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On behalf of Lung Foundation Australia and the Thoracic Society of Australia and New Zealand

Australia and New Zealand

PULMONARY REHABILITATION

CLINICAL PRACTICE GUIDELINES

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ABSTRACT

Aim

The aim of the Pulmonary Rehabilitation Guidelines (Guidelines) is to provide evidence-based recommendations for the practice of pulmonary rehabilitation (PR) specific to Australian and New Zealand healthcare contexts.

Methods

The Guideline methodology adhered to the Appraisal of Guidelines for Research and Evaluation (AGREE) II criteria. Nine key questions were constructed in accordance with the PICO format and reviewed by a COPD consumer group for appropriateness. Systematic reviews were undertaken for each question and recommendations made with the strength of each recommendation based on the GRADE criteria. The Guidelines were externally reviewed by a panel of experts.

Results

The Guideline panel recommended that people with mild to severe COPD should undergo PR to improve quality of life and exercise capacity and to reduce hospital admissions; that PR could be offered in hospital gyms, community centres or at home and could be provided irrespective of the availability of a structured education program; that PR should be offered to people with bronchiectasis, interstitial lung disease and pulmonary hypertension, with the latter in specialised centres. The Guideline panel was unable to make recommendations relating to PR program length beyond eight weeks, the optimal model for maintenance after PR, or the use of supplemental oxygen during exercise training. The strength of each recommendation and the quality of the evidence are presented in the summary.

Conclusion

The Australian and New Zealand Pulmonary Rehabilitation Guidelines present an evaluation of the evidence for nine PICO questions, with recommendations to provide guidance for clinicians and policy makers.

Key words

Bronchiectasis; chronic obstructive pulmonary disease; exercise and pulmonary rehabilitation; guidelines; interstitial lung disease

Short title

Pulmonary rehabilitation guidelines

SUMMARY OF RECOMMENDATIONS

The guideline panel recommends that:

1. a) people with stable chronic obstructive pulmonary disease (COPD) should undergo pulmonary rehabilitation (strong recommendation, moderate quality evidence).

   b) pulmonary rehabilitation is provided after an exacerbation of COPD, within two weeks of hospital discharge (weak recommendation, moderate quality evidence).

2. people with moderate-to-severe COPD (stable or following discharge from hospital for an exacerbation of COPD) should undergo pulmonary rehabilitation to decrease hospitalisations for exacerbations (strong recommendation, moderate-to-low quality evidence).

3. a) home-based pulmonary rehabilitation be offered to people with COPD as an alternative to usual care (weak recommendation, moderate-to-low quality evidence).

   b) home-based pulmonary rehabilitation, including regular contact to facilitate exercise participation and progression, be offered to people with COPD as an alternative to hospital-based pulmonary rehabilitation (weak recommendation, moderate-to-low quality evidence)

   c) community-based pulmonary rehabilitation, of equivalent frequency and intensity as hospital-based programs, be offered to people with COPD as an alternative to usual care (weak recommendation, moderate quality evidence).

4. people with mild COPD (based on symptoms) undergo pulmonary rehabilitation (weak recommendation, moderate-to-low quality evidence).

5. The panel is unable to make a recommendation due to lack of evidence evaluating whether programs of longer duration are more effective than the standard eight-week programs.

6. a) more research is needed to determine the optimal model of maintenance exercise programs ('in research' recommendation).

   b) supervised maintenance programs of monthly, or less frequently, are insufficient to maintain the gains of pulmonary rehabilitation and should not be offered (weak recommendation, low quality evidence).

7. pulmonary rehabilitation be offered to all people with COPD, irrespective of the availability of a structured multidisciplinary group education program (weak recommendation, moderate-to-low quality evidence).

8. further research of oxygen supplementation during training is required in people with COPD who have exercise-induced desaturation to reduce the uncertainty around its lack of effect to date ('in research' recommendation).

9. a) people with bronchiectasis undergo pulmonary rehabilitation (weak recommendation, moderate quality evidence).

   b) people with interstitial lung disease undergo pulmonary rehabilitation (weak recommendation, low quality evidence).

   c) people with pulmonary hypertension undergo pulmonary rehabilitation (weak recommendation, low quality evidence).

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affects 1.5 million Australians, including 1 in 13 people over 40 years of age, [1] with major consequences for participation in work and societal contexts. [2] The cost of COPD in Australia was estimated at $8.8 billion in 2008/9 (most recent figures), with $929 million in direct health system expenditure, due largely to hospital admissions. [3] Indigenous Australians (Aboriginal and Torres Strait Islander Peoples) bear an unequal burden of disease in relation to COPD. Compared to non-Indigenous Australians, the prevalence of COPD is 2.5 times higher, with the death rate being three times higher and the hospitalisation rate five times higher in Indigenous Australians. [4] In New Zealand, COPD affects approximately 200,000 of the population with 14% of adults over 40 years of age having COPD. [5] The cost of COPD in New Zealand is estimated as $NZ 5.6 billion with $NZ 484 million in direct health system expenditure. [5] Indigenous New Zealanders (Māori) have a higher prevalence of COPD, a 4.4 times higher rate of hospital admissions, and 2.2 times more deaths associated with the condition compared with non-Māori. [5, 6]

Pulmonary rehabilitation is considered a key component of the management of people with COPD [7] and has been shown to reduce symptoms of breathlessness and fatigue, improve health-related quality of life (HRQoL), [8] and reduce hospital readmissions after an exacerbation. [9] However, uptake of pulmonary rehabilitation is estimated to be only 5-10% of those people with moderate-to-severe COPD who could benefit [10, 11], related to lack of available programs, poor referral rates and poor patient uptake of existing programs. While international societies have published a number of documents to guide practice in pulmonary rehabilitation, [12-15] none has specifically addressed the provision of pulmonary rehabilitation for people with COPD in the healthcare contexts of Australia or New Zealand. In addition, a growing number of patients with other chronic lung conditions such as bronchiectasis, interstitial lung disease and pulmonary hypertension are referred to Australian and New Zealand pulmonary rehabilitation programs. Evidence for the benefits of pulmonary rehabilitation in these conditions also needs to be evaluated.

SCOPE AND PURPOSE

These Australian and New Zealand Pulmonary Rehabilitation Guidelines are primarily written for health practitioners providing pulmonary rehabilitation and for the much wider group of health professionals who refer patients to pulmonary rehabilitation in Australia or New Zealand. The patient populations to whom the guidelines apply are those with chronic respiratory disease, primarily COPD, with some evidence presented for patients with bronchiectasis, interstitial lung disease, and pulmonary hypertension. Pulmonary rehabilitation for people with cystic fibrosis or lung cancer was considered outside the scope of the guidelines due to the smaller body of evidence pertaining to structured pulmonary rehabilitation for these groups.

METHODOLOGY

Members of the Australian Pulmonary Rehabilitation Network of Lung Foundation Australia and members of the TSANZ were invited to submit an expression of interest to be considered for the writing group. Participants were required to demonstrate expertise in pulmonary rehabilitation and ability to review literature. In total, 28 healthcare professionals were appointed, with 11 of these forming the lead writing group. The writing group had the following representation: twenty-two physiotherapists, two respiratory physicians, one health psychologist, two nurses, and one exercise physiologist. Two members of the lead writing group (SCJ and AEH) had specific expertise in guideline methodology.

The proposal for writing the Australian and New Zealand Pulmonary Rehabilitation guidelines was endorsed by the Clinical Care and Resources Subcommittee of the TSANZ and the process was supported and coordinated by Lung Foundation Australia. The guideline methodology adhered to the Appraisal of Guidelines for Research and Evaluation (AGREE) II criteria. [16]

The research questions addressed in the guidelines were based on the writing group's considered view of the most important questions related to pulmonary rehabilitation in Australia and New Zealand, with the intention of limiting the number of questions to less than ten. The questions were constructed in accordance with the PICO (Population, Intervention, Comparator, Outcome) format. There were nine main questions (Table 1), with PICO questions 1-8 relating specifically to people with COPD and PICO question 9 addressing pulmonary rehabilitation for people with bronchiectasis, interstitial lung disease, and pulmonary hypertension. The questions were reviewed by a COPD consumer group (Australian COPD and Patient Advocate Group) which agreed that the questions were appropriate.

Systematic literature searches

The definition of pulmonary rehabilitation agreed by the writing group, to set the parameters for the minimum duration of pulmonary rehabilitation for the literature search, was that used in the most recent Cochrane review: '*Any in-patient, out-patient, community-based or home-based rehabilitation programme of at least four weeks' duration that included exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitation attributable to COPD*'. [8]

Systematic reviews were undertaken for each PICO question using standard methodology, [17] except for question 1 and 9. As the updated Cochrane review of pulmonary rehabilitation had recently been published,[8] the data from that review were used as the basis to answer question 1a and the data from the updated Cochrane review on hospital readmissions [9] were used as a basis to answer question 1b. Recently published systematic reviews of pulmonary rehabilitation for bronchiectasis [18], interstitial lung disease (ILD) [19] and pulmonary hypertension [20] were used to underpin question 9. Literature searches for all other questions were undertaken with the assistance of university librarians. The databases searched were Medline, PreMedline, EMBASE, OVID, CINAHL, Cochrane and Scopus. The search terms for each question are in Supplementary Table S 1. Tables of the studies reviewed for each question are in Supplementary Table S 2. Studies were selected for inclusion in the review if they were randomised controlled trials (RCTs) or systematic reviews that directly addressed the questions. To be included, studies had to report at least one of the pre-specified outcomes of interest, such as exercise capacity, HRQoL, health care utilisation (HCU), anxiety and depression, or mortality.

Appraisal of literature

For each question, at least two members of the writing group read the title and/or abstract of each article from the literature search and decided whether to include the article for full review. At least two reviewers for each question independently extracted data from the same studies. Additional information from authors was requested if necessary. Risk of bias (high, low or unclear risk) for each included study was evaluated based on the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, or any other bias. Where relevant, a meta-analysis was performed to quantify effect size and certainty (Supplementary Figure S 1). Data and meta-analyses from relevant, recent systematic reviews were used when available. The quality of the body of evidence for each recommendation was evaluated using the GRADE (Gradings of Recommendations, Assessment, Development and Evaluation) system [21] which considered within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (GRADE evidence tables are in Supplementary Table S 4). The strength of each recommendation was formulated based on the GRADE criteria which consider the quality of the evidence and trade-offs between desirable and undesirable outcomes, confidence in effect estimates, patient values and preferences, and resource implications. [22] In GRADE methodology, 'strong' and 'weak' recommendations are considered as categorical terminology on an underlying continuum, with anchor categories of 'strong against', weak against', 'weak for' and 'strong for'. [22] The Evidence to Recommendation tables that detail the items considered when making the decision regarding the strength of the recommendations are in Supplementary Table S 4 and these tables should be read in conjunction with each recommendation to provide the reader with the reasoning behind the decision regarding the strength of each recommendation. A 'strong' recommendation means that *all or almost all* informed patients would choose the recommended intervention as described; adherence to this recommendation could be used in clinical practice as a quality criterion or performance indicator. A 'weak' recommendation

means that *most* informed patients would choose the recommendation as described; clinicians must help each patient arrive at a management decision consistent with his or her values and preferences [23]. An 'in-research' recommendation means that there is insufficient evidence to recommend the intervention and more research could clarify the effects of the intervention and would be worthwhile. [22]

All members of the writing group (n=28) were asked to vote on each recommendation as 'agree', 'disagree' or 'abstain'. The voting results are shown at the end of each of the Evidence to Recommendation tables in Supplementary Table S 4. After review of the guidelines by an Expert Advisory Group, minor alterations were made to the text but no major changes were made to the recommendations. The guidelines were reviewed by the New Zealand Cardiothoracic Physiotherapy Special Interest Group, consumer representatives, the Clinical Care and Resources Sub-Committee, Nursing, COPD, Physiotherapy and OLIV Special Interest Groups of the TSANZ. The Australian and New Zealand Pulmonary Rehabilitation Guidelines will be disseminated through key stakeholder groups such as the Lung Foundation Australia (including the Australian Pulmonary Rehabilitation Network), Lung Foundation New Zealand, Thoracic Society of Australia and New Zealand, Australian Physiotherapy Association, Physiotherapy New Zealand, Exercise and Sports Science Association Australia, Sport and Exercise Science New Zealand, Royal Australian College of General Practitioners, Royal New Zealand College of General Practitioners, Australian College of Nursing, New Zealand Nurses Organisation, as well as through clinicians registered to receive the COPD-X Guidelines, university programs that provide physiotherapy and exercise physiology programs. The TSANZ will develop quality standards that will be used to evaluate implementation and impact of the Guidelines. The Australian and New Zealand Pulmonary Rehabilitation Guidelines will be reviewed within five years of publication to assess the need for update.

PICO QUESTIONS

Background, Summary of Evidence, Recommendation, Justification and Implementation

PICO 1: **Is pulmonary rehabilitation effective compared with usual care in patients with COPD?**

Background: People with COPD experience breathlessness, reduced functional capacity, reduced HRQoL, and poor psychological wellbeing. Pulmonary rehabilitation, incorporating exercise training and education, is recommended for people with COPD with a view to improving breathlessness, exercise capacity, HRQoL and psychological wellbeing.[12, 15] Pulmonary rehabilitation is typically commenced when a person with COPD is in a stable phase, however, there is increasing evidence that pulmonary rehabilitation plays an important role following an exacerbation of COPD. In Australia and New Zealand, pulmonary rehabilitation following an exacerbation of COPD is typically commenced in the outpatient setting, whereas in some European centres pulmonary rehabilitation occurs in the in-patient setting. The following recommendations are presented for two categories of patients: stable COPD and following an exacerbation of COPD.

(a) Stable COPD

Summary of the evidence: A Cochrane review that examined the evidence for pulmonary rehabilitation in stable COPD included 65 RCTs [8]. Outcomes of interest were confined to measures of exercise capacity and HRQoL. For exercise capacity measured by the six-minute walk test (6MWT), pulmonary rehabilitation compared to usual care resulted in a mean difference (MD) of 44 metres (95% confidence interval [CI] 33 to 55) in favour of pulmonary rehabilitation (38 studies, number of participants (n)= 1879). A sensitivity analysis of studies with lower risk of bias yielded a smaller mean difference in 6MWT for pulmonary rehabilitation compared to usual care (MD 26 metres, 95% CI 21 to 32, 20 studies, n=1188, moderate quality evidence). This MD falls within the range of the minimal important difference (MID) (range 25-33m).[24] For HRQoL, the effect of pulmonary rehabilitation was larger than the MID for all four domains of the Chronic Respiratory Disease Questionnaire (CRQ) (i.e. Fatigue, Emotional Function, Mastery and Dyspnoea) (MID is 0.5 units per domain) [25] and the three components (Symptoms, Impacts, Activity) and Total score of the St George's Respiratory Questionnaire (SGRQ) (MID is -4 points) [25] (SGRQ Total score MD -6.89 units, 95% CI -9.26 to -4.52, 19 studies, n=1146, moderate quality evidence). A sensitivity analysis of studies at lower risk

of bias yielded a slightly smaller MD for SGRQ Total score, but this still exceeded the MID (MD -5.15 units, 95% CI -7.95 to -2.36, 7 studies, n=572, moderate quality evidence due to a high level of heterogeneity). Importantly, the Cochrane Airways Group has decided to close the Cochrane Review of pulmonary rehabilitation, stating that further RCTs comparing pulmonary rehabilitation to conventional care in COPD are no longer warranted since further RCTs will not result in improved quality of evidence or improved precision in the estimate of effect. The Cochrane Airways Group believes that the remaining issues around risk of bias, such as blinding of patients and personnel, cannot be addressed with better study design. [26]

Recommendation: **The guideline panel recommends that people with stable COPD should undergo pulmonary rehabilitation (strong recommendation, moderate quality evidence).**

Justification and implementation: This recommendation places a high value on moderate quality evidence of short-term (immediately following pulmonary rehabilitation) significant and clinically important effects on valued outcomes of improved exercise capacity and HRQoL. [27, 28]

(b) Following an exacerbation of COPD

Summary of the evidence: A Cochrane review that examined the evidence for pulmonary rehabilitation following exacerbations of COPD [9] included 17 randomised controlled trials examining a range of outcomes related to exercise capacity, HRQoL, subsequent hospitalisations, mortality and adverse events. Of the total 17 trials, five commenced pulmonary rehabilitation within two weeks of participants being discharged from hospital for an exacerbation of COPD, [29-33] similar to COPD management in the Australian and New Zealand health care context. Trials that commenced pulmonary rehabilitation during an inpatient stay were excluded. Meta-analyses of these five trials are presented in Figure S 1. A large effect on exercise capacity was found with a MD in 6MWT of 56 metres (95% CI 27 to 85, 2 studies [31, 32], n=116, moderate quality evidence), which exceeded the MID. [24] A large effect on HRQoL was also found (SGRQ Total score MD -10.64 units, 95% CI -15.51 to -5.77, 5 studies [28-32], n=248, moderate quality evidence), which exceeded the MID. [25] Pulmonary rehabilitation commenced within two weeks of hospital discharge tended to reduce repeat hospital admissions (odds ratio [OR] 0.30, 95% CI 0.07 to 1.29, 4 studies [28-31], n=187, moderate quality evidence) with no effect on mortality (OR 0.34, 95% CI 0.05 to 2.34, 2 studies [28,31], n=101, low quality evidence). No adverse events were reported in these studies.

Recommendation: **The guideline panel recommends that pulmonary rehabilitation is provided after an exacerbation of COPD, within two weeks of hospital discharge (weak recommendation, moderate quality evidence).**

Justification and implementation: This recommendation places a high value on moderate quality evidence of short-term (immediately following pulmonary rehabilitation) significant and clinically important effects on valued outcomes of improved exercise capacity, HRQoL and reduced hospital readmissions. [27, 28, 34]

PICO 2: **Does pulmonary rehabilitation affect health care utilisation?**

Background: Exacerbations are common in people with COPD and increase in prevalence with worsening airflow limitation. [35] Hospitalisations for severe exacerbations have major significance as they lead to disease progression, deterioration in HRQoL and increased mortality. [36-38] Within Australia and New Zealand, consistent with international data, severe exacerbations leading to hospitalisation are the primary driver of all COPD-related medical care costs accounting for 50-75% of the direct COPD-associated healthcare costs. [6, 39-41] In 2013-14, the hospitalisation rate for COPD among people aged 55 years and over was 1,008 per 100,000 population in Australia [39] and the average cost of one hospital admission for COPD (2011-12 data) without complications or comorbidities (average length of stay [LOS] 5.0 days) was $A5,500, equivalent to more than 100 general practice consultations. [42] A majority of people with COPD have two or more comorbidities, [43] resulting in an estimated doubling or tripling of the cost of care. [44]

Summary of evidence: The search strategy yielded 2546 citations of which 2505 citations were excluded based on title and abstract. A total of 41 full papers were extracted and reviewed. An additional four papers were sourced from pulmonary rehabilitation statements, systematic reviews and clinical practice guidelines. In total, 45 papers underwent full review of which nine RCTs reported the effect of pulmonary rehabilitation on HCU, defined as the reporting of respiratory-related admissions, length of stay (i.e. the mean or median length of stay for hospital admissions in the follow-up period) or total bed days (i.e. the absolute numbers of days in hospital in the follow-up period) and satisfied the criteria for data extraction. [29-32, 45-49] In five trials, [45-49] patients had stable COPD and in the remaining four trials [29-32] patients commenced pulmonary rehabilitation no later than three weeks following an exacerbation of COPD requiring hospitalisation. Pulmonary rehabilitation was delivered in hospital outpatient departments (6 trials) [29, 31, 32, 45, 46, 48], within the patient's home (2 trials) [30, 47] and in one trial, rehabilitation took place within physiotherapy private practices. [49] The follow-up period for collection of HCU data ranged from 3 months, including the 8-week intervention period, [29, 31] to at least 12 months. [32, 45, 46, 48, 49] Eight RCTs (n=712) evaluated the effect of pulmonary rehabilitation on respiratory-related admissions [29-32, 45-47, 49], four trials (n=358) assessed LOS [32, 45, 47, 48] and two trials (n=241) reported the effect of pulmonary rehabilitation on total bed days. [29, 49] Two trials [31, 45] (n=260) demonstrated that pulmonary rehabilitation significantly reduced hospital admissions, both in those with stable COPD [45] and those who commenced pulmonary rehabilitation within seven days following discharge from hospital for an exacerbation of COPD. [31]

A meta-analysis of the four trials [29-32] (n=194) (Supplementary Figure S 1) in which pulmonary rehabilitation commenced within two weeks of discharge after an exacerbation of COPD showed a trend towards a reduction in readmissions following rehabilitation (Odds Ratio 0.30 [95% CI 0.07 to 1.29]). Of the four RCTs that assessed the effect of pulmonary rehabilitation on LOS, two reported a significant reduction in the mean LOS in the group receiving rehabilitation (9.4 [SD 10.2] vs 18.1 [19.3] days, p=0.021 [45] and 5.9 [0.33] vs 9.3 [4.11] days, p=0.035) [47] with no effect on LOS demonstrated in the remaining two trials. [32, 48] The two trials [29, 49] that reported the effect of pulmonary rehabilitation on total bed days, one of which was in patients with less severe COPD, [49] found no difference between the rehabilitation and control groups, however neither trial was powered to detect changes in HCU. Quality of the evidence was rated down for indirectness (high proportion of males in some studies) and imprecision (small number of participants and large confidence intervals around the estimates).

Only one of the nine RCTs was carried out in Australia [47] and none took place in New Zealand. An additional RCT from Australia [50] (published as abstract only) showed a significant reduction in hospital admissions and LOS following pulmonary rehabilitation compared to a control group. Due to the lack of relevant RCTs carried out in the local health care context, non-RCT evidence from Australia or New Zealand was considered. Six non-RCTs carried out in Australia that compared HCU in the 12 months before and after pulmonary rehabilitation were identified. [51-56] All reported a reduction in hospitalisations for exacerbations of COPD following pulmonary rehabilitation. One study was a large sample (n=267) trial that showed a significant reduction in admissions in the year after compared to the year before a pulmonary rehabilitation program that comprised exercise training alone or in combination with a structured disease-specific education program. [51] A further five observational studies (n=975) of pulmonary rehabilitation delivered in hospital outpatient departments [52-55] and in non-healthcare facilities within the community[56] also reported a reduction in hospitalisations in the 12 months following rehabilitation. Because of their uncontrolled nature, regression to the mean cannot be excluded in these studies. Although there is a paucity of data from RCTs carried out in Australia or New Zealand, given the large body of evidence supporting the benefits of pulmonary rehabilitation it is unlikely that any further RCTs with long-term follow-up, such as are needed for evaluating the effect of pulmonary rehabilitation on HCU, will be undertaken in Australia or New Zealand due to the ethical concerns of denying patients pulmonary rehabilitation where this is available.

Recommendation: **The guideline panel recommends that people with moderate-to-severe COPD (stable or following discharge from hospital for an exacerbation of COPD) should undergo pulmonary rehabilitation to decrease hospitalisations for exacerbations (strong recommendation, moderate-to-low quality evidence).**

Justification and Implementation: This recommendation places a high value on moderate-to-low quality evidence for outcomes that are important to patients. The recommendation is 'strong' since, from a patient's perspective, avoidance of being hospitalised, housebound or confined to bed as a result of an exacerbation has high importance. [34]

PICO 3: **Is a home- or community-based pulmonary rehabilitation program as effective as a hospital-based pulmonary rehabilitation program?**

Background: Despite strong evidence for the benefits of pulmonary rehabilitation highlighted in PICO 1, the proportion of people with COPD who participate in pulmonary rehabilitation is low, estimated at no more than 5-10% of patients with moderate-severe COPD [10, 11]. Most pulmonary rehabilitation programs in Australia and New Zealand have been offered in a hospital outpatient setting and access is limited for patients who do not live close to such centres. A common patient-reported barrier to participating in hospital-based programs is difficulty with transport to the facility [57]. Pulmonary rehabilitation programs conducted in home or community-based settings could help to overcome these barriers and potentially improve access and uptake.

To examine the evidence relating to the effectiveness of home-based and community-based pulmonary rehabilitation programs, three separate comparisons were made:

- Is home-based pulmonary rehabilitation more effective than usual care for people with COPD?
- Is home-based pulmonary rehabilitation as effective as hospital-based pulmonary rehabilitation for people with COPD?
- Is community-based pulmonary rehabilitation more effective than usual care for people with COPD?

We defined home-based pulmonary rehabilitation as programs where the intervention took place in the participant's home, and community-based rehabilitation as programs where the intervention took place in a community-based setting (i.e. not a hospital and not at home). As with all the other questions, the definition of pulmonary rehabilitation intervention in the Cochrane review [8] was used as the criterion for study inclusion with an additional criterion for question 3 that the exercise therapy delivered must include a lower limb endurance training component (i.e. not just 'general exercises'). This was to improve applicability of the guideline findings to Australian and New Zealand practice, where prescription of lower limb endurance exercise is a core part of the prescribed exercise therapy in pulmonary rehabilitation [58, 59].

(a) Is home-based pulmonary rehabilitation more effective than usual care for people with COPD?

Summary of the evidence: Eleven studies were identified that made a direct comparison of home-based pulmonary rehabilitation programs with usual care control. Three examined home-based programs that commenced within 4 weeks of a hospital admission for an exacerbation of COPD [30, 60, 61]; in the other eight studies the participants were in a stable clinical condition. In five studies, home-based exercise sessions were directly supervised to some degree, ranging from every session [30] to once a week [47, 62] or fortnightly. [63, 64] In all 11 studies participants were assessed in a hospital centre. Compared to usual care, home-based pulmonary rehabilitation in people with stable COPD resulted in large improvements in HRQoL substantially greater than the MID for all domains of the CRQ and for the SGRQ Impacts and Activity components, with similar improvements in those attending pulmonary rehabilitation following an exacerbation of COPD (reported for CRQ domains of Dyspnoea, Fatigue and Mastery only), based on moderate quality evidence. For example, in stable COPD the pooled mean difference between home-based pulmonary rehabilitation and control in CRQ-Dyspnoea was 0.77 units (95% CI 0.44 to 1.10, 2 studies [62, 65], n=77) and CRQ-Fatigue was 0.86 units, 95% CI 0.40 to 1.32 units, 2 studies [62, 65], n=77). For the 6MWT in stable COPD the mean difference in favour of home-based pulmonary rehabilitation was 47 metres (95% CI 24 to 71, 3 studies [62, 63, 66], n=222, low quality evidence), exceeding the MID (see Supplementary Figure S 1 for meta-analyses). Quality of the evidence was downgraded due to risk of bias from lack of assessor blinding, imprecision and indirectness due to high proportions of male participants (>90%).

Recommendation: **The guideline panel recommends that home-based pulmonary rehabilitation be offered to people with COPD as an alternative to usual care (weak recommendation, moderate-to-low quality evidence).**

Justification and Implementation: This recommendation places high value on moderate-to-low quality evidence of short-term, moderate effects on outcomes of importance to patients such as enhanced HRQoL, reduced breathlessness and improved exercise tolerance. The strength of the recommendation was 'weak' due to the differing models of home-based rehabilitation programs with lack of evidence regarding the optimal format. Since many of the exercise sessions in home-based programs were unsupervised it is likely that regular contact with a physiotherapist or accredited exercise physiologist who is experienced in prescribing exercise-based rehabilitation is critical to ensure that patients receive a sufficient exercise dose to obtain program benefits. Most of the evidence is derived from participants with stable COPD (more than four weeks after an exacerbation of COPD) providing greater confidence in recommending implementation of home-based pulmonary rehabilitation in this group.

(b) Is home-based pulmonary rehabilitation an effective alternative to hospital-based pulmonary rehabilitation for people with COPD?

Summary of the evidence: A search of the literature located 278 citations including three systematic reviews [8, 67, 68] of studies examining the effectiveness of home-based pulmonary rehabilitation. One additional RCT from Australia, comparing home-based rehabilitation to a standard hospital-based program [69], was published after the search was conducted and was included because of its direct relevance to this question. Of the included studies, six made a direct comparison of home-based with hospital-based pulmonary rehabilitation. [69-74] Two studies were powered for equivalence. [69, 71] In one study every session of home-based exercise was directly supervised by a physiotherapist [74]; the other five home-based programs [69-73] included supervision of the initial session only and/or telephone contact. Three of the studies, including the two largest trials [69, 71], reported regular weekly contact with participants in the home-based intervention [69, 71, 73] but frequency of contact was unreported in the other three studies. [70, 72, 74]

Improvements gained post pulmonary rehabilitation in HRQoL were not statistically different or clinically important between programs conducted in home and hospital settings e.g. CRQ-Dyspnoea MD 0.00 units, 95% CI -0.22 to 0.23, 3 studies, [69-71] n=414 (Supplementary Figure S 1). However, within-group changes exceeded the MID in both settings. [69-71] This finding of similar benefits in HRQoL was consistent in all studies for measures using the CRQ and SGRQ. Changes in HRQoL in both settings exceeded the MID for some but not all domains. Changes in exercise tolerance were not clinically or statistically different between home-based and hospital-based programs for the 6MWT (MD 3.5 metres, 95% CI -12.9 to 19.6, n=255, Supplementary Figure S 1) [69, 70, 72] with similar findings for endurance treadmill test [73] and maximal incremental exercise tests. [73, 74] Quality of the evidence was rated down for risk of bias due to lack of blinding and indirectness due to gender imbalance (60-100% of participants in each study were male).

Recommendation: **The guideline panel recommends that home-based pulmonary rehabilitation, including regular contact to facilitate exercise participation and progression, be offered to people with COPD as an alternative to hospital-based pulmonary rehabilitation (weak recommendation, moderate-to-low quality evidence).**

Justification and Implementation. This recommendation places high value on moderate quality evidence of no significant differences in short-term outcomes of importance to patients (such as enhanced HRQoL, reduced breathlessness and improved exercise tolerance), whether the pulmonary rehabilitation is a hospital-based or home-based program. The strength of the recommendation was 'weak' due to the differing models of home-based rehabilitation programs with lack of evidence regarding the optimal format. Since many of the exercise sessions in home-based programs were unsupervised it is likely that regular contact with a physiotherapist or accredited exercise physiologist who is experienced in prescribing exercise-based rehabilitation is critical to ensure that patients receive a sufficient exercise dose to obtain program benefits.

(c) Is community-based pulmonary rehabilitation more effective than usual care for people with COPD?

Six studies that met our definition of community-based pulmonary rehabilitation [49, 75-79] were identified from an existing Cochrane review. [8] An additional search covering the period not included in the Cochrane review (March 2014 to February 2016) identified one further study. [80]

Summary of the evidence: Of the seven included studies, four implemented community-based programs with exercise sessions of at least moderate intensity supervised twice a week [49, 75, 78, 80] (n=259), consistent with the provision of pulmonary rehabilitation in Australia and New Zealand. In other studies the exercise component was of low intensity [79] or implemented once weekly. [76, 77] Compared with usual care, community based pulmonary rehabilitation resulted in moderate improvements in overall HRQoL (SGRQ Total score MD -4.2 units, 95% CI -6.5 to -1.9, 3 studies, [49, 78, 80] (n=229). Exercise frequency and intensity in these three studies was consistent with typical hospital-based programs in the Australian and New Zealand settings. Pooled data from studies that used the CRQ to measure HRQoL [76, 79] indicated a change in favour of the intervention for the CRQ Dyspnoea domain only (MD 0.53 units, 95% CI 0.03 to 0.80, 2 studies [76, 79], n=343) with no differences in other domains (Supplementary Figure S 1). Both of these studies [76, 79] implemented low intensity or frequency of exercise which may help to explain their lack of effect on the other domains of the CRQ. Endurance exercise capacity showed clinically meaningful improvements from community-based pulmonary rehabilitation compared with control (cycle endurance test MD 221 seconds, 95% CI 5 to 437) [49] and treadmill (MD 194 seconds). [80] Evidence is limited for effectiveness on 6MWT and ISWT due to risk of bias (high attrition and lack of blinding) [75-79], imprecision (6MWT protocol variation) [49] and indirectness (low intensity and frequency of exercise). [76, 77, 79]

Recommendation: **The guideline panel recommends that community-based pulmonary rehabilitation, of equivalent frequency and intensity as hospital-based programs, be offered to people with COPD as an alternative to usual care (weak recommendation, moderate quality evidence).**

Justification and implementation: This recommendation places high value on moderate quality evidence of short-term, moderate effects on outcomes of importance to patients such as enhanced HRQoL, reduced breathlessness and improved exercise tolerance. None of the studies reported whether participants within four weeks after an exacerbation of COPD were included, therefore the recommendation cannot be extended to this group. The optimal model for community-based programs is not known, however the exercise training component must be delivered at a similar frequency and intensity as hospital-based programs in order to achieve clinically meaningful benefits for patients. Implementation of pulmonary rehabilitation in home or community-based settings could help overcome common barriers of availability, access and difficulty travelling to hospital-based programs expressed by people with COPD. [57]

PICO 4: **In people with mild disease severity, is pulmonary rehabilitation more effective than usual care?**

Background: People with COPD present with a range of disease severities, from mild to severe. The Australian COPD-X Guidelines [7] and an international pulmonary rehabilitation statement [15] recommend referral to pulmonary rehabilitation for all patients, regardless of the degree of disease severity. Spruit and colleagues suggest that patients with mild disease may benefit from preventative strategies and maintenance of physical activity, and pulmonary rehabilitation may be, but is not necessarily included in these strategies. [15] Whilst pulmonary rehabilitation is supported by Level I evidence (PICO 1), the effectiveness in mild disease is not as well established. The COPD-X Guidelines define mild COPD as an FEV1 between 60-80% predicted, with few symptoms, breathlessness on moderate exertion and little or no effect on daily activities. [7]

Summary of the evidence: The search strategy yielded 34 citations and hand searching identified a further four citations, 38 in total. Based on evaluation of the abstracts and titles, 30 citations were excluded and

a further four citations were excluded on review of the full papers, leaving four papers for full review and data extraction. Studies defined mild disease in two ways; based on an FEV1 cut off [81-83] or symptoms. [84] The studies based on FEV1 either did not report detailed data for the mild group specifically and did not respond to requests for data [82], or were of very low quality. [81, 83] As such, the focus of this question was limited to studies that used symptoms to categorise disease severity.

A systematic review [84] that examined the effectiveness of pulmonary rehabilitation in COPD patients with a modified Medical Research Council (mMRC) breathlessness score ≤1 included four RCTs [49, 78, 79, 82](n=489). Compared to usual care, pulmonary rehabilitation in people with mild COPD resulted in short-term (up to six months) improvements in HRQoL; MD in the SGRQ was -4.2 units (95% CI -4.5 to -3.9), exceeding the MID [85] (2 studies [78, 82], n=207, moderate quality). Effects on HRQoL were no longer evident at the longest follow-up period of 24 months. Functional exercise capacity (6MWT) showed a mean improvement of 25.7 metres (95% CI 15.8 to 35.5 metres, 4 studies [49, 78, 79, 82], n=313, moderate quality evidence). This just reached the lower end of the MID. [24] Quality of the evidence was rated down for risk of bias, particularly lack of assessor and participant blinding

Recommendation: **The guideline panel recommends that people with mild COPD (based on symptoms) undergo pulmonary rehabilitation (weak recommendation, moderate-to-low quality evidence).**

Justification and implementation: This recommendation places a high value on moderate quality evidence of clinically significant short-term improvement in functional exercise capacity and HRQoL, and low value on cost and uncertainty regarding patient preference. Whilst benefits from pulmonary rehabilitation in patients with symptomatically mild disease are evident, we recognise that patients are heterogeneous in terms of lung function and symptoms. As such, further research is needed to examine the effect of pulmonary rehabilitation in mild disease based on a multidimensional assessment of these variables and an objective assessment of disease severity.

PICO 5: **Are programs of longer duration more effective than the standard eight week programs?**

Background: The duration of pulmonary rehabilitation programs reported in the literature varies from four weeks to 18 months. Pulmonary rehabilitation programs of 8-weeks' duration are commonly recommended in pulmonary rehabilitation statements [15] and guidelines. [12-14] While a large number of pulmonary rehabilitation programs in Australia and New Zealand are conducted over an 8-week duration [58, 59], it is unclear whether significant benefits may be conferred from programs of a longer duration.
Summary of evidence: The search strategy to determine whether differences exist between 8-week pulmonary rehabilitation programs and those of longer duration, in terms of exercise capacity and HRQoL, yielded 6712 citations, of which 6698 citations were excluded based on title and abstract. Fourteen papers were reviewed in full text however no RCTs were identified that directly compared pulmonary rehabilitation programs of 8-weeks to programs of longer duration.

Recommendation: **The panel is unable to make a recommendation due to lack of evidence evaluating whether programs of longer duration are more effective than the standard eight-week programs.**

Justification and Implementation: There is no direct evidence comparing 8-week programs to those of longer duration. In order to provide some guidance for program duration, we extracted data from trials included in the most recent Cochrane review of pulmonary rehabilitation [8] that were consistent with current Australian and New Zealand practice of 2-3 supervised exercise sessions per week. We compared outcomes from RCTs of 8-week pulmonary rehabilitation programs and RCTs of 12-week pulmonary rehabilitation programs. For the outcome of 6MWT, there were six RCTs of 8-week programs compared to usual care (n= 218) [86-91] and four RCTs of 12-week programs compared to usual care (n=225) [72, 75, 92, 93]. Meta-analyses demonstrated a MD for 6MWT of 77 metres (95% CI 54 to 100) for the 8-week programs and 57 metres (95% CI 27 to 88) for the 12-week programs. No significant difference in improvement in 6MWT between programs of different durations was observed (p=0.31). For the

outcome of SGRQ, there were five RCTs of 8-week programs compared to usual care (n= 182) [86-88, 91, 94] and only one RCT of a 12-week pulmonary rehabilitation program compared to usual care (n=26) [92], thus there were insufficient data to compare SGRQ between programs of 8-weeks and 12-weeks duration for HRQoL. For the 8-week programs versus usual care the MD for SGRQ Total score was -9.6 units (95% CI -15 to -4) which is greater than the MID of -4 points. [25] The MD for SGRQ Total score for the study of a 12-week pulmonary rehabilitation program was -5 units (95% CI -14 to 4). (Meta-analyses are in Supplementary Figure S 1).

PICO 6: **Does ongoing supervised exercise at a lower frequency than the initial pulmonary rehabilitation program maintain exercise capacity and quality of life to 12 months in people with COPD?**

Background: These guidelines recommend the use of pulmonary rehabilitation programs for people with stable COPD and following an exacerbation of COPD (PICO 1a and b). However, functional exercise capacity and HRQoL often decline in the 12 months following pulmonary rehabilitation completion. [95, 96] Consequently, ongoing supervised exercise programs are offered following pulmonary rehabilitation. In Australia, 72% of pulmonary rehabilitation programs offer supervised maintenance exercise programs (unpublished Lung Foundation Australia data) at a lower frequency than the initial program (e.g. once a week or once a month). Whether this is the best way to maintain the benefits gained from pulmonary rehabilitation to 12 months and beyond remains unclear.

Summary of evidence: The search strategy yielded 51 citations of which 32 full papers and eight abstracts were extracted and reviewed. Of these, the recommendations in this guideline are based on the review of 11 RCTs that reported maintenance exercise programs consisting of supervised exercise at a lower frequency than the initial pulmonary rehabilitation programs. [49, 79, 95-103] A comparison across the studies was challenging given that three studies reported long-term changes compared to the beginning of the pulmonary rehabilitation programs (pre-rehabilitation) and eight studies compared outcomes to the end of the pulmonary rehabilitation programs (post-rehabilitation). Furthermore, studies were heterogeneous in the delivery of interventions (e.g. frequency of supervised exercise) and measurement of outcomes.

When weekly supervised exercise was performed as a maintenance exercise program, one study (n=22) reported that at 12 months, functional exercise capacity and HRQoL were not significantly different to pre-rehabilitation and showed no differences compared to a group who were supervised monthly. [100] In contrast, in three studies (n=204) where results at 12 months were compared to post-rehabilitation, weekly supervised exercise maintained functional exercise capacity, [79, 103] peak exercise capacity, [103] endurance exercise capacity [103] and HRQoL. [99, 103] However, there was no difference compared to the control groups that consisted of standard care or unsupervised home exercise with regular review. [79, 99, 103] In studies where supervised exercise sessions were progressively reduced (weekly supervised exercise followed by second weekly, followed by monthly) during the maintenance period, two studies (n= 77) reported that at 12 months, exercise capacity was better than pre-rehabilitation in the intervention groups, and that the control groups (unsupervised home exercise) had declined below pre-rehabilitation levels. [98, 102] However, no between group differences were reported. [98, 102] Based on the results of the above studies, there appears to be no added benefit gained from weekly supervised exercise or a reducing frequency of supervised exercise compared to unsupervised home exercise with regular review, as a maintenance exercise program.

When monthly or three monthly supervised exercise was performed as a maintenance exercise program in five studies (n=512), there was a significant decline at 12 months in exercise capacity and HRQoL in both the intervention and control groups, compared to both pre- [49, 101] and post-rehabilitation. [95-97] Based on the results of these studies, maintenance exercise programs of monthly or three monthly supervised exercises are insufficient to maintain exercise capacity or quality of life to 12 months.
The overall quality of the evidence from the above studies was low and rated down for risk of bias (lack of random sequence generation and assessor blinding with unclear allocation) and imprecision (small numbers of studies and participants contributing to meta-analysis with some studies having missing data).

Recommendation: **The guideline panel recommends that: a) more research is needed to determine the optimal model of maintenance exercise programs ('in research' recommendation); b) supervised maintenance programs of monthly or less frequently are insufficient to maintain the gains of pulmonary rehabilitation and should not be offered (weak recommendation, low quality evidence).**

Justification and implementation: The recommendation places a high value on low quality evidence that monthly supervised ongoing exercise is insufficient to maintain outcomes of importance to patients compared to standard care. While there may be benefits of weekly, supervised maintenance exercise, current low quality evidence suggests that it is no better than standard care of unsupervised exercise with regular review. When participants were surveyed following the completion of a 12-month maintenance exercise program, positive attitudes towards both the supervised and unsupervised maintenance exercise programs were reported, with no between-group differences found for the importance of exercise, the benefits of the program or the importance of support from the physiotherapist. [104] Further research is required to clarify the benefits, location and the cost-benefit of weekly supervised exercise as a maintenance program. However, some form of regular ongoing exercise should be encouraged once pulmonary rehabilitation has been completed to sustain the benefits gained.

PICO 7: **Does a structured education program enhance the benefits of pulmonary rehabilitation?**

Background: In Australia and New Zealand, the majority of pulmonary rehabilitation programs have reported providing a structured education program. [58] Health education in this format is provided by members of a multi-disciplinary team to patients as a group audience. Topics are pre-determined and cover the disease (COPD) and aspects of its management, and may be accompanied by written material. Structured education in pulmonary rehabilitation is reported to be valued by patients with COPD. [105] Summary of Evidence: The search strategy yielded 278 citations of which 250 were excluded based on title and abstract. A further 24 citations were excluded on review of the full paper, leaving four papers for full review and data extraction.

Two RCTs compared a twice weekly outpatient pulmonary rehabilitation program that included supervised exercise training and a structured education program to supervised exercise training alone. [51, 106] One of these RCTs was a large Australian trial (n=267). [51] Patients in both models demonstrated significant improvements in key outcomes, however there were no additional benefits attributable to the education program in exercise capacity (6MWT), HRQoL (CRQ), dyspnoea (Medical Research Council [MRC] dyspnoea score), self-efficacy or health behaviour in the short-term or long-term (12 months). In the Australian trial, the findings were limited by a low completion rate in the intervention group (60%) and a large loss to follow up (26%) that was greater in the exercise only group. [51] However, in the secondary outcome of HCU, for which data were available for all participants, there remained no enhanced benefit of the education program in terms of hospitalisations in the 12 months following pulmonary rehabilitation. The smaller trial (n=22) found that the lecture series negatively affected emotional function compared to exercise training alone (p=0.03) despite the additional attention participants received from health care professionals. [106] This trial was not adequately powered to detect differences between groups in most outcomes and lacked blinding. Similarly, an observational study of Italian patients who elected to attend a structured education program (n=226) or not (n=59) in conjunction with supervised exercise training demonstrated no differences between groups in exercise capacity (6MWT), breathlessness (MRC), HRQoL (SGRQ) or responses to a knowledge and learning impact questionnaire. [107] An evaluation of a new structured education program for COPD in pulmonary rehabilitation delivered in 11 hospitals and community-based programs in Northern Ireland demonstrated high patient satisfaction and a significant improvement in knowledge, understanding and self-efficacy. [108] The results from these observational studies are at high risk of bias due to study design, selection bias and lack of blinding. [107, 108]

Recommendation: **The guideline panel recommends that pulmonary rehabilitation be offered to all people with COPD, irrespective of the availability of a structured multidisciplinary group education program (weak recommendation, moderate-to-low quality evidence).**

Justification and implementation: This recommendation places a high value on moderate-to-low quality evidence from a small number of studies. The role of education within pulmonary rehabilitation is highly valued by patients and clinicians. The provision of knowledge in an appropriate format is an essential component of effective patient self-management. It is possible that behaviour change in pulmonary rehabilitation may be further promoted with the addition of self-management interventions. [15, 109] The guideline panel only reviewed structured group education and did not review individualised models of education or self-management interventions for people with COPD and therefore cannot make a recommendation regarding these strategies within the context of pulmonary rehabilitation.

PICO 8: **Do patients who experience oxygen desaturation during exercise have greater improvements if oxygen supplementation is provided during training?**

Background: Exercise-induced oxygen desaturation (EID) is common among people with COPD, with an Australian study indicating that 47% of those referred to a pulmonary rehabilitation program demonstrated a decrease in oxygen saturation to less than 90% during a 6MWT [110]. It is plausible that the intensity of exercise training achieved in a pulmonary rehabilitation program by people with COPD with EID may be compromised, particularly if clinicians attempt to minimise EID by decreasing training intensity or imposing mandatory rests. A reduction in training intensity may have repercussions for the magnitude of training effect achieved. Consequently, oxygen supplementation may be provided in pulmonary rehabilitation programs for people with COPD who experience EID. It has been known for over 50 years that oxygen supplementation can improve exercise capacity in COPD [111] but the effect of oxygen supplementation during exercise training for people with COPD with EID is unclear.

Summary of the evidence: The search strategy yielded 2052 citations of which 2042 were excluded based on title and abstract. A total of 10 full papers were extracted and reviewed. Of these, four RCTs were identified [112-115] addressing the question. The level of evidence of these RCTs was low due to imprecision and high risk of bias from lack of assessor blinding and drop-out.

The results from the RCTs examining whether oxygen supplementation should be provided during exercise training for people with COPD who experience EID were inconsistent. Most of the RCTs [112-114] indicated that there was no difference using supplemental oxygen versus no supplemental oxygen (i.e. compressed air or room air) on exercise capacity, breathlessness and levels of anxiety/depression following exercise training in people with EID. In contrast, one study demonstrated greater improvement in endurance walking capacity using supplemental oxygen during training compared to no supplemental oxygen (i.e. room air). [115] However, the exercise testing protocol in this study at baseline and follow-up was not consistent as the end tests were performed on the gas to which each participant was randomised, and compared to baseline assessment which was performed on room air. This protocol eliminated the ability to conclude whether improvements were due to the acute effects of the supplemental oxygen or due to a training effect. No RCTs examined mortality or HCU.

Recommendation: **The guideline panel recommends further research of oxygen supplementation during training is required in people with COPD who have exercise-induced desaturation, to reduce the uncertainty around its lack of effect to date ('in research' recommendation).**

Justification and implementation: There is insufficient evidence to confirm the benefits of oxygen supplementation during exercise training compared to no oxygen supplementation in people with COPD who have EID. Currently, supplemental oxygen is used in most Australian pulmonary rehabilitation programs to ensure safety and relieve symptoms for people with COPD experiencing EID. The provision of supplemental oxygen during pulmonary rehabilitation increases program costs and restricts the venues where training can be delivered. More research is needed to provide clarity as to whether supplemental oxygen during exercise training should be used in people with COPD who experience EID.

PICO 9: **Is pulmonary rehabilitation effective in chronic respiratory diseases other than COPD?**

PICO 9a: **Is pulmonary rehabilitation effective in people with bronchiectasis?**

Background: Bronchiectasis is characterised by bronchial dilatation secondary to inflammation, infection and reduced mucociliary clearance. People with bronchiectasis experience persistent cough with sputum production, reduced exercise tolerance, breathlessness, fatigue and poor HRQoL. Exacerbations of bronchiectasis are common and are an indicator of poor prognosis. [116] Treatment for bronchiectasis aims to improve control of symptoms, reduce exacerbation frequency, maintain lung function and optimise HRQoL. Such treatment includes careful antibiotic selection and may include airway clearance techniques. [117]

Summary of the evidence: To inform this guideline, a systematic review was used. [18] The search strategy for this review yielded 82 citations and of these, three RCTs with a total of 135 participants with stable bronchiectasis were included. [118-120] HRQoL improved in the pulmonary rehabilitation group compared to control (SGRQ Total score MD -4.6 points, 95% CI -6.5 to -2.6, 2 studies, n=103, moderate quality evidence). The incremental shuttle walk test (ISWT) improved by 64.5 metres compared to control (exceeding the MID [24] (95% CI 49.4 to 79.6 metres, 3 studies, [118-120] n=122, moderate quality evidence). Quality was rated down for risk of bias (lack of assessor blinding in some studies). A single study (n=76) reported no difference between groups for anxiety or depression, although the number of participants with mood disturbance at baseline was low. [118] No studies reported HCU, although one trial reported a lower frequency of exacerbations in the pulmonary rehabilitation group, with a longer time to first exacerbation (8 months vs 6 months, p = 0.047). [118] Longer term follow-up in one study showed that benefits of pulmonary rehabilitation were not sustained at six or 12 months. [118]

> ***Recommendation:*** **The guideline panel recommends that people with bronchiectasis undergo pulmonary rehabilitation (weak recommendation, moderate quality evidence).**
>
> ***Justification and implementation:*** This recommendation places a high value on moderate-to-low quality evidence of clinically significant improvements in exercise capacity and overall HRQoL, and a low value on uncertainty regarding magnitude and duration of benefit. All trials of pulmonary rehabilitation for bronchiectasis have included airway clearance techniques, which may not be a standard component of pulmonary rehabilitation in some settings. As a result, some providers may require extra training in order to deliver pulmonary rehabilitation for people with bronchiectasis.

PICO 9b: **Is pulmonary rehabilitation effective in people with interstitial lung disease?**

Background: The interstitial lung diseases are a diverse group of over 200 chronic lung conditions including idiopathic pulmonary fibrosis (IPF), connective tissue-related ILD, dust-related ILD, granulomatous ILD (e.g. sarcoidosis) and rarer ILDs such as lymphangioleiomyomatosis. They are characterised by varying degrees of interstitial inflammation and fibrosis, a restrictive ventilatory pattern and marked exercise-induced hypoxaemia. People with ILD experience distressing breathlessness on exertion, significant fatigue, reduced HRQoL, as well as high levels of anxiety and depression. There are limited treatment options for many ILDs. For instance in IPF, the most common and most lethal ILD, new pharmacotherapies can slow disease progression but do not provide cure.[23] In this setting, interventions that improve functional capacity and wellbeing may have an important role.

Summary of the evidence: A Cochrane review that examined the evidence for pulmonary rehabilitation in ILD[19] included nine RCTs, of which five were published as abstracts. Compared to usual care, pulmonary rehabilitation resulted in moderate improvements in overall HRQoL (standardised mean difference [SMD] 0.59, 95% CI 0.2 to 0.98, 3 studies, n=106, low quality evidence). Similar improvements were seen for

breathlessness and fatigue domains of HRQoL instruments. Compared to usual care, the 6MWT improved by 44 metres (95% CI 26 to 63, 5 studies, n=162, moderate quality evidence), exceeding the MID. [24] Effects on HRQoL, symptoms and exercise capacity were no longer evident at six months following program completion. [19] Quality of the evidence was rated down for risk of bias, particularly lack of assessor blinding, and for imprecision. Improvements of similar magnitude were reported in a Cochrane review of exercise training in dust-related respiratory disease, which included a small number of participants with dust-related ILD. [121] No RCTs have examined the impact of pulmonary rehabilitation on anxiety or depression in this setting. Single studies have reported effects of pulmonary rehabilitation on 6-month mortality [122] and HCU [123], with no differences between groups.

Recommendation: **The guideline panel recommends that people with interstitial lung disease undergo pulmonary rehabilitation (weak recommendation, low quality evidence).**

Justification and implementation: This recommendation places a high value on moderate-to-low quality evidence of short-term, moderate size effects on outcomes of importance to patients such as reduced breathlessness and enhanced HRQoL. However, the choice to undertake pulmonary rehabilitation may be influenced by the relatively short duration of benefit. There is currently no evidence to suggest that the recommendation should vary according to the type of ILD, or that the exercise prescription should vary from that provided to people with COPD. Because many people with ILD use supplemental oxygen and/or experience profound exercise-induced desaturation, consideration should be given to providing pulmonary rehabilitation in a setting where supplemental oxygen can be provided during training.

PICO 9c: **Is pulmonary rehabilitation effective in people with pulmonary hypertension?**

Background: Pulmonary hypertension (PH) is defined as an increase in the resting mean pulmonary arterial pressure to at least 25 mmHg on right heart catheterisation. [124] Many people with pulmonary hypertension experience breathlessness on exertion, however a range of other important symptoms may be present, including fatigue, dizziness, chest discomfort, chest pain, palpitations, cough, pre-syncope, syncope, lower limb oedema and abdominal distension. For people from Group 1 pulmonary hypertension (pulmonary arterial hypertension, PAH) specific pharmacotherapies are available and have markedly improved prognosis. However, many patients who are stable on medical therapy report significant exercise limitation and impaired HRQoL. [125, 126]

Summary of the evidence: A Cochrane review comparing exercise training to control in PH [20] included six RCTs (n=206) with varying classifications of PH. All participants were stable on medical therapy. Three of the RCTs were from the same group in Germany (n=137) and used a 3-week inpatient rehabilitation program [125, 127, 128], a model that is not available in Australia or New Zealand. HRQoL outcomes showed that, compared to usual care, exercise training improved the physical function score of the 36-Item Short Form Health Survey version 2 (SF-36v2) (MD 6.3 points, 95% CI 0.8 to 13.3, 4 studies, n=118, low quality evidence) and the mental health score of the SF-36v2 (MD 7.4 points, 95% CI 2.6 to 12.2, 3 studies, n=87, very low quality evidence). Compared to usual care, the 6MWT improved by 60 metres (95% CI 30 to 90, 5 studies, n=165, low quality evidence), which exceeded the MID by a large amount. [24] The studies which relied totally on outpatient based exercise programs [129, 130], consistent with the pulmonary rehabilitation model in Australia and New Zealand, reported a smaller mean difference in 6MWT favouring the exercise group of 34 metres (95% CI 1 to 67) (n=36), which still exceeded the MID [24]. No RCTs evaluated anxiety, depression or HCU. Quality of the evidence was rated down for risk of bias (lack of random sequence generation or assessor blinding), indirectness (may represent a selected subgroup of patients with PH) and imprecision (small numbers of studies and participants contributing to meta-analysis).

None of the studies reported significant adverse events during exercise training such as progression of symptoms, progression of PH, right heart failure or death. One study reported that three of 15 exercise group participants had symptoms during training which comprised dizziness without fainting immediately following cycle ergometer training (n=2) and desaturation from 88% to 74% despite oxygen therapy (n=1).

[125] In a cohort study the same investigators reported that 25 of 183 patients (14%) experienced adverse events during a 3-week inpatient rehabilitation program including syncope, pre-syncope, acute respiratory infection, supra-ventricular tachycardia and haemoptysis. [131]

Recommendation: **The guideline panel recommends that people with pulmonary hypertension undergo pulmonary rehabilitation (weak recommendation, low quality evidence).**

Justification and implementation: This recommendation places a high value on low quality evidence of moderate effects on outcomes of importance to patients (quality of life and exercise capacity). Most evidence relates to inpatient exercise training (68% of participants that have undergone exercise training in RCTs), which may allow closer monitoring and supervision than in outpatient programs and is not available in Australia or New Zealand. However no important adverse events have been reported in trials of outpatient exercise training, so there is currently no evidence to suggest that the recommendation should vary according to program setting. Patients should be stable on pharmacotherapy prior to undertaking an exercise training program. There is no evidence to suggest that the recommendation should vary according to class of PH. International guidelines for PH management currently recommend that exercise training should be undertaken '*...by centres experienced in both PH patient care and rehabilitation of compromised patients*'. [124]

DISCUSSION

These pulmonary rehabilitation guidelines address questions considered by a representative multidisciplinary panel of experts in the field and the COPD consumer group to be important in the context of Australian and New Zealand health services. The PICO questions were limited to less than ten and we recognise that these do not encompass all the important questions pertaining to pulmonary rehabilitation. Each question was addressed and recommendations formulated using an evidence-based, systematic process. [21] Strong recommendations were able to be made regarding the effectiveness of pulmonary rehabilitation in improving exercise capacity, HRQoL and reducing hospital admissions for patients with COPD. While there are resources required to provide pulmonary rehabilitation, the cost per quality adjusted life year (QALY) ratios are within the bounds considered to be cost-effective and likely to result in financial benefits to health services. [132] Given the compelling evidence of the benefits of pulmonary rehabilitation, policy makers should ensure appropriate strategies are in place to enable equitable access to pulmonary rehabilitation for people with COPD. Increased availability of pulmonary rehabilitation programs and referral to these programs are vital to ensure improved patient access and increased patient participation in this effective evidence-based intervention.

There were gaps in the available evidence to answer some of the questions. In particular, there was no direct evidence to determine whether pulmonary rehabilitation programs of longer than 8-weeks duration were more effective than the standard 8-week programs that are common in Australia and New Zealand. [58, 59] Some evidence from meta-analyses of programs of 8-weeks' duration (in which exercise was supervised 2-3 times per week) provides confidence that this program duration improves exercise capacity and HRQoL. Limited evidence was available to guide practice for the use of supplemental oxygen during exercise training in people with COPD who experience EID but who are not prescribed long-term oxygen therapy. As approximately 47% of patients referred to pulmonary rehabilitation in Australia experience EID, [133] further high quality research is needed in this area to determine if there are benefits of providing supplemental oxygen during training and whether these benefits are greater than those that can be achieved with training on room air in this patient group. Such research will help to determine whether patients who experience EID need to attend a pulmonary rehabilitation program where supplemental oxygen is available. Currently, a large Australian RCT is underway examining oxygen supplementation during exercise training in people COPD who have EID. [134] Optimal interventions for the long-term maintenance of improvements after completion of a pulmonary rehabilitation program could not be determined, other than the evidence suggesting that monthly maintenance programs are not worthwhile. Maintenance of the benefits of pulmonary rehabilitation is an important area of future research and may link with behaviour change and self-management interventions [109] although these were not addressed in these guidelines.

While most evidence for pulmonary rehabilitation comes from hospital-based programs, the guideline review has demonstrated growing evidence for the effectiveness of pulmonary rehabilitation in other venues such as community or home settings. Such settings may improve access to programs by eliminating some of the known barriers to program attendance, [57] as well as providing patients with choices around venues such as community-based programs, home-based programs or programs provided in primary care by private practitioners. Availability of pulmonary rehabilitation programs in a variety of settings may improve program access and adherence. Appropriate funding is a driver for provision of pulmonary rehabilitation. Currently in Australia, pulmonary rehabilitation is funded through hospital funding models based on the Independent Hospital Pricing Authority, Tier 2 (non-admitted hospital services) classifications [135] and related pricing.[136] While such funding enables some rehabilitation programs to be provided via the hospital system, major changes in funding models are required to enable the wider provision of pulmonary rehabilitation in primary care.

In terms of patient education, the guideline only reviewed patient education delivered in a structured group format, as this is how education has traditionally been delivered in Australian and New Zealand pulmonary rehabilitation programs. [58, 59] The limited number of RCTs showed no additional benefit of structured education to a pulmonary rehabilitation program compared to pulmonary rehabilitation alone. A structured educational format may not be suitable for all patients whose learning styles, needs and cognitive abilities may vary. It was beyond the scope of the guidelines to further explore this area, in particular self-management education was not addressed. Our findings do not diminish the importance of education for people undertaking pulmonary rehabilitation; rather this reinforces the need to establish the most effective methods to assist individuals with COPD to gain the skills and knowledge they require to optimally manage their disease.

The review of pulmonary rehabilitation for patients with mild COPD (based on symptoms) found clinically meaningful benefits in HRQoL and exercise capacity. Traditionally pulmonary rehabilitation programs in Australia and New Zealand have mainly included people with moderate to severe disease, consistent with the initial studies underpinning the efficacy of pulmonary rehabilitation. [8] Many people with mild COPD in Australia and New Zealand are managed by their general practitioner in primary care and are not often referred to pulmonary rehabilitation. However, our review findings demonstrate beneficial outcomes from pulmonary rehabilitation across the spectrum of disease. While the most cost-effective model for providing pulmonary rehabilitation for people with mild disease is unknown, it is possible that less costly community health and fitness programs linked with high quality COPD-specific education programs, which are becoming more available online, [137] are worth evaluating.

There is growing evidence of the effectiveness of pulmonary rehabilitation for chronic lung diseases other than COPD. The guidelines have provided reviews of the benefits of pulmonary rehabilitation for patients with bronchiectasis, ILD and pulmonary hypertension. The recommendations in favour of pulmonary rehabilitation for people with these diagnoses suggest that inclusion criteria should facilitate the participation of such patients in pulmonary rehabilitation programs in Australia and New Zealand. Practitioners providing pulmonary rehabilitation for patients with bronchiectasis, ILD and PH should have adequate skills and knowledge to treat these patient groups and, for some patients, pulmonary rehabilitation may need to be provided in centres with disease-specific expertise.

Given the higher incidence of COPD in Indigenous Australian [4] and New Zealand communities [5] it is important that Indigenous people with COPD have access to pulmonary rehabilitation. One barrier to attendance at pulmonary rehabilitation may be the lack of attention to cultural needs within mainstream programs. [138] Currently in Australia, no pulmonary rehabilitation programs are specifically designed to accommodate the cultural needs of Aboriginal and Torres Strait Islander Peoples and there is little empirical data on what these needs are. In New Zealand, pulmonary rehabilitation programs provided for Māori people by Māori organisations have identified that attendance is enhanced by the opportunity to make culturally meaningful connections with other patients and staff within the program, having culturally appropriate information available and communicating in a common Māori language. [138] It is imperative that greater efforts are made to ensure safe cultural environments for the delivery of pulmonary rehabilitation, either by Indigenous health professionals providing the pulmonary rehabilitation programs or by mainstream programs providing a culturally appropriate environment to encourage and maintain attendance.

These pulmonary rehabilitation guidelines have evaluated the evidence related to the questions posed and provide general recommendations. For information on the practical aspects of providing pulmonary rehabilitation and individualising interventions for patients, clinicians should access the Pulmonary Rehabilitation Toolkit [139] which provides extensive information on establishing a pulmonary rehabilitation program, patient assessment, exercise training, patient education, and patient reassessment.

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TABLE 1: PICO QUESTIONS

PICO Question	Population	Intervention	Comparator	Outcome
1. Is pulmonary rehabilitation effective compared with usual care in patients with COPD?	a. Stable COPD	Pulmonary rehabilitation	Usual care	HRQoL (including dyspnoea & fatigue) Exercise capacity Mortality Anxiety and depression
	b. Following an exacerbation of COPD	Pulmonary rehabilitation (non-inpatient) within 2-4 weeks of hospital discharge	Usual care	HRQoL (including dyspnoea & fatigue) Exercise capacity Hospital readmissions Mortality

PICO Question	Population	Intervention	Comparator	Outcome
2. Does pulmonary rehabilitation affect health care utilisation?	Stable COPD or following an exacerbation of COPD	Pulmonary rehabilitation	Usual care	Hospital admissions Length of stay Total bed days Exacerbations Emergency department presentations General practitioner visits

3. Is a home-based or community pulmonary rehabilitation program as effective as a hospital-based pulmonary rehabilitation program?

PICO Question	Population	Intervention	Comparator	Outcome
3a. Is home-based pulmonary rehabilitation more effective than usual care for people with COPD?	Stable COPD or following an exacerbation of COPD	Home-based pulmonary rehabilitation	Usual care	HRQoL (including dyspnoea & fatigue) Exercise capacity Mortality Anxiety and depression Healthcare utilisation
3b. Is home-based pulmonary rehabilitation as effective as hospital-based pulmonary rehabilitation for people with COPD?	Stable COPD or following an exacerbation of COPD	Pulmonary rehabilitation	Hospital-based pulmonary rehabilitation	HRQoL (including dyspnoea & fatigue) Exercise capacity Mortality Anxiety and depression Healthcare utilisation
3c. Is community-based pulmonary rehabilitation more effective than usual care for people with COPD?	Stable COPD or following an exacerbation of COPD	Community-based pulmonary rehabilitation	Usual care	HRQoL (including dyspnoea & fatigue) Exercise capacity Mortality Anxiety and depression Healthcare utilisation

PICO Question	Population	Intervention	Comparator	Outcome
4. In people with mild disease severity, is pulmonary rehabilitation more effective than usual care?	Stable COPD	Pulmonary rehabilitation	Usual care	HRQoL (including dyspnoea & fatigue) Exercise capacity Mortality Anxiety and depression Healthcare utilisation

PICO Question	Population	Intervention	Comparator	Outcome
5. Are programs of longer duration more effective than the standard eight-week programs?	Stable COPD or following an exacerbation of COPD	Pulmonary rehabilitation of longer than 8-weeks	Pulmonary rehabilitation of 8-weeks	HRQoL (including dyspnoea & fatigue) Exercise capacity Mortality Anxiety and depression Healthcare utilisation

PICO Question	Population	Intervention	Comparator	Outcome
6. Does ongoing supervised exercise at a lower frequency than the initial pulmonary rehabilitation program, maintain exercise capacity and quality of life to 12 months?	Stable COPD	Maintenance exercise program	Usual care	HRQoL (including dyspnoea & fatigue) Exercise capacity Mortality Anxiety and depression Healthcare utilisation

PICO Question	Population	Intervention	Comparator	Outcome
7. Does a structured education program enhance the benefits of pulmonary rehabilitation?	Stable COPD or following an exacerbation of COPD	Pulmonary rehabilitation with a structured education program	Pulmonary rehabilitation without a structured education program	HRQoL (including dyspnoea & fatigue) Exercise capacity Mortality Anxiety and depression Healthcare utilisation Disease knowledge Self-efficacy

PICO Question	Population	Intervention	Comparator	Outcome
8. Do patients who experience oxygen desaturation during exercise have greater improvements if oxygen supplementation is provided during training?	COPD with exercise-induced oxygen desaturation	Pulmonary rehabilitation with oxygen supplementation	Pulmonary rehabilitation without oxygen supplementation	HRQoL (including dyspnoea & fatigue) Exercise capacity Mortality Anxiety and depression Healthcare utilisation

9. Is pulmonary rehabilitation effective in chronic respiratory diseases other than COPD?

PICO Question	Population	Intervention	Comparator	Outcome
9a. Is pulmonary rehabilitation effective in people with bronchiectasis?	Bronchiectasis	Pulmonary rehabilitation	Usual care	HRQoL (including dyspnoea & fatigue) Exercise capacity Healthcare utilisation Anxiety and depression Mortality
9b. Is pulmonary rehabilitation effective in people with interstitial lung disease?	Bronchiectasis Interstitial lung disease	Pulmonary rehabilitation	Usual care	HRQoL (including dyspnoea & fatigue) Exercise capacity Healthcare utilisation Anxiety and depression Mortality
9c. Is pulmonary rehabilitation effective in people with pulmonary hypertension?	Pulmonary hypertension	Pulmonary rehabilitation	Usual care	HRQoL (including dyspnoea & fatigue) Exercise capacity Healthcare utilisation Anxiety and depression Mortality

PICO = Population, Intervention, Comparator, Outcome; COPD = chronic obstructive pulmonary disease; HRQoL = health-related quality of life.

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