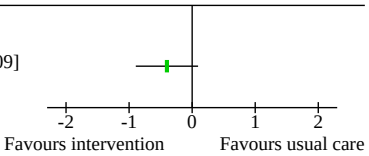


Footnotes

(1) ED visit; 52 weeks follow-up

Analysis 1.7. Comparison 1: Intervention versus usual care, Outcome 7: Exacerbations - mean number per person

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Random, 95% CI
1.7.1 Rehabilitation							
Rose 2018 (1)	1.5	2.3	236	1.9	3.1	234	-0.40 [-0.89 , 0.09]

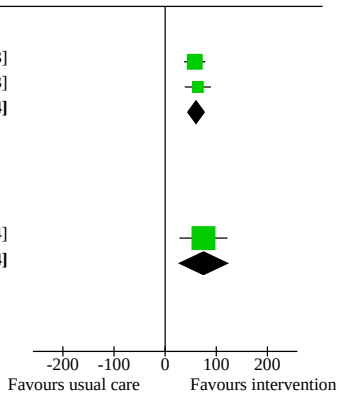


Footnotes

(1) 52 weeks follow-up

Analysis 1.8. Comparison 1: Intervention versus usual care, Outcome 8: Functional status - 6MWT

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Random, 95% CI
1.8.1 Rehabilitation								
Budnevskiy 2015 (1)	402	47.3286	35	344	41.4126	35	60.0%	58.00 [37.17 , 78.83]
McNamara 2013b (2)	48	39	15	-16	32	15	40.0%	64.00 [38.47 , 89.53]
Subtotal (95% CI)			**50**			**50**	**100.0%**	**60.40 [44.26 , 76.54]**
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%								
Test for overall effect: Z = 7.33 (P < 0.00001)								
1.8.2 Multicomponent intervention								
Bernocchi 2018 (3)	60	131	45	-15	82	35	100.0%	75.00 [28.06 , 121.94]
Subtotal (95% CI)			**45**			**35**	**100.0%**	**75.00 [28.06 , 121.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.13 (P = 0.002)								
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.56), I² = 0%								

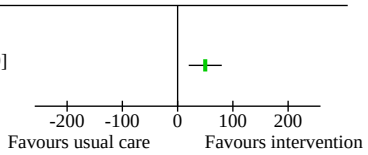


Footnotes

(1) 52 weeks follow-up
(2) 8 weeks follow-up
(3) 17 weeks follow-up

Analysis 1.9. Comparison 1: Intervention versus usual care, Outcome 9: Functional status - ISWT

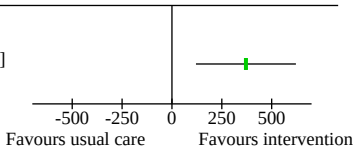
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.9.1 Rehabilitation							
McNamara 2013b (1)	49	42	15	-1	41.5326	15	50.00 [20.11 , 79.89]



Footnotes
(1) 8 weeks follow-up

Analysis 1.10. Comparison 1: Intervention versus usual care, Outcome 10: Functional status - ESWT

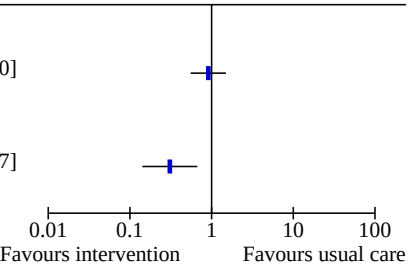
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.10.1 Rehabilitation							
McNamara 2013b (1)	321	357	15	-50	343	15	371.00 [120.46 , 621.54]



Footnotes
(1) Endpoint score, meters; 8 weeks follow-up

Analysis 1.11. Comparison 1: Intervention versus usual care, Outcome 11: All-cause hospital admissions - people experiencing one or more

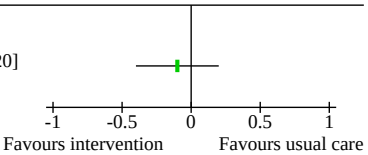
Study or Subgroup	Intervention Events	Total	Usual care Events	Total	Odds Ratio M-H, Random, 95% CI
1.11.1 Organisation of care					
Walker 2018 (1)	41	154	45	158	0.91 [0.55 , 1.50]
1.11.2 Multicomponent intervention					
Bernocchi 2018 (2)	21	56	37	56	0.31 [0.14 , 0.67]



Footnotes
(1) 39 weeks follow-up
(2) 17 weeks follow-up

Analysis 1.12. Comparison 1: Intervention versus usual care, Outcome 12: All-cause hospital admissions - mean number per person

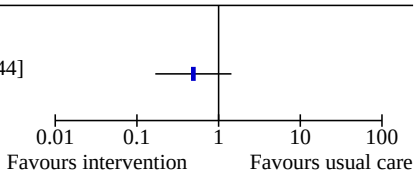
Study or Subgroup	Intervention Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.12.1 Organisation of care							
Rose 2018 (1)	0.8	1.5	236	0.9	1.8	234	-0.10 [-0.40 , 0.20]



Footnotes
(1) 52 weeks follow-up

Analysis 1.13. Comparison 1: Intervention versus usual care, Outcome 13: Respiratory-related hospital admissions

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
1.13.1 Multicomponent intervention						
Bernocchi 2018 (1)	6	56	11	56	0.49 [0.17 , 1.44]	

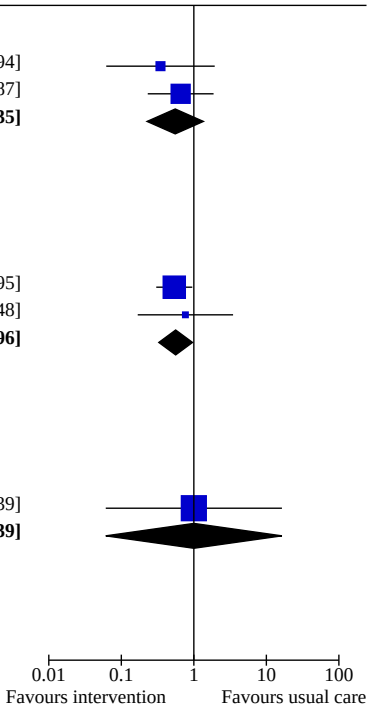


Footnotes

(1) 17 weeks follow-up

Analysis 1.14. Comparison 1: Intervention versus usual care, Outcome 14: All-cause mortality (deaths)

Study or Subgroup	Intervention Events	Intervention Total	Usual care Events	Usual care Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
1.14.1 Pharmacotherapy							
EUCTR2010-021412-42-GB (1)	2	32	5	31	26.9%	0.35 [0.06 , 1.94]	
Gottlieb 2020 (2)	7	57	10	57	73.1%	0.66 [0.23 , 1.87]	
Subtotal (95% CI)		**89**		**88**	**100.0%**	**0.55 [0.23 , 1.35]**	
Total events:	9		15				
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 1 (P = 0.53); I² = 0%							
Test for overall effect: Z = 1.30 (P = 0.19)							
1.14.2 Organisation of care							
Rose 2018 (3)	21	236	36	234	87.5%	0.54 [0.30 , 0.95]	
Walker 2018 (4)	3	154	4	158	12.5%	0.76 [0.17 , 3.48]	
Subtotal (95% CI)		**390**		**392**	**100.0%**	**0.56 [0.33 , 0.96]**	
Total events:	24		40				
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%							
Test for overall effect: Z = 2.12 (P = 0.03)							
1.14.3 Multicomponent intervention							
Bernocchi 2018 (5)	1	56	1	56	100.0%	1.00 [0.06 , 16.39]	
Subtotal (95% CI)		**56**		**56**	**100.0%**	**1.00 [0.06 , 16.39]**	
Total events:	1		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
Test for subgroup differences: Chi² = 0.16, df = 2 (P = 0.92), I² = 0%							

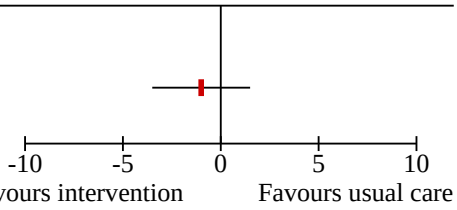


Footnotes

(1) 4 weeks follow-up
(2) 25 weeks follow-up
(3) 52 weeks follow-up
(4) 39 weeks follow-up
(5) 17 weeks follow-up

Analysis 1.15. Comparison 1: Intervention versus usual care, Outcome 15: Anxiety HADS-A

Study or Subgroup	MD	SE	Mean Difference IV, Random, 95% CI
1.15.1 Rehabilitation			
McNamara 2013b (1)	-1	1.2755	-1.00 [-3.50 , 1.50]

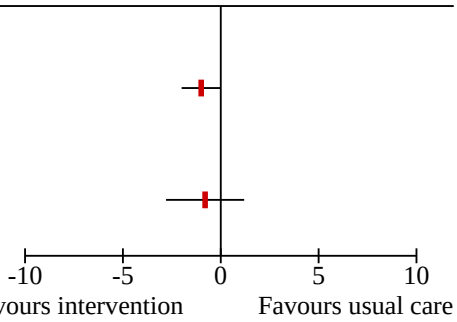


Footnotes

(1) 8 weeks follow-up

Analysis 1.16. Comparison 1: Intervention versus usual care, Outcome 16: Depression HADS-D

Study or Subgroup	MD	SE	Mean Difference IV, Random, 95% CI
1.16.1 Rehabilitation			
McNamara 2013b (1)	-1	0.5102	-1.00 [-2.00 , -0.00]
1.16.2 Organisation of care			
Rose 2018 (2)	-0.8	1.0184	-0.80 [-2.80 , 1.20]



Footnotes

(1) 8 weeks follow-up

(2) 52 weeks follow-up

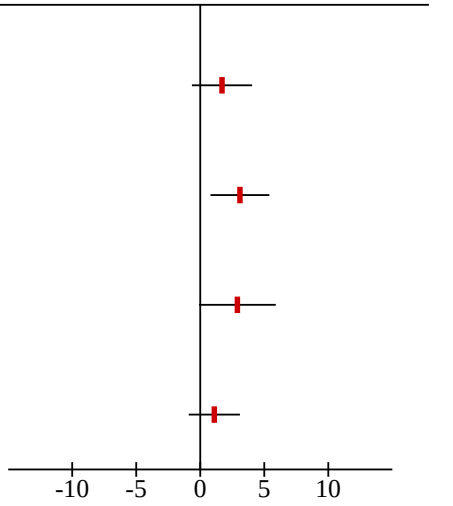
Comparison 2. Intervention versus active comparison

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Quality of life - CRQ domains	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1.1 Dyspnoea	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1.2 Fatigue	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1.3 Emotion	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1.4 Mastery	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.2 Functional status - 6MWT	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.2.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Functional status - ESWT	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.3.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.4 Functional status - ISWT	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.4.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.5 Anxiety HADS-A	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.5.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.6 Depression HADS-D	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.6.1 Rehabilitation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Intervention versus active comparison, Outcome 1: Quality of life - CRQ domains

Study or Subgroup	MD	SE	Mean Difference IV, Random, 95% CI
2.1.1 Dyspnoea			
McNamara 2013b (1)	1.7	1.199	1.70 [-0.65 , 4.05]
2.1.2 Fatigue			
McNamara 2013b	3.1	1.1735	3.10 [0.80 , 5.40]
2.1.3 Emotion			
McNamara 2013b	2.9	1.5306	2.90 [-0.10 , 5.90]
2.1.4 Mastery			
McNamara 2013b	1.1	1.0204	1.10 [-0.90 , 3.10]

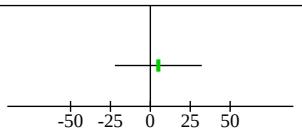


Footnotes

(1) 8 weeks follow-up

Analysis 2.2. Comparison 2: Intervention versus active comparison, Outcome 2: Functional status - 6MWT

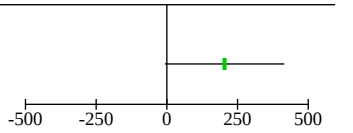
Study or Subgroup	Intervention Mean	SD	Total	Active comparator Mean	SD	Total	Mean Difference IV, Random, 95% CI
2.2.1 Rehabilitation							
McNamara 2013b (1)	48	39	15	43	37	15	5.00 [-22.21 , 32.21]



Footnotes
(1) 8 weeks follow-up

Analysis 2.3. Comparison 2: Intervention versus active comparison, Outcome 3: Functional status - ESWT

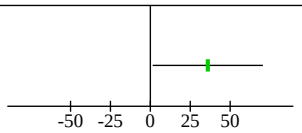
Study or Subgroup	Intervention Mean	SD	Total	Active comparator Mean	SD	Total	Mean Difference IV, Random, 95% CI
2.3.1 Rehabilitation							
McNamara 2013b (1)	321	357	15	117	216	15	204.00 [-7.16 , 415.16]



Footnotes
(1) change from baseline within group; 8 weeks follow-up

Analysis 2.4. Comparison 2: Intervention versus active comparison, Outcome 4: Functional status - ISWT

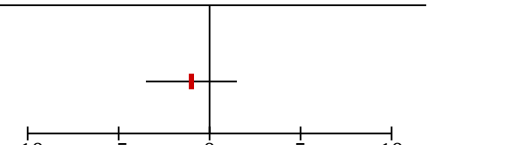
Study or Subgroup	Intervention Mean	SD	Total	Active comparator Mean	SD	Total	Mean Difference IV, Random, 95% CI
2.4.1 Rehabilitation							
McNamara 2013b (1)	49	43	15	13	53	15	36.00 [1.46 , 70.54]



Footnotes
(1) 8 weeks follow-up

Analysis 2.5. Comparison 2: Intervention versus active comparison, Outcome 5: Anxiety HADS-A

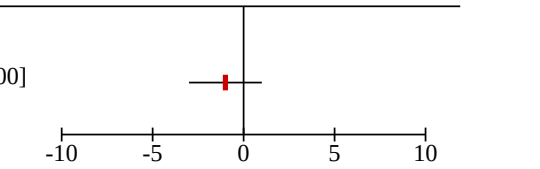
Study or Subgroup	MD	SE	Mean Difference IV, Random, 95% CI
2.5.1 Rehabilitation			
McNamara 2013b (1)	-1	1.2755	-1.00 [-3.50 , 1.50]



Footnotes
(1) 8 weeks follow-up

Analysis 2.6. Comparison 2: Intervention versus active comparison, Outcome 6: Depression HADS-D

Study or Subgroup	MD	SE	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
2.6.1 Rehabilitation				
McNamara 2013b (1)	-1	1.0204	-1.00 [-3.00 , 1.00]	



Footnotes

(1) 8 weeks follow-up

ADDITIONAL TABLES

Table 1. Risk of bias assessment for qualitative studies

Study ID	Is there a statement of research aims?	Is a qualitative approach justified?	Was the research design appropriate to address the aims?	Was the recruitment strategy appropriate to address the aims?	Were data collected in a way that addressed the research issue?	Was the researcher/participant relationship adequately considered?	Have ethical issues been taken into consideration?	Was the data analysis sufficiently rigorous?	Was there a clear statement of findings?	Overall assessment
Middlemass 2017	Yes	Yes	Can't tell	Yes	Can't tell	No	Yes	Yes	Yes	Some concerns
	To test the HITAM and see if it could be used to increase the adoption of HIT. HIT has been shown to reduce mortality. Many with LTC are over 60 and HIT is not always accepted.	Pre- and post-interviews to ascertain perceptions/experience on the HITAM elements. However, no rationale for adopting a qualitative and framework approach.	The study design (instrumental, collective case design) is not justified.	Selection process for interviews included those who had taken part in the pilot and those assigned to the Rx. One was not interviewed and was unwell.	Setting of interviews (home or telephone) was not justified. Not clear if interviewers were in-depth or semi-structured. Not justified why interviews were chosen rather than focus groups. Interview schedule was used and is made available. Interviews were audio-recorded. Data saturation is not mentioned.	The interviewer's role is not described or examined.	Ethical approval obtained and informed written consent to take part in two taped interviewers to ascertain views if using the equipment.	Process of analysis is well described, although unsure how the framework was formed. Quotes provided to support themes. Contrasting data are taken into account and described.	Explicit well organised findings and multiple researchers involved in the process.	-

Abbreviations: HITAM: Health Information Technology Acceptance Model; LTC: long term condition.

Table 2. Framework and map of interventions identified from included studies

Interventions (identified from GOLD 2021 guideline and Cochrane Airways subtopic list.)	Study	Interventions	Evidence type (quantitative, qualitative or mixed methods)	Comorbidities
• Reducing risk factors * Smoking cessation	-		-	-
• Vaccination * Pneumococcal * Influenza	-		-	-
• Pharmacotherapies * Short-acting inhalers (e.g. SABA) * Long-acting inhalers (e.g. LABA, LAMA, ICS) * Phosphodiesterase-4 (PDE4) inhibitors (e.g. Roflumilast) * Mucolytic agents * Combination inhalers and triple therapy * Methyl xanthines * Oral corticosteroids * Antibiotics * Statins * Alpha-1 antitrypsin augmentation therapy * Biomarker mediated therapy	EUC-TR2010-021412-42-GB	Inhaler optimisation and best supportive care vs UC	Quantitative	All had lung cancer
	Gottlieb 2020	Management: optimising COPD treatment vs UC	Quantitative	All had lung cancer or head and neck cancer, and some had other comorbidities including ischaemic heart diseases, heart failure, depression/anxiety, osteoporosis, cerebrovascular disease, diabetes
• Rehabilitation * Pulmonary rehabilitation * Exercise therapy (e.g. upper limb exercise, ongoing physical exercise after pulmonary rehabilitation) * Complementary therapies (e.g. active mind-body therapy, Tai chi, singing)	Budnevskiy 2015	Pulmonary rehabilitation vs UC	Quantitative	All had metabolic syndrome
	McNamara 2013b	Water-based exercise training vs land-based exercise training vs UC	Quantitative	One or more physical comorbidities: musculoskeletal, or neurological, or obesity
• Self-management	-	-	-	-
• Organisation of care * Support services (e.g. social care, specialist respiratory nurse) * Integrated care * Telehealthcare * Digital management interventions * Home care * Integrated disease management (e.g. disease management programming) * Interventions to promote or increase adherence to PR or other treatments	Rose 2018	Case management vs UC	Quantitative	Two or more comorbidities: cardiovascular disease, including coronary artery disease, hypertension and congestive heart failure, diabetes, depression, osteopenia, osteoporosis, and gastro-oesophageal reflux disease.
	Walker 2018 Middlemass 2017	Telemonitoring vs UC	Quantitative Qualitative	One or more non-pulmonary comorbidity: congestive heart failure or ischaemic heart disease or both, hyperten-

Table 2. Framework and map of interventions identified from included studies *(Continued)*

				sion, osteoporosis, hyperlipidaemia, osteoporosis, sleep-related disordered breathing.
• Other treatments * Oxygen therapy and ventilatory support (e.g. NIV, ambulatory oxygen) * Nutritional support * Lung volume reduction surgery * Lung transplantation * Supportive, palliative, end of life and hospice care * Psychotherapy * interventions for sexual dysfunction * Self-help groups	-	-	-	-
• Multicomponent intervention	Bernocchi 2018	Maintenance rehabilitation and telemonitoring vs UC. Following inpatient rehabilitation participants randomised to personalised discharge plus nurse telephone support and telemonitoring, plus physiotherapist personalised rehabilitation vs UC	Quantitative	All had cardiovascular disease

UC: usual care

Table 3. Summary of interventions

Study	Duration (weeks)	Intervention	Comparison	Setting	Provider	Materials/method	Delivery	Tailoring
Pharmacotherapy								
EUC-TR2010-021412-42-GB	4	Pharmacotherapy: inhaler optimisation and best supportive care	UC	Outpatient	NR	Evohaler 100 µg, Spiriva 18 mg via Handihaler, fluticasone propionate 500 µg	Inhaler	Considered the poor prognosis of patients with lung cancer: intervention group treated with maximum inhaled therapy
Gottlieb 2020	25	Management: optimising COPD treatment	UC	Outpatient clinic	Pulmonary physician	Two visits at 12 and 24 weeks in an outpatient clinic where the adjustment of COPD treatment was considered	Dialogue with the participants	Adjustment of COPD treatment considered at each visit
Rehabilitation								
Budnevskiy 2015	52	Pulmonary rehabilitation	UC	NR	NR	Series of seminars covering treatment and prevention of COPD and MS. Physical training: therapeutic exercises.	Group seminars	Exercises took into account concomitant MS
Gurgun 2013	8	Pulmonary rehabilitation and nutritional support	PR or UC	Outpatient clinic	Dietician	Dietary counselling and oral supplementation in combination with exercise training	Supervised exercise training, dietary counselling	Daily nutrition intake of the patient was checked
McNamara 2013b	8	Water-based exercise training	Land-based exercise training or UC	Hospital hydrotherapy pool	Physiotherapist	Exercise in a hydrotherapy pool: warm-up, lower limb endurance, upper limb endurance, and cool down	Supervised exercise	Training intensity measured, participants chose the most comfortable level of water immersion
Organisation of care								
Rose 2018	52	Case management	UC	Outpatient	Case-manager	Education based on 'Living Well with COPD', ongoing communication with physician and hospital specialist	Education session at enrolment, telephone	Individualised action plan

Table 3. Summary of interventions *(Continued)*

							consultations	
Walker 2018	39	Telemonitoring	UC	Outpatient	Study nurse	CHROMED monitoring platform	Wearable device	Respiratory alert triggered contact with the nurse if worsening was detected
Multicomponent intervention								
Bernocchi 2018	17	Inpatient rehabilitation, personalised discharge, nurse telephone support and telemonitoring, physiotherapist personalised maintenance rehabilitation	Inpatient rehabilitation, UC	Participants' home	Nurse; physiotherapist	Exercise programme, mini-ergometer, pedometer and diary. Participants provided with a pulse oximeter, and a portable one-lead ECG	PT instruction; weekly phone call with NT; weekly phone call with PT	Personalised exercise programme

Abbreviations: COPD: Chronic obstructive pulmonary disease; MS: metabolic syndrome; NT: Nurse Tutor; PT:Physiotherapist tutor; UC: usual care

Table 4. Summary of baseline characteristics

Study	COPD severity	Comorbidities (%) Intervention	Comorbidities (%) Control	Ethnicity	Male (%)		Age (Mean, SD)	
					Intervention	Control	Intervention	Control
Bernocchi 2018	Mild to very severe	Cardiovascular disease (100%)	Cardiovascular disease (100%)	NR	88	75	71 (9)	70 (9.5)
Budnevskiy 2015	Moderate	Metabolic syndrome (100%)	Metabolic syndrome (100%)	NR	66	71	NR	NR
EUCTR2010-021412-42-GB	NR	Lung cancer (100%)	Lung cancer (100%)	NR	34	38	68 (59 to 75)*	67 (61 to 71)*
Gottlieb 2020	Mild to severe	Lung cancer (84%); head-and-neck cancer (16%); Ischaemic heart disease/heart failure (12.3%);	Lung cancer (82.5%); head-and-neck cancer (17.5%); ischaemic heart disease/heart failure (10.5%); Depres-	NR	58	69	67.8 (8.3)	67.2 (8.1)

Table 4. Summary of baseline characteristics *(Continued)*

		Depression/anxiety (3.5%); Osteoporosis (12.3%); Cerebrovascular disease (14%); Diabetes (14%)	sion/anxiety (3.5%); Osteoporosis (10.5%); Cerebrovascular disease (8.8%); Diabetes (8.8%)					
McNamara 2013b	NR	Water-based group: Musculoskeletal (50%); neurological (5.5%); obesity (44.5%) Land-based group: Musculoskeletal (65%); neurological (5%); obesity (30%)	Musculoskeletal (47%); neurological (0%); obesity (53%)	NR	Water-based group: 28 Land-based group: 50	47	Water-based group: 72 (10) Land-based group: 73(7)	70 (9)
Rose 2018	Moderate to severe	Two or more comorbidities: cardiovascular disease (75%); diabetes (18%); depression (17%); Osteopenia and osteoporosis (30%); Gastro-oesophageal reflux disease (14%); Hypothyroidism (9%); Osteoarthritis (9%); Glaucoma and cataracts (9%); Cachexia and malnutrition (10%); Chronic kidney disease (7%); Anxiety (6%); Peripheral muscle dysfunction (6%); Obstructive sleep apnoea (5%); Lung cancer (6); Cerebrovascular accident (3%)	Two or more comorbidities: cardiovascular disease (76%); diabetes (22%); depression (20%); Osteopenia and osteoporosis (29%); Gastro-oesophageal reflux disease (12%); Hypothyroidism (9%); Osteoarthritis (9%); Glaucoma and cataracts (9%); Cachexia and malnutrition (8%); Chronic kidney disease (7%); Anxiety (7%); Peripheral muscle dysfunction (6%); Obstructive sleep apnoea (6%); Lung cancer (6%); Cerebrovascular accident (4%)	NR	50	44	71 (9.2)	71 (9.7)
Walker 2018	Mild to very severe	One or more non-pulmonary comorbidities: Congestive heart failure (12%); ischaemic heart disease (25%; Congestive heart failure plus ischaemic heart disease (12%); hypertension (72%); Sleep-related disordered breathing (11%); Os-	One or more non-pulmonary comorbidities: Congestive heart failure (8%); ischaemic heart disease (23%; Congestive heart failure plus ischaemic heart disease (13%); hypertension (68%); Sleep-related disordered breathing (6%); Osteoporosis (15%); Hyperlipidemia (58%)	NR	66	66	71 (66.0 to 75.8)*	71 (65.3 to 76.0)*

Table 4. Summary of baseline characteristics *(Continued)*

		teoporosis (17%); Hyperlipidemia (53%)

*median, interquartile range
Abbreviations: NR: not reported

Table 5. Summary of relevant quantitative study outcomes

Study ID	Outcome domain	Outcome measure	End point time (weeks)
Bernocchi 2018	All-cause hospital admissions	Number of events	17
	Functional status	6MWT	
	Functional status	PASE	
	Mortality (all-causes)	Number of events	
	Quality of life	MLHFQ	
	Quality of life	CAT	
	Quality of life	Dyspnoea MRC	
	Respiratory hospital admissions	Number of events	
	Functional status	6MWT	
	Quality of life	CAT (total)	
	Quality of life	SGRQ (total)	
	Quality of life	Dyspnoea MRC	
Budnevskiy 2015	Functional status	6MWT	52 weeks
	Quality of life	CCQ	
	Quality of life	CAT (total)	
	Quality of life	SGRQ (total)	
EUC-TR2010-021412-42-GB	Adverse events	Number of events	4
	Mortality (all-causes)	Number of events	
	Quality of life	Dyspnoea	
Gottlieb 2020	Mortality (all-causes)	Number of events	25
	Quality of life	CAT (total)	
McNamara 2013b	Anxiety symptoms	HADS-A (anxiety)	8
	Depression symptoms	HADS-D (depression)	
	Functional status	ESWT	
	Functional status	6MWT	
	Functional status	ISWT	

Table 5. Summary of relevant quantitative study outcomes *(Continued)*

	Functional status	ESWT	
	Quality of life	CRDQ dyspnoea	
Rose 2018	All-cause hospital admissions	Mean & SD	
	All-cause hospital admissions	Risk difference	52
	Anxiety symptoms	HADS-A (anxiety)	
	Depression symptoms	HADS-D (depression)	
	Exacerbations	Exacerbation (ED visit)	
	Mortality (all-causes)	Number of events	
	Quality of life	SGRQ (total)	
Walker 2018	All-cause hospital admissions	Hospitalisation rate	39
	All-cause hospital admissions	Number of people experiencing one or more events	
	Exacerbations	Exacerbation rate moderate exacerbations	
	Mortality (all-causes)	Number of events	
	Quality of life	CAT (total)	
	Quality of life	PHQ-9	
	Quality of life	EQ-5D utility	
	Quality of life	EQ-5D VAS	

6MWT: 6-Minute Walk Test; CAT: COPD Assessment Test; CCQ: COPD clinical questionnaire; CRQ: Chronic Respiratory Disease Questionnaire; CSES: Coping Self-Efficacy Scale; EQ-5D: EuroQuol-5D; ESWT: Endurance Shuttle Walk Test; HADS: Hospital Anxiety and Depression Scale; ICFS: Identity-Consequence Fatigue Score; ISWT: Incremental Shuttle Walk Test; MLHFQ: Minnesota Living with Heart Failure Questionnaire; MRC: Medical Research Council; PASE: Physical Activity Profile; PHQ-9: Patient Health Questionnaire-9; PIH: Partners in Health scale; SGRQ: St George's Respiratory Questionnaire; VAS: Visual Analogue Scale.

Table 6. First and second order constructs of qualitative studies

Study	Aims	Main themes and example quotes provided in study report	Author comments provided in the study report	Conclusions - review author team interpretation of study results
Middlemass 2017 **, UK**	To explore the usefulness of the HITAM for understanding acceptance of HIT in older people (≥ 60 years age)	**Health status, beliefs and concerns** **Unchanging nature of condition:** Patients accepted that their chronic condition was unlikely to change and that ageing and (eventual) death was inevitable: "*I'm getting older and I'm not going to get any better. I haven't got*	**Acceptance of illness**: Some patients had accepted the life-restricting (and sometimes life-threatening) limitations of their LTCs	Beliefs about condition influence motivation to engage in HIT

Table 6. First and second order constructs of qualitative studies *(Continued)*

with COPD and associated heart diseases	*young genes to repair everything. So, if I can pummel along the way I am, I'll accept it".*		
	Withdrawal of face-to-face communication: "*But I would hope they would still do their person- to-person contact [and] that they wouldn't just forget."*	**Concern of losing face to face contact:** Patients were concerned that they would lose face-to-face communication with their HCP when using TM	HCP face to face interaction is reassuring that their condition is actively being monitored
	Reminder of illness and anxiety : *"This is reminding me every day, then I should think I wonder what my reading is, how good it is or how bad it is and I thought no, get away from illness you know. Every time as soon I started thinking about it, I started thinking about my illness..."*	**Fear of illness:** Patients perception of telemonitoring was linked to fear of reminders of how serious their condition was, which led to them not continuing with home monitoring	Belief that HIT causes anxiety about condition which can lead to non-adherence/
	Information **Subjective norms:** *"I think if my very close relatives…and if the GP said it is essential… I would say I'm definitely going ahead with it"*	**Increased motivation to comply with HIT:** Close relatives and GP influenced and increased individuals' perceptions of using HIT	Input from HCP and relatives increases acceptance to use HIT
	Technology **Unreliable technology:** *"...a couple of times it didn't go through very well, but that was an internet problem".*	**Unreliable technology**: Poor internet connectivity and data transmission in rural areas led to generation of technical alerts, which led to the study research nurse visiting the patient to find out what the problem was.	HIT can be beneficial for those who cannot visit HCP face to face, however, this can be limited by Internet connectivity
	HIT Self-efficacy: *"The very first time I really got panicked. But then the next day when I did it, it was easier, but I was at the start of a chest infection, which did affect me… It helped my husband stood beside me and was chatting saying yeah you're doing fine, not long to go, just a little bit of encouragement"*	**Increased self-efficacy:** Both HCPs and patients' significant others were key to them using the TM equipment.	Patients' relatives and HCPs can help to reduce apprehension of using HIT in the initial stages
	Perceived usefulness **Daily monitoring of conditions:** "...I *feel more comfortable knowing that somebody's checking it all the time, you know they're looking at it every day..."*	**Confidence of daily monitoring:** Patients perception of being linked to a HCP checking data and ready to act on change in health status led them to feel safe about using HIT.	Patients' perceptions are dependent on knowing that HCP involvement is linked to HIT
	Factors affecting usefulness **Lack of feedback**: *"I'm in a vacuum. I'm doing something, I'm sending it off to you, [but] there's no feedback..."*	**Lack of feedback**: there was lack of two-way communication between the patient and HCP	Lack of feedback from HCP resulted in reduced perception of usefulness of HIT

Table 6. First and second order constructs of qualitative studies *(Continued)*

	Behaviour **Self-management and health care utilisation:** Patients felt that their condition stabilised after joining the study and did not need to go to the GP so often: *"I've been less to the surgery... Because I think it's helped me sort everything out. I'm much better on the medication I'm on now for my blood pressure."*	**Improved self-management and reduced need to see the GP:** Patients' condition stabilised whilst enrolled in the study, and GP visits also declined.	HIT may lead to changes in behaviour towards improving patients' self-management and a reduced need to visit the GP

Abbreviations: HITAM: Health Information Technology Acceptance Model

APPENDICES

Appendix 1. Database search strategies

Appendix 2a: Searches to identify reports of RCTs

Source	Search strategy	Results retrieved
Cochrane Airways Trials Register (Date of most recent search:6 January 2021)	1 MESH DESCRIPTOR Lung Diseases, Obstructive AND INSEGMENT 2 MESH DESCRIPTOR Pulmonary Disease, Chronic Obstructive EXPLODE ALL AND INSEGMENT 3 emphysema*:ti,ab,kw AND INSEGMENT 4 (chronic* NEAR3 bronchiti*):ti,ab,kw AND INSEGMENT 5 (obstruct* NEAR3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)):ti,ab,kw AND INSEGMENT 6 (COPD or COAD or COBD or AECB or AECOPD):ti,ab. AND INSEGMENT 7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 AND INREGISTER 8 MESH DESCRIPTOR COMORBIDITY EXPLODE ALL AND INSEGMENT 9 (multidisease* or multi-disease* or ((multiple or coexist* or co-exist*) NEAR2 (illness* or disease* or condition* or syndrom* or disorder*))):ti,ab,kw AND INREGISTER 10 (multimorbid* or multi-morbid*):ti,ab,kw AND INREGISTER 11 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND INREGISTER 12 (comorbid* or co-morbid*):ti,ab,kw AND INSEGMENT 13 (chronic* NEXT (illness* or disease* or condition* or disorder*)):ti,ab,kw AND INREGISTER 14 other health condition*:ti,ab,kw AND INREGISTER 15 other medical condition*:ti,ab,kw AND INREGISTER 16 (associated NEAR2 (disease* or disorder* or condition* or illness* or syndrome*)):ti,ab,kw AND INREGISTER 17 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 AND INREGISTER 18 #17 AND #7 AND INREGISTER 19 (multidisease* or multi-disease* or ((multiple or coexist* or co-exist*) NEXT (illness* or disease* or condition* or syndrom* or disorder*))):ti,ab,kw AND INSEGMENT 20 (multimorbid* or multi-morbid*):ti,ab,kw AND INSEGMENT 21 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND INSEGMENT 22 (chronic* NEXT (illness* or disease* or condition* or disorder*)):ti,ab,kw AND INSEGMENT 23 other health condition*:ti,ab,kw AND INSEGMENT 24 other medical condition*:ti,ab,kw AND INSEGMENT	June 2019 = 1234 February 2020 = 55 January 2021 = 53

(Continued)

	25 (associated NEAR2 (disease* or disorder* or condition* or illness* or syndrome*)):ti,ab,kw AND INSEGMENT 26 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 AND INREGISTER 27 #17 AND #7 AND INREGISTER	
CENTRAL (via CRS Web) (Date of most recent search:6 January 2021)	1 MESH DESCRIPTOR Lung Diseases, Obstructive AND CENTRAL:TARGET 2 MESH DESCRIPTOR Pulmonary Disease, Chronic Obstructive EXPLODE ALL AND CENTRAL:TARGET 3 emphysema*:ti,ab,kw AND CENTRAL:TARGET 4 (chronic* NEAR3 bronchiti*):ti,ab,kw AND CENTRAL:TARGET 5 (obstruct* NEAR3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)):ti,ab,kw AND CENTRAL:TARGET 6 (COPD or COAD or COBD or AECB or AECOPD):ti,ab. AND CENTRAL:TARGET 7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 AND CENTRAL:TARGET 8 MESH DESCRIPTOR COMORBIDITY EXPLODE ALL AND CENTRAL:TARGET 9 (comorbid* or co-morbid*):ti,ab,kw AND CENTRAL:TARGET 10 (multidisease* or multi-disease* or ((multiple or coexist* or co-exist*) NEAR2 (illness* or disease* or condition* or syndrom* or disorder*))):ti,ab,kw AND CENTRAL:TARGET 11 (multimorbid* or multi-morbid*):ti,ab,kw AND CENTRAL:TARGET 12 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND CENTRAL:TARGET 13 (chronic* NEXT (illness* or disease* or condition* or disorder*)):ti,ab,kw AND CENTRAL:TARGET 14 other health condition*:ti,ab,kw AND CENTRAL:TARGET 15 other medical condition*:ti,ab,kw AND CENTRAL:TARGET 16 (associated NEAR2 (disease* or disorder* or condition* or illness* or syndrome*)):ti,ab,kw AND CENTRAL:TARGET 17 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 AND CENTRAL:TARGET 18 #17 AND #7 AND CENTRAL:TARGET	June 2019=2967 February 2020=451 January 2021=328
MEDLINE (Ovid) (Date of most recent search:6 January 2021)	1 Lung Diseases, Obstructive/ 2 exp Pulmonary Disease, Chronic Obstructive/ 3 emphysema$.tw. 4 (chronic$ adj3 bronchiti$).tw. 5 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw. 6 (COPD or COAD or COBD or AECB or AECOPD).ti,ab. 7 or/1-6 8 exp COMORBIDITY/ 9 (comorbid$ or co-morbid$).tw. 10 (multidisease$ or multi-disease$ or ((multiple or coexist$ or co-exist$) adj2 (illness$ or disease$ or condition$ or syndrom$ or disorder$))).ti,ab. 11 (multimorbid$ or multi-morbid$).tw. 12 exp Chronic Disease/ 13 (chronic$ adj2 (illness$ or disease$ or condition$ or disorder$)).tw. 14 other health condition$.tw. 15 other medical condition$.tw. 16 (associated adj2 (disease$ or disorder$ or condition$ or illness$ or syndrome$)).tw. 17 or/8-16 18 7 and 17 19 (controlled clinical trial or randomised controlled trial).pt. 20 (randomised or randomised).ab,ti. 21 placebo.ab,ti. 22 dt.fs. 23 randomly.ab,ti. 24 trial.ab,ti. 25 groups.ab,ti.	June 2019: 7609 February 2020: 771 Jnaury 2021=450

(Continued)

	26 or/19-25 27 Animals/ 28 Humans/ 29 27 not (27 and 28) 30 26 not 29 31 18 and 30	
Embase (Ovid) (Date of most recent search:6 January 2021)	1 chronic obstructive lung disease/ 2 chronic bronchitis/ 3 exp lung emphysema/ 4 emphysema$.tw. 5 (chronic$ adj3 bronchiti$).tw. 6 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw. 7 (COPD or AECB or AECOPD).ti,ab. 8 or/1-7 9 comorbidity/ 10 (comorbid$ or co-morbid$).tw. 11 (multidisease$ or multi-disease$ or ((multiple or coexist$ or co-exist$) adj2 (illness$ or disease$ or condition$ or syndrom$ or disorder$))).ti,ab. 12 (multimorbid$ or multi-morbid$).tw. 13 exp chronic disease/ 14 (chronic$ adj (illness$ or disease$ or condition$ or disorder$)).tw. 15 other health condition$.tw. 16 other medical condition$.tw. 17 (associated adj2 (disease$ or disorder$ or condition$ or illness$ or syndrome$)).tw. 18 or/9-17 19 8 and 18 20 Randomized Controlled Trial/ 21 randomisation/ 22 controlled clinical trial/ 23 Double Blind Procedure/ 24 Single Blind Procedure/ 25 Crossover Procedure/ 26 (clinica$ adj3 trial$).tw. 27 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw. 28 exp Placebo/ 29 placebo$.ti,ab. 30 random$.ti,ab. 31 ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw. 32 (crossover$ or cross-over$).ti,ab. 33 or/20-32 34 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ 35 human/ or normal human/ or human cell/ 36 34 and 35 37 34 not 36 38 33 not 37 39 19 and 38	June 2019=5262 February 2020=906 January 2021=584
CINAHL (EBSCO) (Date of most recent search: 11 June 2019)	S42 S18 AND S41 S41 S40 NOT S39 S40 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 S39 S37 NOT S38 S38 (MH "Human") S37 S34 OR S35 OR S36 S36 TI (animal model*) S35 (MH "Animal Studies")	June 2019=971 February 2020=not searched January 2021=not searched

(Continued)

	S34 (MH "Animals+") S33 AB (cluster W3 RCT) S32 MH (crossover design) OR MH (comparative studies) S31 AB (control W5 group) S30 PT (Randomized Controlled Trial) S29 (MH "Placebos") S28 MH ("sample size") AND AB (assigned OR allocated OR control) S27 TI (trial) S26 AB (random*) S25 TI (randomised OR randomised) S24 (MH "Cluster Sample") S23 (MH "Pretest-Posttest Design") S22 (MH "Random Assignment") S21 (MH "Single-Blind Studies") S20 (MH "Double-Blind Studies") S19 (MH "Randomized Controlled Trials") S18 S7 AND S17 S17 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 S16 AB (associated N1 (disease* or disorder* or condition* or illness* or syndrome*)) OR TI (associated N1 (disease* or disorder* or condition* or illness* or syndrome*)) S15 "other medical condition*" S14 "other health condition*" S13 AB (chronic* N1 (illness* or disease* or condition* or disorder*)) OR TI (chronic* N1 (illness* or disease* or condition* or disorder*)) S12 (MH "Chronic Disease+") S11 AB (multimorbid* or multi-morbid*) OR TI (multimorbid* or multi-morbid*) S10 AB (multidisease* or multi-disease* or ((multiple or coexist* or co-exist*) N2 (illness* or disease* or condition* or syndrom* or disorder*))) OR TI (multidisease* or multi-disease* or ((multiple or coexist* or co-exist*) N2 (illness* or disease* or condition* or syndrom* or disorder*))) S9 AB (comorbid* or co-morbid*) OR TI (comorbid* or co-morbid*) S8 (MH "Comorbidity") S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6 S6 AB (COPD or AECB or AECOPD) S5 AB (obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) OR TI (obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) S4 AB (chronic* N3 bronchiti*) OR TI (chronic* N3 bronchiti*) S3 AB (emphysema*) OR TI (emphysema*) S2 (MH "Lung Diseases, Obstructive") S1 (MH "Pulmonary Disease, Chronic Obstructive+")	
PsycINFO (Ovid) (Date of most recent search: 11 June 2019)	1 exp chronic obstructive pulmonary disease/ 2 emphysema$.tw. 3 (chronic$ adj3 bronchiti$).tw. 4 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw. 5 (COPD or COAD or COBD or AECB or AECOPD).ti,ab. 6 or/1-5 7 comorbidity/ 8 (comorbid$ or co-morbid$).tw. 9 (multidisease$ or multi-disease$ or ((multiple or coexist$ or co-exist$) adj2 (illness$ or disease$ or condition$ or syndrom$ or disorder$))).ti,ab. 10 (multimorbid$ or multi-morbid$).tw. 11 chronic illness/ 12 (chronic$ adj2 (illness$ or disease$ or condition$ or disorder$)).tw. 13 other health condition$.tw. 14 other medical condition$.tw.	June 2019=185 February 2020=not searched January 2021=not searched

(Continued)

	15 (associated adj2 (disease$ or disorder$ or condition$ or illness$ or syndrome$)).tw. 16 or/7-15 17 6 and 16 18 exp clinical trials/ 19 random$.tw. 20 (clinical adj5 trial$).tw. 21 (control$ adj5 trial$).tw. 22 ((clinical or control$ or comparativ$) adj5 (study or studies)).tw. 23 placebo$.tw. 24 (single blind$ or single-blind$).tw. 25 (double blind$ or double-blind$).tw. 26 (triple blind$ or triple-blind$).tw. 27 or/18-26 28 17 and 27	
Web of Science Core Collection* (Date of most recent search:6 January 2021)	#11 #10 AND #7 #10 #9 OR #8 #9 TITLE: ((randomised OR randomised OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)))) #8 TOPIC: ((randomised OR randomised OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)))) #7 #6 AND #3 #6 #5 OR #4 #5 TI=(comorbid* or co-morbid* or multi-morbid* or multimorbid* or multidisease* or multi-disease* or "multiple disease*") #4 TS=(comorbid* or co-morbid* or multi-morbid* or multimorbid* or multi-disease* or multi-disease* or "multiple disease*") #3 #2 OR #1 #2 TITLE: ((COPD OR AECOPD OR emphysema OR "chronic bronchitis" OR "chronic obstructive pulmonary disease")) #1 TOPIC: ((COPD OR AECOPD OR emphysema OR "chronic bronchitis" OR "chronic obstructive pulmonary disease"))	June 2019=529 February 2020=47 January 2021=40
ClinicalTrials.gov (Date of most recent search:6 January 2021)	Study type: all Condition: COPD Other Search terms: comorbidity OR comorbidities OR multi -morbidity OR multi-morbidities	June 2019=56 February 2020=0 January 2021=4
WHO trials registry (Date of most recent search: 10 June 2019)	Condition: COPD Other Search terms: comorbidity OR comorbidities OR multi-morbidity OR multi-morbidities	June 2019=3 February 2020=not searched January 2021=not searched

*Core collection= Science Citation Index Expanded (SCI-EXPANDED); Social Sciences Citation Index (SSCI); Arts & Humanities Citation Index (A&HCI); Conference Proceedings Citation Index- Science (CPCI-S); Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH); Emerging Sources Citation Index (ESCI) --2015-present

Appendix 2b: Search to identify reports of qualitative studies

Source	Search strategy	Results retrieved

(Continued)

Cochrane Airways Trials Register (Date of most recent search: 17 June 2019)	1 MESH DESCRIPTOR Lung Diseases, Obstructive AND INREGISTER 2 MESH DESCRIPTOR Pulmonary Disease, Chronic Obstructive EXPLODE ALL AND INREGISTER 3 emphysema*:ti,ab,kw AND INREGISTER 4 (chronic* NEAR3 bronchiti*):ti,ab,kw AND INREGISTER 5 (obstruct* NEAR3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)):ti,ab,kw AND INREGISTER 6 (COPD or COAD or COBD or AECB or AECOPD):ti,ab. AND INREGISTER 7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 AND INREGISTER 8 MESH DESCRIPTOR COMORBIDITY EXPLODE ALL AND INREGISTER 9 (comorbid* or co-morbid*):ti,ab,kw AND INREGISTER 10 (multidisease* or multi-disease* or ((multiple or coexist* or co-exist*) NEXT (illness* or disease* or condition* or syndrom* or disorder*))):ti,ab,kw AND INREGISTER 11 (multimorbid* or multi-morbid*):ti,ab,kw AND INREGISTER 12 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND INREGISTER 13 (chronic* NEXT (illness* or disease* or condition* or disorder*)):ti,ab,kw AND INREGISTER 14 other health condition*:ti,ab,kw AND INREGISTER 15 other medical condition*:ti,ab,kw AND INREGISTER 16 (associated NEAR2 (disease* or disorder* or condition* or illness* or syndrome*)):ti,ab,kw AND INREGISTER 17 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 AND INREGISTER 18 #17 AND #7 AND INREGISTER 19 MESH DESCRIPTOR Qualitative Research EXPLODE ALL AND INREGISTER 20 MESH DESCRIPTOR Interview AND INREGISTER 21 theme* or thematic AND INREGISTER 22 qualitative* AND INREGISTER 23 MESH DESCRIPTOR Nursing Methodology Research AND INREGISTER 24 questionnaire* AND INREGISTER 25 ethnological research AND INREGISTER 26 ethnograph* AND INREGISTER 27 ethnonursing AND INREGISTER 28 phenomenol* AND INREGISTER 29 (grounded NEAR1 (theor* or study or studies or research or analys)) AND INREGISTER 30 (emic or etic or hermeneutic* or heuristic* or semiotic*) or (data NEAR1 saturat*) or participant observ* AND INREGISTER 31 (social construct* or (postmodern* or post-structural*) or (post structural* or poststructural*) or post modern* or post-modern* or feminis* or interpret*) AND INREGISTER 32 (action research or cooperative inquir* or co operative inquir* or co-operative inquir*) AND INREGISTER 33 (humanistic or existential or experiential or paradigm*) AND INREGISTER 34 (field NEAR1 (study or studies or research)) AND INREGISTER 35 human science AND INREGISTER 36 biographical method AND INREGISTER 37 theoretical sampl* AND INREGISTER 38 ((purpos* NEAR4 sampl*) or (focus NEAR1 group*)) AND INREGISTER 39 (account or accounts or unstructured or openended or open ended or text* or narrative*) AND INREGISTER 40 (life world or life-world or conversation analys* or personal experience* or theoretical saturation) AND INREGISTER 41 ((lived or life) NEAR1 experience*) AND INREGISTER 42 cluster sampl* AND INREGISTER 43 observational method* AND INREGISTER 44 content analysis AND INREGISTER 45 (constant NEAR (comparative or comparison)) AND INREGISTER 46 ((discourse* or discurs*) NEAR3 analys*) AND INREGISTER	June 2019: 225 February 2020: not searched January 2021=not searched

(Continued)

	47 narrative analys* AND INREGISTER 48 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 AND INREGISTER 49 #48 AND #18 AND INREGISTER	
CENTRAL (via CRS Web) (Date of most recent search: 8 January 2021)	1 MESH DESCRIPTOR Lung Diseases, Obstructive AND CENTRAL:TARGET 2 MESH DESCRIPTOR Pulmonary Disease, Chronic Obstructive EXPLODE ALL AND CENTRAL:TARGET 3 emphysema*:ti,ab,kw AND CENTRAL:TARGET 4 (chronic* NEAR3 bronchiti*):ti,ab,kw AND CENTRAL:TARGET 5 (obstruct* NEAR3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)):ti,ab,kw AND CENTRAL:TARGET 6 (COPD or COAD or COBD or AECB or AECOPD):ti,ab. AND CENTRAL:TARGET 7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 AND CENTRAL:TARGET 8 MESH DESCRIPTOR COMORBIDITY EXPLODE ALL AND CENTRAL:TARGET 9 (comorbid* or co-morbid*):ti,ab,kw AND CENTRAL:TARGET 10 (multidisease* or multi-disease* or ((multiple or coexist* or co-exist*) NEXT (illness* or disease* or condition* or syndrom* or disorder*))):ti,ab,kw AND CENTRAL:TARGET 11 (multimorbid* or multi-morbid*):ti,ab,kw AND CENTRAL:TARGET 12 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND CENTRAL:TARGET 13 (chronic* NEXT (illness* or disease* or condition* or disorder*)):ti,ab,kw AND CENTRAL:TARGET 14 other health condition*:ti,ab,kw AND CENTRAL:TARGET 15 other medical condition*:ti,ab,kw AND CENTRAL:TARGET 16 (associated NEAR2 (disease* or disorder* or condition* or illness* or syndrome*)):ti,ab,kw AND CENTRAL:TARGET 17 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 AND CENTRAL:TARGET 18 #17 AND #7 AND CENTRAL:TARGET 19 MESH DESCRIPTOR Qualitative Research EXPLODE ALL AND CENTRAL:TARGET 20 MESH DESCRIPTOR Interview AND CENTRAL:TARGET 21 theme* or thematic AND CENTRAL:TARGET 22 qualitative* AND CENTRAL:TARGET 23 MESH DESCRIPTOR Nursing Methodology Research AND CENTRAL:TARGET 24 questionnaire* AND CENTRAL:TARGET 25 ethnological research AND CENTRAL:TARGET 26 ethnograph* AND CENTRAL:TARGET 27 ethnonursing AND CENTRAL:TARGET 28 phenomenol* AND CENTRAL:TARGET 29 (grounded NEAR1 (theor* or study or studies or research or analys)) AND CENTRAL:TARGET 30 (emic or etic or hermeneutic* or heuristic* or semiotic*) or (data NEAR1 saturat*) or participant observ* AND CENTRAL:TARGET 31 (social construct* or (postmodern* or post-structural*) or (post structural* or poststructural*) or post modern* or post-modern* or feminis* or interpret*) AND CENTRAL:TARGET 32 (action research or cooperative inquir* or co operative inquir* or co-operative inquir*) AND CENTRAL:TARGET 33 (humanistic or existential or experiential or paradigm*) AND CENTRAL:TARGET 34 (field NEAR1 (study or studies or research)) AND CENTRAL:TARGET 35 human science AND CENTRAL:TARGET 36 biographical method AND CENTRAL:TARGET 37 theoretical sampl* AND CENTRAL:TARGET 38 ((purpos* NEAR4 sampl*) or (focus NEAR1 group*)) AND CENTRAL:TARGET 39 (account or accounts or unstructured or openended or open ended or text* or narrative*) AND CENTRAL:TARGET	June 2019: 684 February 2020: 105 January 2021=152

(Continued)

	40 (life world or life-world or conversation analys* or personal experience* or theoretical saturation) AND CENTRAL:TARGET 41 ((lived or life) NEAR1 experience*) AND CENTRAL:TARGET 42 cluster sampl* AND CENTRAL:TARGET 43 observational method* AND CENTRAL:TARGET 44 content analysis AND CENTRAL:TARGET 45 (constant NEAR (comparative or comparison)) AND CENTRAL:TARGET 46 ((discourse* or discurs*) NEAR3 analys*) AND CENTRAL:TARGET 47 narrative analys* AND CENTRAL:TARGET 48 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 AND CENTRAL:TARGET 49 #48 AND #18 AND CENTRAL:TARGET	
MEDLINE (Ovid) (Date of most recent search: 8 January 2021)	1 Lung Diseases, Obstructive/ 2 exp Pulmonary Disease, Chronic Obstructive/ 3 emphysema$.tw. 4 (chronic$ adj3 bronchiti$).tw. 5 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw. 6 (COPD or COAD or COBD or AECB or AECOPD).ti,ab. 7 or/1-6 8 exp COMORBIDITY/ 9 (comorbid$ or co-morbid$).tw. 10 (multidisease$ or multi-disease$ or ((multiple or coexist$ or co-exist$) adj2 (illness$ or disease$ or condition$ or syndrom$ or disorder$))).ti,ab. 11 (multimorbid$ or multi-morbid$).tw. 12 exp Chronic Disease/ 13 (chronic$ adj2 (illness$ or disease$ or condition$ or disorder$)).tw. 14 other health condition$.tw. 15 other medical condition$.tw. 16 (associated adj2 (disease$ or disorder$ or condition$ or illness$ or syndrome$)).tw. 17 or/8-16 18 7 and 17 19 qualitative research/ 20 Interview/ 21 (theme$ or thematic).mp. 22 qualitative.af. 23 Nursing Methodology Research/ 24 questionnaire$.mp. 25 ethnological research.mp. 26 ethnograph$.mp. 27 ethnonursing.af. 28 phenomenol$.af. 29 (grounded adj (theor$ or study or studies or research or analys?s)).af. 30 (emic or etic or hermeneutic$ or heuristic$ or semiotic$).af. or (data adj1 saturat$).tw. or participant observ$.tw. 31 (social construct$ or (postmodern$ or post-structural$) or (post structural$ or poststructural$) or post modern$ or post-modern$ or feminis$ or interpret$).mp. 32 (action research or cooperative inquir$ or co operative inquir$ or co-operative inquir$).mp. 33 (humanistic or existential or experiential or paradigm$).mp. 34 (field adj (study or studies or research)).tw. 35 human science.tw. 36 biographical method.tw. 37 theoretical sampl$.af. 38 ((purpos$ adj4 sampl$) or (focus adj group$)).af.	June 2019: 3571 February 2020: 432 January 2021=267

(Continued)

	39 (account or accounts or unstructured or openended or open ended or text$ or narrative$).mp. 40 (life world or life-world or conversation analys?s or personal experience$ or theoretical saturation).mp. 41 ((lived or life) adj experience$).mp. 42 cluster sampl$.mp. 43 observational method$.af. 44 content analysis.af. 45 (constant adj (comparative or comparison)).af. 46 ((discourse$ or discurs$) adj3 analys?s).tw. 47 narrative analys?s.af. 48 or/19-47 49 18 and 48	
Embase (Ovid) (Date of most recent search: 8 January 2021)	1 chronic obstructive lung disease/ 2 chronic bronchitis/ 3 exp lung emphysema/ 4 emphysema$.tw. 5 (chronic$ adj3 bronchiti$).tw. 6 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw. 7 (COPD or AECB or AECOPD).ti,ab. 8 or/1-7 9 comorbidity/ 10 (comorbid$ or co-morbid$).tw. 11 (multidisease$ or multi-disease$ or ((multiple or coexist$ or co-exist$) adj2 (illness$ or disease$ or condition$ or syndrom$ or disorder$))).ti,ab. 12 (multimorbid$ or multi-morbid$).tw. 13 exp chronic disease/ 14 (chronic$ adj (illness$ or disease$ or condition$ or disorder$)).tw. 15 other health condition$.tw. 16 other medical condition$.tw. 17 (associated adj2 (disease$ or disorder$ or condition$ or illness$ or syndrome$)).tw. 18 or/9-17 19 8 and 18 20 exp qualitative research/ 21 exp interview/ 22 (theme$ or thematic).ti,ab. 23 qualitative.af. 24 nursing methodology research/ 25 questionnaire$.ti,ab. 26 ethnological research.ti,ab. 27 ethnograph$.ti,ab. 28 ethnonursing.ti,ab. 29 phenomenol$.ti,ab. 30 (grounded adj (theor$ or study or studies or research or analys?s)).ti,ab. 31 (life stor$ or women* stor$).ti,ab. 32 (emic or etic or hermeneutic$ or heuristic$ or semiotic$).af. or (data adj1 saturat$).ti,ab. or participant observ$.ti,ab. 33 (social construct$ or (postmodern$ or post-structural$) or (post structural$ or poststructural$) or post modern$ or post-modern$ or feminis$ or interpret$).ti,ab. 34 (action research or cooperative inquir$ or co operative inquir$ or co-operative inquir$).ti,ab. 35 (humanistic or existential or experiential or paradigm$).ti,ab. 36 (field adj (study or studies or research)).ti,ab. 37 human science.ti,ab. 38 biographical method.ti,ab. 39 theoretical sampl$.ti,ab. 40 ((purpos$ adj4 sampl$) or (focus adj group$)).ti,ab.	June 2019: 4285 February 2020: 824 January 2021=474

(Continued)

	41 (account or accounts or unstructured or openended or open ended or text$ or narrative$).ti,ab. 42 (life world or life-world or conversation analys?s or personal experience$ or theoretical saturation).ti,ab. 43 ((lived or life) adj experience$).ti,ab. 44 cluster sampl$.ti,ab. 45 observational method$.ti,ab. 46 content analysis.ti,ab. 47 (constant adj (comparative or comparison)).ti,ab. 48 ((discourse$ or discurs$) adj3 analys?s).ti,ab. 49 narrative analys?s.ti,ab. 50 or/20-49 51 19 and 50	
CINAHL (EBSCO) (Date of most recent search: 8 January 2021)	S67 S18 AND S65 S66 S18 AND S65 S65 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 S64 narrative analysis S63 constant N1 (comparative OR comparison) S62 (discourse* OR discurs*) N3 analys?s S61 content analysis S60 questionnaire* S59 observational method* S58 theme* or thematic S57 cluster sampl* S56 (lived OR life) N1 experience* S55 life world or life-world or conversation analys?s or personal experience* or theoretical saturation S54 account or accounts or unstructured or openended or open ended or text* or narrative* S53 focus N1 group* S52 purpos* N4 sampl* S51 theoretical sampl* S50 biographical method S49 human science S48 field N1 (stud* or research) S47 humanistic or existential or experiential or paradigm* S46 action research or cooperative inquir* or co operative inquir* or co-operative inquir* S45 social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis* or interpret* S44 participant observ* S43 data N1 saturat* S42 emic or etic or hermeneutic* or heuristic* or semiotic* S41 women's stor* S40 life stor* S39 grounded N1 (theor* OR study OR studies OR research OR analys?s) S38 phenomenol* S37 ethnograph* S36 Ethnonursing S35 (MH "Cluster Sample+") S34 (MH "Life Experiences+") S33 (MH "Phenomenology") S32 (MH "Theoretical Sample") S31 (MH "Field Studies") S30 (MH "Observational Methods+") S29 (MH "Purposive Sample")	June 2019: 1345 February 2020: 90 January 2021=62

(Continued)

	S28 (MH "Qualitative Validity+") S27 (MH "Constant Comparative Method") S26 (MH "Content Analysis") S25 (MH "Discourse Analysis") S24 (MH "Focus Groups") S23 (MH "Questionnaires+") S22 (MH "Research, Nursing") S21 (MH "Qualitative Studies+") S20 (MH "Audiorecording") S19 (MH "Interviews+") S18 S7 AND S17 S17 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 S16 AB (associated N1 (disease* or disorder* or condition* or illness* or syndrome*)) OR TI (associated N1 (disease* or disorder* or condition* or illness* or syndrome*)) S15 "other medical condition*" S14 "other health condition*" S13 AB (chronic* N1 (illness* or disease* or condition* or disorder*)) OR TI (chronic* N1 (illness* or disease* or condition* or disorder*)) S12 (MH "Chronic Disease+") S11 AB (multimorbid* or multi-morbid*) OR TI (multimorbid* or multi-morbid*) S10 AB (multidisease* or multi-disease* or ((multiple or coexist* or co-exist*) N2 (illness* or disease* or condition* or syndrom* or disorder*))) OR TI (multi-disease* or multi-disease* or ((multiple or coexist* or co-exist*) N2 (illness* or disease* or condition* or syndrom* or disorder*))) S9 AB (comorbid* or co-morbid*) OR TI (comorbid* or co-morbid*) S8 (MH "Comorbidity") S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6 S6 AB (COPD or AECB or AECOPD) S5 AB (obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) OR TI (obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) S4 AB (chronic* N3 bronchiti*) OR TI (chronic* N3 bronchiti*) S3 AB (emphysema*) OR TI (emphysema*) S2 (MH "Lung Diseases, Obstructive") S1 (MH "Pulmonary Disease, Chronic Obstructive+")	
PsycINFO (Ovid) (Date of most recent search: 17 June 2019	1 exp chronic obstructive pulmonary disease/ 2 emphysema$.tw. 3 (chronic$ adj3 bronchiti$).tw. 4 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw. 5 (COPD or COAD or COBD or AECB or AECOPD).ti,ab. 6 or/1-5 7 comorbidity/ 8 (comorbid$ or co-morbid$).tw. 9 (multidisease$ or multi-disease$ or ((multiple or coexist$ or co-exist$) adj2 (illness$ or disease$ or condition$ or syndrom$ or disorder$))).ti,ab. 10 (multimorbid$ or multi-morbid$).tw. 11 chronic illness/ 12 (chronic$ adj2 (illness$ or disease$ or condition$ or disorder$)).tw. 13 other health condition$.tw. 14 other medical condition$.tw. 15 (associated adj2 (disease$ or disorder$ or condition$ or illness$ or syndrome$)).tw. 16 or/7-15 17 6 and 16 18 qualitative research/ 19 (theme$ or thematic).mp. 20 qualitative.af.	June 2019: 497 February 2020: not searched January 2021=not searched

(Continued)

	21 questionnaire$.mp. 22 ethnological research.mp. 23 ethnograph$.mp. 24 ethnonursing.af. 25 phenomenol$.af. 26 (grounded adj (theor$ or study or studies or research or analys?s)).af. 27 (life stor$ or women* stor$).mp. 28 (emic or etic or hermeneutic$ or heuristic$ or semiotic$).af. or (data adj1 saturat$).tw. or participant observ$.tw. 29 (social construct$ or (postmodern$ or post-structural$) or (post structural$ or poststructural$) or post modern$ or post-modern$ or feminis$ or interpret$).mp. 30 (action research or cooperative inquir$ or co operative inquir$ or co-operative inquir$).mp. 31 (humanistic or existential or experiential or paradigm$).mp. 32 (field adj (study or studies or research)).tw. 33 human science.tw. 34 biographical method.tw. 35 theoretical sampl$.af. 36 ((purpos$ adj4 sampl$) or (focus adj group$)).af. 37 (account or accounts or unstructured or openended or open ended or text$ or narrative$).mp. 38 (life world or life-world or conversation analys?s or personal experience$ or theoretical saturation).mp. 39 ((lived or life) adj experience$).mp. 40 cluster sampl$.mp. 41 observational method$.af. 42 content analysis.af. 43 (constant adj (comparative or comparison)).af. 44 ((discourse$ or discurs$) adj3 analys?s).tw. 45 narrative analys?s.af. 46 or/18-45 47 17 and 46	
Web of Science Core Collection* (Date of most recent search: 8 January 2021)	ALL FIELDS: ((COPD OR AECOPD OR emphysema OR "chronic bronchitis" OR "chronic obstructive pulmonary disease")) AND ALL FIELDS: ((comorbid OR comorbidity OR comorbidities OR multi-morbidity OR multi-morbidities or multimorbid OR multiple disease*)) AND ALL FIELDS: ((qualitative or interview or questionnaire or ethnograph* or ethnological or phenomenol* or "grounded theory" or "grounded research" or "grounded study" or "focus group"))	June 2019: 1085 February 2020: 120 January 2021=92
ClinicalTrials.gov (Date of most recent search: 19 June 2019)	Study type: all Condition: COPD Other Search terms: (comorbidity OR comorbidities OR multi-morbidity OR multi-morbidities) AND (qualitative OR interview OR ethnograph* OR ethnological OR phenomenol* OR "grounded theory" OR "grounded research" OR "grounded study" OR "focus group")	June 2019: 19 February 2020: not searched January 2021=not searched
WHO trials registry (Date of most recent search: 19 June 2019)	COPD AND qualitative (using simple search interface)	June 2019: 14 February 2020: not searched January 2021=not searched

*Core collection= Science Citation Index Expanded (SCI-EXPANDED); Social Sciences Citation Index (SSCI); Arts & Humanities Citation Index (A&HCI); Conference Proceedings Citation Index- Science (CPCI-S); Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH); Emerging Sources Citation Index (ESCI) --2015-present

Appendix 2. Summary search record

Appendix 3a: summary search record for RCTs

Source	Searched from	Date of most recent search	Results (before duplicates removed)			Totals
			June 2019	February 2020	January 2021	
Airways Register (via CRS*)	Inception	06/01/2021	1234	55	53	1342
CENTRAL (via CRS*)	Inception	06/01/2021	2967	451	328	3746
MEDLINE (Ovid) ALL	1946	06/01/2021	7609	771	450	8830
Embase (Ovid)	1974	06/01/2021	5262	906	584	6752
CINAHL (EBSCO)	1937	11/06/2019	971	*Not searched*	*Not searched*	971
PsycINFO (Ovid)	1967	11/06/2019	185	*Not searched*	*Not searched*	185
Web of Science Core Collection	1970	06/01/2021	529	47	40	616
Clinicaltrials.gov	Inception	06/01/2021	56	0	4	60
WHO trials portal	Inception	10/06/2019	3	*Not searched*	*Not searched*	3
Totals			**18816**	**2230**	**1459**	**22505**

*CRS=Cochrane Register of Studies

Appendix 3b: summary search record for qualitative studies

Source	Searched from	Date of most recent search	Results (before duplicates removed)			Totals
			June 2019	February 2020	January 2021	
Airways Register (via CRS*)	Inception	17/06/2019	225	*Not searched*	*Not searched*	225
CENTRAL (via CRS*)	Inception	19/02/2020	684	105	152	941
MEDLINE (Ovid) ALL	1946	19/02/2020	3571	432	267	4270
Embase (Ovid)	1974	19/02/2020	4285	824	474	5583
CINAHL (EBSCO)	1937	19/02/2020	1345	90	62	1497
PsycINFO (Ovid)	1967	17/06/2019	497	*Not searched*	*Not searched*	497

(Continued)

Web of Science Core Collection	1970	19/02/2020	1085	120	92	1297
Clinicaltrial.gov	Inception	19/06/2019	19	*Not searched*	*Not searched*	19
WHO trials portal	Inception	19/06/2019	14	*Not searched*	*Not searched*	14
Totals			**11725**	**1571**	**1047**	**14343**

HISTORY

Protocol first published: Issue 8, 2019

Date	Event	Description
14 August 2019	Amended	Two references corrected to reflect that they are Cochrane Reviews rather than protocols (Pollok 2018; Pollok 2019).

CONTRIBUTIONS OF AUTHORS

ED: drafting of Background and Methods sections of the protocol, screening references, study selection, data extraction, risk of bias assessment, data entry and analysis, GRADE assessment, write-up of full review.

SJ: drafting of Background and Methods sections of the protocol, screening references, study selection, data extraction, risk of bias assessment, data analysis, GRADE assessment, write-up of full review.

ES: drafting of 'Search methods' and search results sections, design and conduct of search strategies, screening references, study selection, data extraction, analysis and interpretation, drafting elements of full review, approval of final draft of full review.

SH: drafting of Background and Methods sections of the protocol, arbitrating conflicts, assisting with the qualitative analysis, analysis and interpretation, editing final draft, approval of final draft of full review.

MM: drafting of Background and Methods sections of the protocol, conceptual and clinical advice on protocol, editing final draft, approval of final draft of full review.

AH: drafting of Background and Methods sections of the protocol, conceptual and clinical advice on protocol, analysis and interpretation, editing final draft, approval of final draft of full review.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor): edited the review; advised on methodology; approved the review prior to publication.
Chris Cates (Co-ordinating Editor): checked the planned methods and checked the data in the review.
Sally Spencer: edited the review.
Emma Jackson (Assistant Managing Editor): co-ordinated the editorial process, co-ordinated peer review and edited the references and other sections.
Sarah Hodgkinson (Associate Editor at the Cochrane CET): edited the review and provided independent appraisal as Emma Dennett is the managing editor at Cochrane Airways and line managed by Chris and Rebecca.

DECLARATIONS OF INTEREST

ED: is the managing editor of Cochrane Airways group, St George's, University of London. This review was managed and sent out to peer review by Emma Jackson (Assistant Managing Editor for Cochrane Airways) and approved by an editor at the Cochrane Circulation and Breathing Network.

SJ: is employed full-time as a systematic reviewer, paid by an NIHR programme grant to complete work on this review.

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External sources

- All, Other

  The authors declare that no such funding was received for this systematic review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In the protocol we missed self-management as an obvious category of intervention that we would have expected to find, so this has been added.
- We failed to specify outcomes for the summary of findings tables a priori, so included the following outcomes in the SOF table: quality of life (SGRQ and CAT), exacerbations, functional status (6MWD), all-cause hospital admissions, all-cause mortality, anxiety and depression.
- We excluded studies that targeted interventions to a subset of people who exhibited a pronounced symptom of COPD, e.g. hypercapnia, chronic respiratory failure, cough, acute hypercapnic respiratory failure (AHRF), chronic ventilatory failure, chronic alveolar hypoventilation.
- We excluded studies of people with COPD who were at high risk of another disease (but who had not received a diagnosis) e.g. cardiovascular disease.
- We clarified that we included studies of any duration.
- Trial authors were not contacted, so we removed the requirement for a 10-year smoking history.