The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2023

Current COPD Guidelines Committee

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These guidelines have been developed and revised by Lung Foundation Australia and the Thoracic Society of Australia and New Zealand as part of a national COPD program.

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Table of Contents

Foreword

Chronic Obstructive Pulmonary Disease (COPD) places an enormous burden on people living with this lung condition and on the Australian healthcare system. The prevalence of COPD in Australians over the age of 40 is estimated to be 7.5% (Toelle 2013). COPD was the 5th leading cause of death in Australia in 2017 (AIHW 2021). In 2015–16, COPD cost the Australian health system an estimated $977 million (AIHW 2020). The Australian Institute of Health and Welfare estimates that **COPD is the foremost cause of preventable hospitalisations** amongst chronic health conditions (AIHW 2019). Furthermore, COPD was the third leading specific cause of total disease burden in Australia in 2015 (AIHW & NIAA 2020).

There is a great deal of work to be done to better understand the prevalence and outcomes of COPD in First Nations people. The prevalence of COPD among First Nations people is estimated to be 2.3 times as high as in non-Indigenous Australians (AIHW 2020). The mortality rate of COPD among First Nations people was 2.7 times as high as the non-Indigenous Australians rate (AIHW 2020). The ultimate aim of these guidelines is to improve health outcomes for all Australians with COPD by translating the latest evidence-based recommendations into everyday clinical practice.

In 2001 a multidisciplinary steering committee was convened by the Thoracic Society of Australia and New Zealand (TSANZ) and Lung Foundation Australia (LFA) to write guidelines for the management of COPD, specific for the Australasian context. The guidelines were launched as '**COPD-X**' and first published as a supplement to The Medical Journal of Australia in 2003. The guidelines strive to provide clear recommendations relevant for Australian healthcare workers, accompanied by a discussion of the evidence.

COPD-X provides guidance for ***C***ase finding and confirming diagnosis, ***O***ptimising function, ***P***revention of deterioration, ***D***evelopment of care plans and management of e***X***acerbations. COPD-X highlights the critical role of reducing risk factors (particularly through smoking avoidance and cessation), optimising function with multidisciplinary care, improving treatment of comorbidities and referring symptomatic patients to pulmonary rehabilitation. The guidelines promote the concept of 'stepwise management'; beginning with one pharmacological intervention and evaluating response before adding another agent. The guidelines also emphasise the importance of non-pharmacological therapy for COPD. The recommendations made in the guidelines are applicable across multiple care settings. The guidelines recognise that a patient-centred approach involving a team of healthcare workers is required for optimal outcomes.

The COPD-X Guidelines Committee is a multidisciplinary group of clinicians convened by LFA, that meets quarterly to review the current COPD literature and update the guidelines. With such frequent updates and literature reviews, COPD-X should be seen as an early example of 'Living Guidelines'. This approach allows the guidelines to constantly evolve in order to meet the needs of people with COPD.

All changes and updates to the guidelines are made by consensus and quarterly digital updates are published online. TSANZ endorses the quarterly updates and the Guidelines have received endorsement from The Royal Australian College of General Practitioners. Across the entire spectrum of COPD care, the Guidelines aim to provide a detailed discussion of the evidence followed by a summary of recommendations. The Guidelines are freely accessible via the LFA website in an easily searchable web-based format and offered as a pdf.

To accompany the comprehensive Guidelines, LFA has launched a complementary suite of resources to assist Australian health care practitioners caring for individuals with COPD. In 2014, the 'COPD-X Concise Guide for Primary Care' was published with the aim of providing a practical point-of-care guide for primary care physicians. In 2020, this was relaunched as the '**Concise Guide**' acknowledging that the guidelines provide a wide range of clinicians with succinct, evidence-based recommendations.

'**Stepwise Management of COPD'** is a graphical, single page summary of the pharmacological and non-pharmacological therapies across the severity continuum of COPD that encapsulates the management principles outlined in COPD-X.

Our greatest challenge lies in guideline implementation. Our key goal is to translate the evidence-based recommendations in COPD-X into everyday practice across Australia. For this knowledge translation to occur, a multi-faceted approach across platforms will be required. Strategies will need to include digital integration, such as software for clinical decision support systems and prompts in electronic health records that aid with management decisions accompanied by professional education delivered by traditional and innovative techniques. Dimensions of impact of uptake of the guidelines should be measured, to enhance reach and impact of key recommendations, and maintenance of knowledge translation.

It is our hope that these Guidelines will advance clinical practice and standardise COPD care. The ultimate aim of these Guidelines is to improve health outcomes and optimise quality of life for people with COPD.

Professor Ian Yang and Associate Professor Eli Dabscheck
Co-Chairs, COPD Guidelines Committee
June 2021

The origins of the COPD-X guidelines

THESE GUIDELINES are the outcome of a joint project of the Thoracic Society of Australia and New Zealand and Lung Foundation Australia. The guidelines aim to:

- effect changes in clinical practice based on sound evidence; and
- shift the emphasis from a predominant reliance on pharmacological treatment of COPD to a range of interventions which include patient education, self-management of exacerbations and pulmonary rehabilitation.

These guidelines deal mainly with the management of established disease and exacerbations. However, this is only one element of the COPD Strategy of Lung Foundation Australia, which has the long-term goals of:

- primary prevention of smoking;
- improving rates of smoking cessation;
- early detection of airflow limitation in smokers before disablement; and
- improved management of stable disease and prevention of exacerbations.

In May 2001 a multidisciplinary steering committee was convened by the Thoracic Society of Australia and New Zealand (TSANZ) and The Australian Lung Foundation in accordance with the National Health and Medical Research Council recommendations for guideline development (National Health and Medical Research Council 1998). The Committee agreed to use the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Report (NHLBI/WHO Workshop Report April 2001) as the prime evidence base, together with systematic reviews and meta-analyses from the Cochrane Database. The GOLD Report, released in April 2001, was produced by an international panel of experts in collaboration with the United States National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO). The levels of evidence in the current guidelines were assigned according to the system developed by the NHLBI (**Box 1**). Any changes to the guidelines have been based on subsequent versions of the GOLD report and on the results of systematic reviews or consistent evidence from well conducted randomised controlled trials.

The Guidelines Steering Committee supervised the development of specific items such as the COPDX Plan and a management handbook for primary care clinicians. Drafts of these documents were widely circulated to key stakeholder groups and professional organisations. In addition, the draft guidelines were published on the Internet http://www.lungnet.com.au (now www.lungfoundation.com.au) and access to them was advertised in a national newspaper. The draft guidelines were circulated to all members of the TSANZ and Australian Divisions of General Practice. All comments received were reviewed by the Steering Committee. The Guidelines were then published as a supplement to The Medical Journal of Australia in March 2003.

The Steering Committee then resolved to establish a COPD Guidelines Implementation Committee and a Guidelines Evaluation Committee. The terms of reference of the Evaluation Committee included scientific assessment of the impact of the guidelines on clinical practice and rigorous examination of the relevant medical literature to ensure the guidelines remain up to date. Any suggested modifications were circulated to members of the COPD Coordinating Committee and other key stakeholders prior to ratification. Following this, the Guidelines were submitted to the COPD Special Interest Group of the Thoracic Society of Australia and New Zealand for endorsement.

Associate Professor David K McKenzie and Professor Peter Frith.
Principal authors and members of the COPD Implementation Committee.
July 2005

COPD-X Methodology

COPD-X is produced by Lung Foundation Australia's COPD Guidelines Committee, which meets to evaluate the current literature and undertake quarterly updates of the Guidelines. The Committee is comprised of a multidisciplinary group of national COPD opinion leaders with expertise in evidence-based medicine, as well as Lung Foundation Australia staff who represent consumer priorities and lived experience perspectives in relevant discussions as the national peak consumer organisation.

A PubMed systematic literature search is performed quarterly by the Guidelines Coordinator for new papers in COPD, emphysema and chronic bronchitis, encompassing systematic reviews, clinical trials, and cohort and case-control studies. Guidelines committee members also propose studies for inclusion in the screening and subsequent review process, noting their awareness of key evidence being published in their respective areas of expertise. The Guidelines co-chairs screen all abstracts for inclusion. Relevant papers are critically appraised by a committee member with expertise in that area.

At the full Committee meeting, a decision about whether to cite a paper is made by consensus, and wording for incorporation is discussed. When making changes to Guideline recommendations, the Committee preferences randomised controlled trials and meta-analyses. The healthcare setting and patient population are also considered for relevance. Study methodology, bias, consistency of results, applicability to local practice and magnitude of benefit are all considered. Potential harms and side effects are also discussed and reported. The Committee discusses all potential Guideline changes and always reaches a group consensus. Guideline updates are focused on changes that are likely to modify or influence practice. Any disagreement is resolved with discussion.

All recommendations are linked to the key evidence used in making the recommendation and this evidence is routinely reviewed and updated. Evidence summaries and tables are provided in the Guidelines. Economic evaluation and funding implications are beyond the scope of the Guidelines in their current format. Although current resources do not allow routine audit and analysis with respect to the impact of and adherence to the Guidelines, independent researchers frequently use the Guidelines to audit local practice.

The Guidelines are endorsed by the Thoracic Society of Australia New Zealand (TSANZ). The TSANZ Clinical Care and Resources Sub-committee provides biannual external review and considers key findings and updates, and the strength of recommendations. The reviewers provide written feedback that is addressed by the co-Chairs and expert members as applicable. Furthermore, within the Lung Foundation Australia, key stakeholders such as general practitioners are also invited to provide regular feedback. Following the external approval process, the updated Guidelines including a summary of changes., are uploaded quarterly to the COPD-X website (https://copdx.org.au/).

Ongoing administrative, technical, logistical and financial support for the development of the COPD-X Guidelines is provided by Lung Foundation Australia as part of its national COPD program. This program receives sponsorship funding from a number of industry partners. Industry partners of Lung Foundation Australia have no direct or indirect influence over the content of the COPD-X Guidelines. Lung Foundation Australia has complete editorial and design control over the content of the COPD-X Guidelines as well as all other resources, promotions and educational programs. All members of the Guidelines committee serve as volunteers. No funding body has any influence on content or recommendations. Where applicable, Lung Foundation Australia funds members' travel and accommodation for in-person Guidelines meetings. Committee members' conflicts of interest are declared on an annual basis and can be viewed at: https://copdx.org.au/copd-x-plan/copd-guidelines-committee-past-and-present/conflicts-of-interest/. Any relevant potential conflict is addressed during the quarterly meetings.

Levels of evidence

THE KEY RECOMMENDATIONS and levels of evidence incorporated in the COPD-X Guidelines were originally based largely on the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which used the evidence ranking system of the US National Heart, Lung and Blood Institute (NHLBI) (NHLBI/WHO Workshop Report April 2001). The NHLBI scheme is shown in **Box 1**. For comparison, the National Health and Medical Research Council (NHMRC) (National Health and Medical Research Council 1998) levels of evidence are also shown, along with the equivalent NHLBI categories.

For this update, the COPD-X Guidelines Committee reclassified NHLBI level A as NHMRC level I and NHLBI level B as NHMRC level II evidence. All citations to NHLBI level C were individually reviewed and reclassified as NHMRC level II, III-2, III-3 or IV evidence. On closer examination, some references originally classified as level C were actually considered level D. As NHLBI level D is not recognised in the NHMRC classification, these levels were removed whilst the bibliographic citations were retained.

Box 1: Levels of evidence

a) National Heart, Lung, and Blood Institute (NHLBI) categories

NHLBI category	Sources of evidence	Definition
A	Randomised controlled trials (RCTs) extensive body of data	Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomised controlled trials (RCTs) limited body of data	Evidence is from endpoints of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, category B pertains when few randomised trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Non-randomised trials, observational studies	Evidence is from outcomes of uncontrolled or non-randomised trials or from observational studies.
D	Panel consensus, judgement	The panel consensus is based on clinical experience or knowledge that does not meet the above criteria.

b) National Health and Medical Research Council (NHMRC) Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
I[4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect	All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study • Interrupted timer series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Key Recommendations of the COPD-X Guidelines

C: Case finding and confirm diagnosis		
	NHMRC level of evidence	**Strength of recommendation***
Smoking is the most important risk factor in COPD development.	I	Strong
Smoking cessation reduces mortality.	I	Strong
A thorough history and examination is the first step in COPD diagnosis.	III-2	Strong
COPD is confirmed by the presence of persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.7$).	III-2	Strong
Diagnosis of COPD should be accompanied by regular assessment of severity.	III-2	Strong
If FEV_1 increases >400 mL following bronchodilator, consider asthma, or coexisting asthma and COPD.	III-2	Strong
Further investigations may help a) confirm or exclude other conditions (either coexisting or with similar symptoms to COPD) and b) assess the severity of COPD.	III-2	Strong
Referral to specialist respiratory services may be required.	III-2	Strong
O: Optimise Function		
Assessment is the first step to optimising function.	III-2	Strong
Optimise pharmacotherapy using a stepwise approach.	I	Strong
Adherence and inhaler technique need to be checked on a regular basis.	I	Strong
Non-pharmacological strategies (such as pulmonary rehabilitation and regular exercise) should be provided to all patients with COPD.	I	Strong
Comorbid conditions are common in patients with COPD.	III-2	Strong
Palliative care - ideally from a multidisciplinary team which includes the primary care team - should be considered early, and should include symptom control and addressing psychosocial issues	II	Weak
Pulmonary rehabilitation improves quality of life and exercise capacity and reduces COPD exacerbations	I	Strong

Lung volume reduction (surgical and endobronchial) improves lung function, exercise capacity and quality of life.	I	Weak
Long term macrolide antibiotics may reduce exacerbations in people with moderate to severe COPD and frequent exacerbations.	I	Weak
Long term non-invasive ventilation should be considered in people with stable COPD and hypercapnia to reduce mortality.	I	Weak
P: Prevent deterioration		
Smoking cessation is the most important intervention to prevent worsening of COPD.	II	Strong
Preventing exacerbations has a key role in preventing deterioration.	III-2	Strong
Vaccination reduces the risks associated with influenza and pneumococcal infection.	I	Strong
Mucolytics may benefit certain patients with COPD.	I	Strong
Long-term oxygen therapy has survival benefits for COPD patients with hypoxaemia.	I	Strong
D: Develop a plan of care		
Good chronic disease care anticipates the wide range of needs in patients with COPD.	I	Strong
Clinical support teams working with the primary healthcare team can help enhance quality of life and reduce disability for patients with COPD.	III-2	Weak
Patients may benefit from self-management support.	I	Strong
Patients may benefit from support groups and other community services.	III-2	Weak
COPD exacerbation action plans reduce emergency department visits and hospital admissions.	I	Strong
X: Manage eXacerbations		
A COPD exacerbation is characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication or hospital admission.	III-2	Strong

Early diagnosis and treatment of exacerbations may prevent hospital admission and delay COPD progression.	III-2	Strong
Multidisciplinary care may assist home management of some patients with an exacerbation.	I	Weak
Inhaled bronchodilators are effective for initial treatment of exacerbations.	I	Strong
Systemic corticosteroids reduce the severity of and shorten recovery from exacerbations.	I	Strong
Exacerbations with clinical features of infection (increased volume and change in colour of sputum and/or fever) benefit from antibiotic therapy.	I	Strong
Controlled oxygen delivery (0.5-2.0 L/min) is indicated for hypoxaemia in patients with exacerbations.	II	Strong
When using supplemental oxygen for hypoxia in COPD exacerbations, target SpO2 88–92% improves survival.	II	Strong
Non-invasive ventilation (NIV) is effective for patients with rising P_aCO_2 levels.	I	Strong
Non-invasive ventilation improves survival for people with COPD and acute hypercapnic respiratory failure	I	Strong
Consider pulmonary rehabilitation at any time, including during the recovery phase following an exacerbation.	I	Strong
Patients with COPD discharged from hospital following an exacerbation should receive comprehensive follow-up led by the primary healthcare team.	I	Strong

*The GRADE system was used to grade the strength of recommendations (Andrews 2013, Guyatt 2008)

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C: Case finding and confirm diagnosis

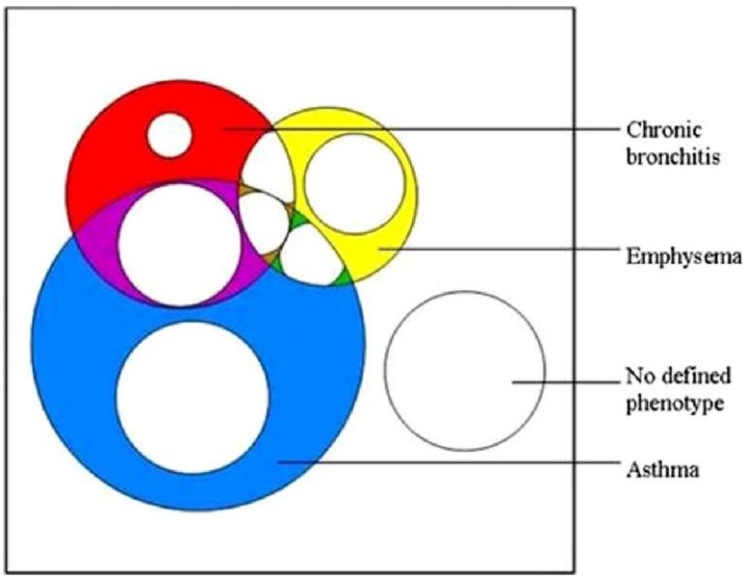
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation which is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases (Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023). In clinical practice, diagnosis is usually based on:

- Symptoms of exertional breathlessness, cough and sputum
- A history of smoking, or exposure to other noxious agents
- $FEV_1/FVC<0.7$ post-bronchodilator

Small-airway narrowing (with or without chronic bronchitis) and emphysema caused by smoking are the common conditions resulting in COPD. Chronic bronchitis is daily sputum production for at least three months of two or more consecutive years. Emphysema is a pathological diagnosis and consists of alveolar dilatation and destruction. Breathlessness with exertion, chest tightness and wheeze are the results of airway narrowing and impaired gas exchange. The loss of lung elastic tissue in emphysema may result in airway wall collapse during expiration, leading to dynamic hyperinflation and consequent increased work of breathing.

The irreversible component of airflow limitation is the end result of inflammation, fibrosis and remodelling of peripheral airways. Airflow limitation leads to non-homogeneous ventilation, while alveolar wall destruction and changes in pulmonary vessels reduce the surface area available for gas exchange. In advanced COPD there is a severe mismatching of ventilation and perfusion leading to hypoxaemia. Hypercapnia is a late manifestation and is caused by a reduction in ventilatory drive. Pulmonary hypertension and cor pulmonale are also late manifestations and reflect pulmonary vasoconstriction due to hypoxia in poorly ventilated lung, vasoconstrictor peptides produced by inflammatory cells and vascular remodelling. The clinical features and pathophysiology of COPD can overlap with asthma, as most COPD patients have some reversibility of airflow limitation with bronchodilators. The follow up of a cohort of children aged 10 to 16 initially recruited in 1964 demonstrated that childhood participants who had wheezy bronchitis (n=53) and asthma (n=38) had an increased risk (OR 1.81 and 6.37 respectively) of COPD by mean age of 61, compared to cohort controls (n=239). Multivariate analysis details of adjustment for smoking were not provided (Tagiyeva 2016). A meta-analysis of six prospective cohort studies following children with or without wheezing into adulthood found an association between childhood atopic wheezing and prevalence of COPD in adulthood (RR 5.307, 95% CI 1.033 to 27.271, P=0.046) (Ma 2018). By contrast, some non-smokers with chronic asthma develop irreversible airway narrowing. The overlap between chronic bronchitis, emphysema and asthma and their relationship to airflow limitation and COPD are illustrated in **Figure 1**. This proportional Venn diagram presents data from the Wellington Respiratory Survey which recruited participants over the age of 50 and invited them to have detailed lung function testing and chest CT scans (Marsh 2008). It can be seen that almost all patients with both chronic bronchitis and emphysema meet the GOLD definition of COPD, as do most with both chronic bronchitis and asthma. Patients with chronic bronchiolitis, bronchiectasis and cystic fibrosis may also present with similar symptoms and partially reversible airflow limitation.

Figure 1: COPD Phenotypes



The diagram (reproduced from Thorax 2008;63:761-7 with permission from the BMJ Publishing Group and corrected in Thorax 2015;70:905 to now include the clear circle in the middle of the emphysema circle) presents the different phenotypes within the Wellington Respiratory Survey study population. The large black rectangle represents the full study group. The clear circles within each coloured area represent the proportion of patients with COPD (post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC), 0.7). The isolated clear circle represents patients with COPD who did not have an additional defined phenotype of asthma, chronic bronchitis or emphysema.

In recent years there has been a focus on the prevalence and implications of the coexistence of asthma and COPD. A systematic review and meta-analysis of 19 studies found that the prevalence of co-existing asthma in patients with COPD was 27% in population-based studies and 28% in hospital-based studies (Alshabanat 2015). Both this review and systematic reviews by Gibson (Gibson 2015) and Nielsen (Nielsen 2015) found an increased frequency of exacerbations in patients with features of both asthma and COPD compared to those with COPD alone.

Treatable Traits

Treatable Traits is a new treatment paradigm proposed for the management of people with airway diseases. The treatment approach has been suggested as a way to progress precision or personalised medicine in COPD and asthma (Agusti 2017, Agusti 2016, McDonald 2019b). Patients are first assessed through a detailed clinical history and identification of airway disease risk factors (e.g. smoking history, history of allergies, occupational exposures, family history, respiratory disease in early life); spirometry and measures of airway inflammatory biomarkers, including exhaled nitric oxide fraction (FeNO) and blood eosinophils. These assessments will indicate a high or low probability of the presence of an airway disease (Agusti 2016).

Following this confirmation, it is recommended that each individual undergoes a multidimensional assessment to identify treatable traits and an individualised treatment plan is implemented based on the presence of traits.

In order to be considered a trait, the following criteria should be met. Traits should be identifiable using a trait identification marker, clinically relevant and modifiable (McDonald 2019b).

Traits are grouped into three domains – pulmonary and extrapulmonary traits and behaviours/ risk-

factors. While overall management according to treatable traits is a concept, the treatment of each individual trait is supported in most cases through RCT evidence. A systematic review of interventions targeting treatable traits in obstructive airways diseases found these interventions were effective in improving HRQoL and were also associated with small to medium reductions in hospitalizations, 1-year all-cause mortality, dyspnoea, anxiety, and depression (Sarwar 2022) [evidence level I]. Meta-analysis of the 4 COPD-only studies demonstrated a significant improvement in SGRQ -5.82 (95% CI -9.17 to -2.47).

C1. Aetiology and natural history

Smoking is the most important risk factor in COPD development (Fletcher 1977, Burrows 1977) [evidence level I, strong recommendation]

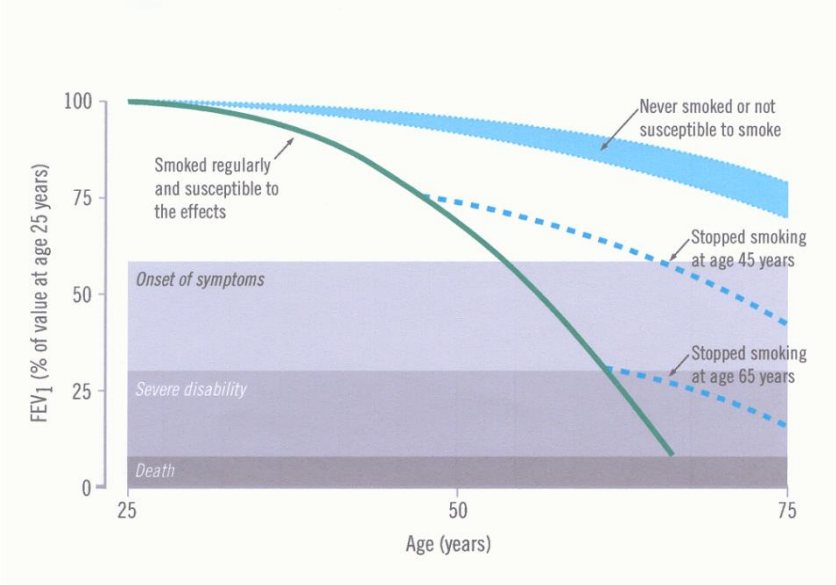
Cigarette smoking is the most important cause of COPD (Fletcher 1977, Burrows 1977, Matheson 2018). There is a close relationship between the amount of tobacco smoked and the rate of decline in forced expiratory flow in one second (FEV_1), although individuals vary greatly in susceptibility (Fletcher 1977). Around half of all smokers develop some airflow limitation, and 15 to 20% will develop clinically significant disability (Fletcher 1977). Even smokers who do not meet spirometric criteria for COPD may have respiratory symptoms and reduced physical activity. They may have other subtle abnormalities of lung function (Elbehairy 2016). Smokers are also at risk of developing lung cancer, and cardiovascular disease such as ischaemic heart disease and peripheral vascular disease.

In susceptible smoker's, cigarette smoking results in a steady decline in lung function, with a decrease in FEV_1 of 25–100 mL/year (Fletcher 1977). While smoking cessation may lead to minimal improvements in lung function, more importantly it will slow the rate of decline in lung function and delay the onset of disablement. At all times smoking cessation is important to preserve remaining lung function (Fletcher 1977).

Impairment increases as the disease progresses but may not be recognised because of the slow pace of the disease. The time course of development of COPD and disability and the influence of smoking cessation are illustrated in **Figure 2**.

The annual decline in FEV_1 has been measured in 5,041 patients with moderate to very severe COPD followed for 4 years (Tashkin 2013). The decline in post-bronchodilator measurements was greater than pre-bronchodilator, which might represent progression of disease or tachyphylaxis [evidence level III-2].

Figure 2: Time-course of chronic obstructive pulmonary disease (COPD) (Fletcher 1977)



The figure (adapted from Fletcher C and Peto R. The natural history of chronic airflow obstruction. BMJ 1977;1:1645-1648 and reproduced with permission from the BMJ Publishing Group) shows the rate of loss of forced expiratory flow in one second (FEV_1) for a hypothetical, susceptible smoker, and the potential effect of stopping smoking early or late in the course of COPD. Other susceptible smokers will have different rates of loss, thus reaching "disability" at different ages. The normal FEV_1 ranges from below 80% to above 120%, so this will affect the starting point for the individual's data (not shown).

Hookah (a type of water pipe) smoking is increasing, particularly in developing countries. In an Iranian study involving 245 adults aged ≥35 years who had at least 15 years of hookah smoking history and matching controls, the prevalence of COPD among hookah smokers was 10.2%; higher rates were found in older age, longer duration of hookah smoking; in men; history of ≥3 hookahs/day; history of cough for ≥2 years; history of sputum for ≥2 years; and a history of dyspnoea for ≥2 years (Bahtouee 2018).

Exposure to second hand smoke (SHS) is also associated with increased risk of developing COPD. Chen et al in a meta-analysis 15 studies (6 cross-sectional studies, 6 case-control studies, and 3 cohort studies) with 25,592 participants found that SHS exposure was associated with an increased risk of COPD (OR 2.25; 95% CI 1.40 to 3.62, $p < 0.01$, $I^2 = 98\%$, for heterogeneity based on a random-effects analysis model). The risk was higher in those with exposure of more than 5 years (OR 4.38; 95% CI 1.28 to 15.00, $p < 0.01$, $I^2 = 89\%$ for heterogeneity based on a random effects analysis model) (Chen 2023) [evidence level I].

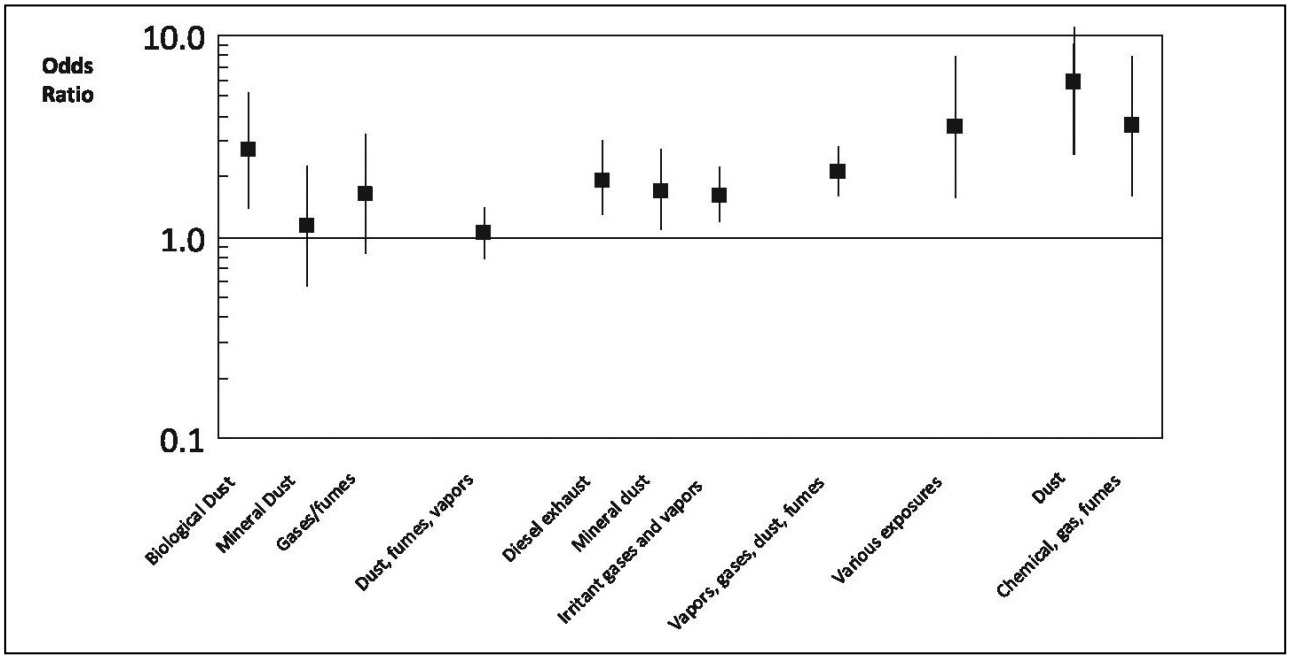
In addition to cigarette smoking, there are a number of other recognised risk factors for COPD (Omland 2014, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023) (see **Box 2**). COPD almost always arises from a gene environment interaction. The best characterised genetic predisposition is $alpha_1$ antitrypsin deficiency, but multiple other genes each make a small contribution and further investigation is required. The risk of COPD is related to the total burden of inhaled particles and oxidative stress in the lung.

Analysing the lifetime job-histories of ~100,000 individuals from a UK general population found that the following specific occupation categories are associated with an increased COPD risk: sculptor, painter, engraver, art restorer; gardener, groundsman, park keeper; food, drink and tobacco processor; plastics processor, moulder; agriculture, and fishing occupations not elsewhere classified; and warehouse stock handler, stacker. These associations were confirmed among never-smokers and never-asthmatics and were influenced by employment duration. Gathering job-history and focused

preventive strategies in COPD high-risk jobs are warranted (De Matteis 2019).

Occupational dust exposure might be responsible for 20 to 30% of COPD. This is consistent with the findings of a European study (Lytras 2018). This has long been recognised in coal miners (Santo Tomas 2011), but biological dust has also been identified as a risk factor, particularly in women (Matheson 2005). Non-smoking women involved in the spinning, weaving and knitting of cotton or silk have an increased risk of death from COPD (Cui 2011). Biological dust exposure is also associated with chronic sputum production, dyspnoea and work inactivity in male patients (Rodriguez 2008). Livestock farmers are also at increased risk of developing chronic bronchitis and COPD (Eduard 2009). Dairy farmers have increased wheeze and morning phlegm and increased rates of decline in FEV_1 compared to controls. These effects appear to be associated more with exposure to animal feed than handling hay or straw (Thaon 2011). Lifetime cumulative exposure to pesticides is associated with risk of developing COPD (De Matteis 2022). Each year of exposure to diesel exhaust increases the risk of dying from COPD by 2.5% (Hart 2009). An analysis of a Swiss cohort of 4,267 patients without asthma found that COPD was associated with high occupational exposures to minerals, biological dusts, vapours/fumes, vapours, gases, dust or fumes (VGDF). The findings were clearer in non-smokers and those without chronic bronchitis (Mehta 2012) [evidence level III-2]. A meta-analysis of 6 cross-sectional studies found that occupational exposure to respirable quartz dust was associated with a pooled reduction in FEV_1 of -4.62 (95% CI -7.18, -2.06) % predicted (Bruske 2014). A case control study conducted within a large managed care organisation found that self-reported exposures to vapours, gas, dust and fumes on the longest held job were responsible for 31% of COPD (Blanc 2009). Joint exposure both to smoking and occupational factors markedly increased the risk of COPD [evidence level III-2]. Evidence of emphysema and gas trapping on CT scans was associated with self-reported occupational exposures to dust and fumes in both men and women who were former or current smokers (Marchetti 2014). A summary of the risks of COPD associated with biological or mineral dusts, gases, fumes / vapours, diesel exhaust, irritant gases / vapours, chemical gas / fumes and various other occupational exposures appears in **Figure 3** (reproduced from Diaz-Guzman et al 2012 (Diaz-Guzman 2012) with permission).

Figure 3: Risk of occupational exposure for COPD from selected studies



Pathak et al (2019) conducted a systematic review and meta-analysis of the risk of COPD due to indoor air pollution from biomass cooking fuel. Eligible studies were case-control, retrospective cohort and cross-sectional, conducted in adults. COPD was assessed using any diagnostic criteria. A total of

35 studies with 73,122 participants were included. The pooled analysis showed that exposure to indoor air pollution due to solid biomass fuels increased the risk of COPD by 2.65 (95% CI 2.13–3.31).

Fortunately, the air quality in most Australian and New Zealand cities is relatively good and cooking with biomass fuels (coal, wood, dung, crop waste etc.) is uncommon. However, a panel study of 84 moderate to severe COPD patients found that indoor pollutant exposure, including PM2.5 and NO_2 (oxides of nitrogen) was associated with increased respiratory symptoms and risk of COPD exacerbation (Hansel 2013) [evidence level III-2].

Prasad et al (2022) used modelling of exposure at an individual level and respiratory questionnaire and respiratory function testing data to examine the effect of a 6-week period of coal fire PM2.5 exposure from a 2014 Hazelwood open cut coal mine. A dose–response association between particle exposure and COPD in non-smokers and increased chronic cough in current smokers was observed (Prasad 2022) [evidence level III-2].

Failure to achieve maximum lung function increases the risk of COPD in later life (Bui 2018, Lange 2015). Premature birth is associated with the development of COPD (Bui 2022). This association is compounded by smoking [Evidence level III-B]. There is some evidence that women might be more susceptible to the effects of tobacco smoke (Aryal 2014) [evidence level III-2]. Beyond the age of 45-50 years, female smokers appear to experience an accelerated decline in FEV_1 compared with male smokers (Gan 2006) [evidence level II]. On the other hand, a family-based case control study involving high resolution chest CT scans found that men demonstrated more low attenuation areas consistent with emphysema than did women (Camp 2009) [evidence level III-2]. Nor is it known whether the increased risk among lower socioeconomic groups is due to greater exposure to pollution, poorer nutrition, more respiratory infection or other factors.

Novel risk factors for COPD have been reviewed by an assembly of the American Thoracic Society (Eisner 2010a). Exposure to second-hand (Environmental) Tobacco Smoke was consistently associated with various definitions of COPD; there was a temporal relationship, dose response gradient and biological plausibility. Meta-analysis of 12 studies found a pooled odds ratio of 1.56 (95% CI 1.40 - 1.74). There was sufficient evidence that exposure to smoke from burning biomass fuels was associated with development of COPD in women. Meta-analysis of 15 studies found a pooled odds ratio of 2.23 (95% CI 1.72 - 2.90), but there was significant heterogeneity between studies. [evidence level III-2]. Whilst the risk of biomass smoke in men has only been assessed in three studies, there also appears to be a similarly increased risk of COPD (OR 4.3, 95% CI 1.85-10) (Hu 2010). Pulmonary tuberculosis can lead to scarring and irreversible loss of lung function, however there is currently insufficient evidence that this is clinically similar to COPD caused by cigarette smoking (Eisner 2010a). After extensive adjustment for potential confounders, a self-reported past history of TB had an adjusted odds of 3.78 (95% CI 2.87-4.98) of a diagnosis of COPD in a review of studies which were exclusively of low- and middle-income countries. This review comprised 12396 people aged 35 to 95, of cross-sectional data from 13 low- and middle-income countries and three continents. Overall prevalence of COPD was 8.8%, and those with a history of TB had an overall COPD prevalence of 25.9% (Kamenar 2021) [evidence level III-2]. The authors suggested that previously underestimated endobronchial spread and airway fibrosis as the mechanism.

Box 2: Risk Factors for COPD

- Genetic factors
- Age and sex
- Lung growth and development, premature birth
- Exposure to particles
  - Tobacco smoke, active and second-hand smoke (SHS)
  - Occupational dusts, organic and inorganic
  - Indoor air pollution from heating and cooking with bio-mass in poorly vented dwellings
  - Outdoor air pollution, including landscape fire smoke
- Socioeconomic status
- Asthma and airway hyper-reactivity
- Chronic bronchitis
- Infections, particularly tuberculosis and childhood respiratory infections

In the Tasmanian Longitudinal Health Study, there were five different asthma /allergy trajectory patterns demonstrated in the prospective cohort of participants. This cohort included n=7380 initial participants at seven years of age, to n=2689 of the original participants at 53 years of age. Those with early onset-onset persistent asthma and allergies were most likely to develop COPD (OR 5.3, 95% CI 3.2-8.6.), followed by late-onset asthma and allergies (OR 3.8, 95% CI 2.4-4.6) (Bui 2021). This highlights the need for a personal approach including the management of treatable traits to potentially prevent progression to COPD. A past history of childhood asthma has been shown to be independently associated with a 3-fold (95% CI 2.25-4.00) increase in prevalence of adulthood COPD in a meta-analysis of 11 studies, which included 4294 people with and 44381 people without COPD (Ali 2022) [evidence level III]. Smoking status and other recognised risk COPD factors were adjusted for across this study.

Early life risk factors that could lead to lung problems in later life are discussed further by the European Lung Foundation. https://europeanlung.org/en/information-hub/keeping-lungs-healthy/early-life-risk-factors/

C1.1 Natural history

Although FEV_1 has long been accepted as the single best predictor of mortality in population studies in COPD (Fletcher 1977, Peto 1983) studies have suggested various other indices, which may also predict mortality. In patients with established COPD, degree of hyperinflation as measured by inspiratory capacity/ total lung capacity (IC/TLC) ratio was independently associated with all cause and COPD mortality (Casanova 2005). Exercise capacity (as measured by the 6-minute walk distance (6MWD), incremental shuttle walk distance (ISWD), or peak VO_2 during a cardiopulmonary exercise test, body mass index and dyspnoea score (measured with the modified Medical Research Council Scale) have all been shown to predict mortality better than FEV_1 in patients with established disease. Several of these latter indices are incorporated together in a single score, the BODE index (Body mass index, degree of Obstruction as measured by FEV_1, Dyspnoea score and Exercise capacity measured by 6MWD) or the i-BODE index, in which the ISWD replaces the 6MWD strongly predicts mortality (Celli 2004, Williams 2012). A simplified ADO index (Age, Dyspnoea score and Obstruction) has been developed in a Swiss cohort and shown to predict three-year mortality in a Spanish cohort (Puhan 2009b) [evidence level III-2]. Further studies are awaited including validation in an Australian cohort of COPD patients. Nonetheless, FEV_1 continues to have utility as a predictor of all-cause mortality in COPD. In one study that followed patients after an exacerbation, the five-year survival rate was only about 10% for those with an FEV_1 <20% predicted, 30% for those with FEV_1 of 20 to 29% predicted and about 50% for those with an FEV_1 of 30 to 39% predicted (Connors 1996). Patients with an FEV_1 <20% predicted and either homogeneous emphysema on high resolution computed tomography (HRCT) or a diffusing capacity of lung for carbon monoxide (D_LCO) test <20% predicted are at high risk for death after LVRS and unlikely to benefit from the intervention (National Emphysema Treatment

Trial Research 2001). A review of 15 COPD prognostic indices found that although the prognostic information of some has been validated, they lack evidence for implementation. Impact studies will be required in the future to determine whether such indices improve COPD management and patient outcomes (Dijk 2011).

Continued smoking and airway hyperresponsiveness are associated with accelerated loss of lung function (Tashkin 1996). However, even if substantial airflow limitation is present, cessation of smoking may result in some improvement in lung function and will slow progression of disease (Tashkin 1996, Anthonisen 2002).

The development of hypoxaemic respiratory failure is an independent predictor of mortality, with a three-year survival of about 40% (Medical Research Council Working Party 1981). Long term administration of oxygen increases survival to about 50% with nocturnal oxygen (Medical Research Council Working Party 1981) and to about 60% with oxygen administration for more than 15 hours a day (Nocturnal Oxygen Therapy Trial Group 1980) (see also section P). There may be a differential in benefit between men and women. A study (Ekstrom 2010) of Swedish patients receiving long term oxygen therapy demonstrated that overall, women had a lower risk of death than men; nonetheless, when compared with expected death rates for the population, women had a higher *relative* mortality with a standardised mortality rate (SMR) of 12 (95% CI;11.6-12.5) compared with 7.4 (95% CI 7.1-7.6) [evidence level III-2].

The natural history of COPD is characterised by progressive deterioration with episodes of acute deterioration in symptoms referred to as an exacerbation. A large study that included 4951 patients from 28 countries found that health-related quality of life (HRQoL), measured by the St George's Respiratory Questionnaire (SGRQ), deteriorated faster in patients with more severe disease (Jones 2011a). Patients then classified as in GOLD stage II who received placebo showed an overall improvement, while those in GOLD stages III and IV deteriorated. When all participants from the different arms were included, the change in SGRQ at three years correlated weakly with change in FEV_1: $r = -0.24$, $p < 0.0001$ and there was no difference in this relationship between men and women. However, a significantly faster deterioration in the SGRQ score relative to FEV_1 % predicted was seen in older patients (greater 65 years).

Admission to hospital with an exacerbation of COPD complicated by hypercapnic respiratory failure is associated with a poor prognosis. A mortality of 11% during admission and 49% at two years has been reported in patients with a partial pressure of carbon dioxide (PCO_2) >50mmHg (Connors 1996). For those with chronic carbon dioxide retention (about 25% of those admitted with hypercapnic exacerbations), the five-year survival was only 11% (Connors 1996).

The Tasmanian Longitudinal Health Study investigated spirometry patterns in a cohort of 2422 subjects at ages 7, 13, 18, 45, 50, and 53 years (n=2422) (Dharmage 2023) [evidence level III-2]. The finding of obstructive and mixed pattern phenotypes may contribute to early detection of individuals who are at risk of developing COPD, while a restrictive phenotype predicted a high prevalence of comorbidities (obesity, diabetes, cardiovascular conditions, hypertension, and obstructive sleep apnoea). These findings could assist with targeted early management (Dharmage 2023). Five asthma phenotypes have also been identified in this study, four of which were strongly associated with developing COPD by age 53 years old (Tan 2023) [evidence level III-2].

A report from the multicentre, observational, prospective COPDGene study indicated that the presence of mucous plugs on CT chest was associated with higher all-cause mortality in the 4363 subjects who had smoked >10 pack years and in whom mucous plug scores had been measured (Diaz 2023) [evidence level III-2]. However, the CT methods used submillimetric slice thickness, which might not be routinely acquired in clinical practice. Also, as this was an observational study it cannot be concluded that mucous plugs cause death.

C2. Diagnosis

C2.1 History

A thorough history and examination is the first step in COPD diagnosis [evidence level III-2, strong recommendation]

The main symptoms of COPD are breathlessness, cough and sputum production. Patients often attribute breathlessness to ageing or lack of fitness. A persistent cough, typically worse in the mornings with mucoid sputum, is common in smokers. Other symptoms such as chest tightness, wheezing and airway irritability are common (Thompson 1992). Further, many people with COPD have low levels of physical activity and demonstrate reduced exercise tolerance on formal testing (Watz 2014, Cote 2007b). People with chronic cough and sputum are at increased risk of exacerbation (Burgel 2009) [evidence level III-2]. Exacerbations, usually infective, occur from time to time and may lead to a sharp deterioration in coping ability. Fatigue, poor appetite and weight loss are more common in advanced disease.

The effect of breathlessness on daily activities can be quantified easily in clinical practice using the Modified Medical Research Council (mMRC) Dyspnoea Scale (see **Box 3**) (Celli 2004, Fletcher 1960).

Box 3: Modified Medical Research Council (mMRC) Dyspnoea Scale for grading the severity of breathlessness during daily activities

Grade	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 metres or after a few minutes on level ground
Grade 4	I am too breathless to leave the house, or I am breathless when dressing or undressing

The COPD Assessment Test (CAT) (Jones 2009) is relatively short, easily scored and provides an alternative to approximately 17 other reported and longer questionnaires such as the St George's Respiratory Questionnaire (SGRQ) and the Chronic Disease Respiratory Questionnaire (CRQ). It may provide useful information when taking a history from patients. The CAT quantifies the impact COPD has on a patient's wellbeing and daily life, with the aim of facilitating communication between healthcare professionals and patients. The test is comprised of eight questions pertaining to cough, sputum, chest tightness, exercise tolerance, ability to perform activities of daily living, confidence in leaving the home, sleep and energy levels. Each question is scored on a 6-point scale (0 to 5) yielding a total possible score of 40 for the questionnaire. The total CAT score provides a broad clinical picture of the impact of COPD on an individual patient with scores of >30, 21-30, 10-20 and <10 corresponding to very high, high, moderate and low impact respectively. A total score of 5 is the upper limit of normal in a healthy non-smoker (Jones 2011b). A systematic review (Gupta 2014) that included 36 studies carried out in 32 countries reported the CAT to be reliable, valid and responsive as a health-related quality of life (HRQoL) instrument. The MCID for improvement is a difference of 2 (Cazzola 2015b). The CAT is freely available in many languages (see https://www.catestonline.org/hcp-homepage.html). It is easy and quick to complete, and score. A meta-analysis of eight studies of the CAT questionnaire demonstrates moderately strong predictive values for aspects of COPD including a valid diagnosis, likelihood of exacerbations, depression, lung

function and mortality (Karloh 2016).

C2.2 Physical examination

The sensitivity of physical examination for detecting mild to moderate COPD is poor (Badgett 1993). Wheezing is not an indicator of severity of disease and is often absent in stable, severe COPD. In more advanced disease, physical features commonly found are hyperinflation of the chest, reduced chest expansion, hyperresonance to percussion, soft breath sounds and a prolonged expiratory phase. Right heart failure may complicate severe disease.

During an exacerbation, tachypnoea, tachycardia, use of accessory muscles, tracheal tug and cyanosis are common.

The presence and severity of airflow limitation are impossible to determine by clinical signs (Badgett 1993). Objective measurements such as spirometry are essential. Peak expiratory flow (PEF) is not a sensitive measure of airway function in COPD patients, as it is effort dependent and is dominated by large airway resistance and has a wide range of normal values (Kelly 1988).

C2.3 Spirometry

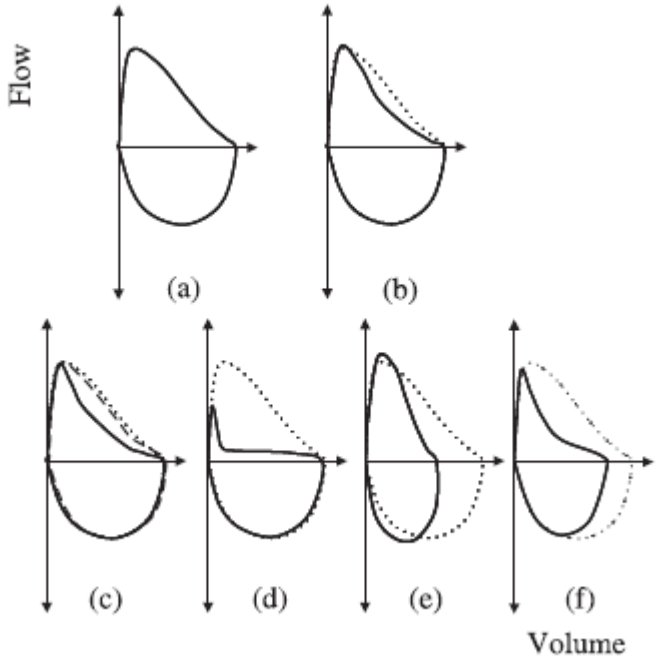
COPD is confirmed by the presence of persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.7$) [evidence level III-2, strong recommendation]

Because COPD is defined by demonstration of airflow limitation, which is not fully reversible, spirometry is essential for its diagnosis (see **Figure 4**), and this may be performed in the community or prior to discharge from hospital (Rea 2011). Most spirometers provide predicted ("normal") values obtained from healthy population studies, and derived from formulas based on height, age, sex and ethnicity.

Airflow limitation is not fully reversible when, after administration of bronchodilator medication, the ratio of FEV_1 to forced vital capacity (FVC) is <70% and the FEV_1 is <80% of the predicted value. The ratio of FEV_1 to vital capacity (VC) is a sensitive indicator for mild COPD. FEV_1/FEV6 has a high level of agreement with FEV_1/FVC on both the fixed ratio and Lower Limit of Normal (LLN) criteria for the diagnosis of COPD (Bhatt 2014a). There is controversy regarding the optimal cut-off to define airflow limitation (FEV_1/FVC less than 0.7 versus lower limit of normal). There is evidence that the fixed ratio can lead to over diagnosis of COPD in older populations, under diagnosis in younger people (Cerveri 2008, Vollmer 2009, Swanney 2008) and may lead to gender imbalances as women have higher FEV_1/FVC than their male counterparts (Guerra 2009). A systematic review of 11 studies which examined the relationship of each criterion with clinical outcomes found both were related to clinical outcomes and concluded that on current evidence one could not be preferred over the other. The LLN appeared to be a better criterion in older patients with less severe airflow limitation (van Dijk 2014); however, a study by Bhatt (Bhatt 2014b) shows that the fixed cut-off of 0.7 identified more people with CT diagnosed emphysema.

Concerning healthcare utilisation and COPD mortality, a population-based study of 11, 077 adults in the US found that an FEV_1/FVC ratio of <0.70 identified individuals who were at risk of COPD hospitalisations and COPD-related mortality, with equal or better accuracy than other ratios ranging from 0.75 to 0.65, and with more accuracy than the lower limit of normal (Bhatt 2019) [evidence level III-2]. This study supported using the fixed FEV_1/FVC ratio of <0.70 to identify individuals at risk of clinically significant COPD.

Figure 4: Comparison of flow-volume curves for spirometry



The dotted line for all curves represents a normal flow–volume curve in a young adult. (a) and (b) depict typical flow–volume curve shapes for spirometry within normal limits for a young adult and older person, respectively. Note that the expiratory limb of (b) has some concavity despite the result being within normal limits. (c) shows an example of airway obstruction with almost complete reversibility. The baseline curve (solid line) has concavity, typical of airflow obstruction. The post-bronchodilator curve (dashed line) has returned to close to the 'normal' curve (dotted). (d) depicts significant airflow obstruction. (e) represents the pattern often seen with restriction. The curve appears to be compressed along the volume axis, but the expiratory limb does not appear to have any concavity. (f) portrays an obstructive pattern. Note also that the volume appears to be reduced. This pattern may represent obstruction with a reduced FVC due to gas trapping or may represent a mixed obstructive/restrictive ventilatory pattern. Measurement of static lung volumes are required for determination.
(Figure reproduced from Interpreting Lung Function Tests: A Step-by-Step Guide, First Edition. Brigitte M. Borg, Bruce R. Thompson and Robyn E. O'Hehir. © 2014 John Wiley & Sons, Ltd. with permission from Wiley)

The spirometric tests require high levels of patient effort and cooperation, and there are important quality criteria that should be met in conducting spirometry (Miller 2005).

Indications for spirometry include:

- breathlessness that seems inappropriate;
- chronic (daily for two months) or intermittent, unusual cough;
- frequent or unusual sputum production;
- relapsing acute infective bronchitis; and
- risk factors such as exposure to tobacco smoke, occupational dusts and chemicals, and a strong family history of COPD.

There is evidence of both underdiagnosis (Toelle 2013) and misdiagnosis of COPD in the community (Zwar 2011). In a community-based study of 1615 participants with a range of respiratory symptoms, but not recalling a diagnosis of respiratory disease, 8.4% had spirometry results consistent with asthma and 12.1% subjects had spirometry results consistent with COPD (Alhabeeb 2022). This highlights the prevalence of undiagnosed airways disease. These undiagnosed subjects also had more severe respiratory symptoms as assessed by the COPD Assessment Test (CAT), and poorer health-related quality of life as assessed by the St. George's Respiratory Questionnaire (SGRQ) compared to subjects with no airflow obstruction. This study highlights a beneficial yield of airways disease diagnoses, in adults who have respiratory symptoms but without a diagnosis, by performing spirometry.

In a systematic review examining under and overdiagnosis in primary healthcare settings Perrett et al (2023) found that based on evidence from three studies of symptomatic smokers the prevalence of spirometry-confirmed COPD without a diagnosis documented in their health records was 14%–26%. The same review found substantial evidence of misdiagnosis. Based on four case series of COPD diagnosed documented in primary healthcare records, only between 50% and 75% of subjects had airflow obstruction on postbronchodilator spirometry performed by study researchers (Perret 2023) [evidence level III-1]. In a general practice setting, patients with comorbidities may be more commonly mis-diagnosed with COPD. In a study of 1,050 smokers or ex-smokers identified from 41 Melbourne general practices, two-thirds were current smokers (Liang 2018). More than one-third of participants with a prior diagnosis of COPD did not meet the spirometric definition of the disorder. 1 in 6 participants not previously diagnosed with COPD had spirometry test results consistent with COPD. Spirometric assessment is important in these patients to minimise this risk (Zwar 2011). Two pulmonologists reviewed 333 patients with physician-diagnosed COPD and/or asthma. The patients had two or more emergency room visits or admissions over the preceding 12 months, with prospective evaluation over the next 10 months. The study found that a third of these patients had neither asthma nor COPD, and a quarter may not even have any form of airflow limitation. The study highlighted the importance of spirometry in making the correct diagnosis, which had been performed in less than a third of the patients studied (Jain 2015). Respiratory symptoms are of clinical importance even in those current or former smokers with preserved lung function (Woodruff 2016). Further evidence is required for optimal management of these patients.

Inaccurate diagnosis related to lack of use of spirometry is also an issue in the hospital setting. Habteslassie et al (2021) conducted a retrospective audit of inpatient separations in one Victorian hospital. A total of 2239 inpatient separations occurred in 1469 individuals who had a clinical diagnosis of COPD in the period October 2016 to March 2018. Spirometry results were not available in 43.6% (n = 641) of the sample and a further 19.7% (n = 289) had spirometry results available at the time of admission that did not demonstrate fixed airflow obstruction. The authors noted the risks of inappropriate treatment related to the lack of diagnostic accuracy (Habteslassie 2021).

In a Danish study (Katsimigas 2019) of opportunistic screening for COPD carried out in symptomatic smokers and ex-smokers (n=6,710), BMI <25 kg/m_2 and BMI >35 kg/m_2, increasing age and an increasing number of pack-years smoked were all important predictors for COPD (diagnosed in 17.7% in this study). GPs should target these patients for case finding to facilitate early diagnosis and initiate early interventions.

Aaron et al (Aaron 2017) studied two longitudinal cohorts of patients with mild to moderate COPD on post-bronchodilator spirometry at baseline and found that transient episodes of diagnostic instability occurred commonly and that 12 to 27% of patients reversed their diagnosis of COPD over a 4-to-5-year period. Diagnostic reversal was most common for patients who quit smoking during the study period. These findings suggest there is considerable variability of spirometry results around the FEV_1/FVC threshold and that a single spirometric assessment may not be reliable for diagnosing COPD in patients with mild to moderate airflow limitation. If spirometry results are around the threshold, repeat spirometry should be performed to confirm diagnosis.

C2.4 Flow volume tests

Electronic spirometers allow for the simultaneous measurement of flow and volume during maximal expiration. Reduced expiratory flows at mid and low lung volumes are the earliest indicators of airflow limitation in COPD and may be abnormal even when FEV_1 is within the normal range (>80%).

C2.5 COPD case finding

The US Preventive Services Task Force reviewed the evidence on screening asymptomatic adults for COPD using questionnaires or office-based screening pulmonary function testing from January 2000 to January 2015. The review found no direct evidence to determine the benefits and harms of screening

or to determine the benefits of treatment in screen-detected populations. On this basis, screening of asymptomatic adults was not recommended (Guirguis-Blake 2016, U. S. Preventive Services Task Force 2016). A targeted systematic review commissioned by the USPSTF to update the evidence on the effectiveness of screening asymptomatic adults found no new studies over the subsequent period January 1, 2015, to March 25, 2021 (Webber 2022) [evidence level I].

Simple lung function tools can assist practitioners in the case finding of individuals who have undiagnosed COPD. The devices measure the amount of exhaled air in the first 1 and 6 seconds of expiration (FEV_1, FEV_6) and calculate FEV_1/FEV_6, which is the ratio of the amount of air forcibly exhaled in the first second relative to the first 6 seconds. Schnieders et al (2021) published a systematic review and meta-analysis of the performance of micro-spirometers or two questionnaires compared to post-bronchodilator spirometry for detection of COPD. The meta-analysis included 17 studies. The overall area under the curve (AUC) of micro-spirometers was 0.84 (95% CI 0.80–0.89). For questionnaires the AUC for the COPD population screener (COPD-PS) questionnaire was 0.77 (95% CI 0.63–0.85) and the COPD diagnostic questionnaire (CDQ) was 0.72 (95% CI 0.64–0.78) (Schnieders 2021). If spirometry is unavailable either a micro spirometer or questionnaire are useful tests for early detection.

Lung Foundation Australia's *Position Paper: COPD case finding in community settings*, https://lungfoundation.com.au/resources/copd-case-finding-position-paper/ recommends that previously undiagnosed individuals aged 35 years or older should be assessed with the symptom checklist, followed by a 'COPD screening device' with an FEV_1/FEV_6 cut-off < 0.75. Individuals with an FEV_1/FEV_6 ratio < 0.75 should undergo formal diagnostic spirometry. Symptomatic individuals with an FEV_1/FEV_6 ratio ≥ 0.75 should be encouraged to visit their general practitioner as they may be at risk of other diseases or lung conditions and may require more formalised testing.[1]

In a retrospective analysis of health data in Canada (Johnson 2020), over 99% of people with COPD had incurred at least one visit in any of the previous 5 years prior to recording of the diagnosis. This study highlights the potential for earlier diagnosis, and intervention.

COPD is commonly undiagnosed, until presentation requiring a hospital admission. A review of 39 studies with a variety of case finding strategies, including five studies comparing earlier diagnostic strategies with usual care, has found that postal questionnaire approaches had poor results, while active opportunistic case finding through primary care had greater chance of detection (Haroon 2015). Practice led symptom questionnaires of patients clinically suspected to have COPD, followed by diagnostic assessment, had the best diagnostic yields. Widespread population screening for COPD is not recommended (Guirguis-Blake 2016, U.S. Preventive Services Task Force 2016).

Based upon an analysis of 4,484 COPD subjects in the 'Genetic Epidemiology of COPD cohort', DeMeo et al demonstrated that females are more susceptible to the effects of COPD than males with respect to symptom burden, including severity of dyspnoea, and exacerbation risk, especially in younger females. Given this greater COPD burden, the study highlighted the potential of under diagnosis as well as under treatment of COPD in females (DeMeo 2018). Retrospective data suggests that females are at higher risk of presenting with a moderate or severe exacerbation than men (Stolz 2019). A large study (29,678) of randomly selected residents of Copenhagen aged between 40 and 80 found 11% had FEV_1/FVC <0.70 and FEV_1 <80% of predicted on pre-bronchodilator spirometry. Treatable problems were identified in many of these participants, including smoking (45%), insufficient physical activity (12%), obesity (28%), undiagnosed hypertension (28%) and undiagnosed hypercholesterolaemia (48%) (Çolak 2022).

Patients that are added to a COPD register as a result of a systematic screening programme (Haroon 2020) received significantly higher levels of appropriate clinical care. However only one in five case-found patients were actually registered in the database to potentially go on to receive such care. Case

[1] Level of evidence could not be assigned due to heterogeneity

finding is only likely to improve clinical care if patients with newly identified disease are promptly added to an active primary care COPD register.

C3. Assessing the severity of COPD

Diagnosis of COPD should be accompanied by regular assessment of severity [evidence level III-2, strong recommendation]

Spirometry is the most reproducible, standardised and objective way of measuring airflow limitation, and FEV_1 is the variable most closely associated with prognosis (Peto 1983). The grades of severity according to FEV_1 and the likely symptoms and complications are shown in **Box 4**. However, it should be noted that some patients with an FEV_1 >80% predicted, although within the normal range, may have airflow limitation (FEV_1/FVC ratio <70%).

A Spanish cohort study of 611 COPD patients found that the British Thoracic Society classification (which is very similar to **Box 4**) had the optimal sensitivity and specificity against the criterion of all cause and respiratory mortality over 5 years (Esteban 2009). There were also significant differences in health-related quality (HRQoL) of life between different stages of the disease [evidence level III-2].

Exacerbations are an important complication of COPD (see X: Manage eXacerbations). The future risk of exacerbations should be assessed in patients with COPD. Exacerbations are more frequent with increased severity of COPD. The most important risk factor for exacerbations is a history of past exacerbations; other factors include gastro-oesophageal reflux, poorer quality of life and elevated white cell count (Hurst 2010). A systematic literature review that included data from 76 studies confirmed that a past history of exacerbations is the most important predictor of future exacerbation risk (Hurst 2022) [evidence level I].

Box 4: Classification of severity of chronic obstructive pulmonary disease (COPD)

	MILD	**MODERATE**	**SEVERE**
	Few symptoms	Breathless walking on level ground	Breathless on minimal exertion
Typical Symptoms	Breathless on moderate exertion	Increasing limitation of daily activities	Daily activities severely curtailed
	Cough and sputum production	Recurrent chest infections	Exacerbations of increasing frequency and severity
	Little or no effect on daily activities	Exacerbations requiring oral corticosteroids and/or antibiotics	
Typical Lung Function	$FEV_1 \approx$ 60-80% predicted	$FEV_1 \approx$ 40-59% predicted	$FEV_1 <$ 40% predicted

FEV_1=forced expiratory volume in one second
Box adapted from Lung Foundation Australia's Stepwise Management of Stable COPD available at https://lungfoundation.com.au/resources/?search=stepwise

C4. Assessing acute response to bronchodilators

The response to bronchodilators is determined to:

- assign a level of severity of airflow limitation (post- bronchodilator); and
- help confirm asthma.

The details for this assessment are outlined in **Box 5**.

The change in FEV_1 after an acute bronchodilator reversibility test indicates the degree of reversibility of airflow limitation. This is often expressed as a percentage of the baseline measurement (e.g., 12% increase). An increase in FEV_1 of more than 12% and 200 mL is greater than average day-to-day variability and is unlikely to occur by chance (Sourk 1983, Pellegrino 2005). An analysis of cross-sectional data from 3,922 healthy never smokers in the BOLD study (Tan 2012) found that the 95th percentiles (95% CI) for bronchodilator response were 284 ml (263 to 305) absolute change in forced expiratory volume in 1 second from baseline. However, this degree of reversibility is not diagnostic of asthma and is frequently seen in patients with COPD (e.g., the FEV_1 increases from 0.8 L to 1.0 L when the predicted value is, say, 3.5 L). The diagnosis of asthma relies on an appropriate history and complete, or at least substantial, reversibility of airflow limitation (see also below).

Box 5: Assessment of acute response to inhaled beta-agonist at diagnosis

Preparation

- Patients should be clinically stable and free of respiratory infection.
- Withhold inhaled short-acting bronchodilators in the previous six hours, long-acting beta-agonists in the previous 12 hours, or sustained-release theophyllines in the previous 24 hours.

Spirometry

- Measure baseline spirometry (pre-bronchodilator). An FEV_1 <80% predicted and FEV_1/FVC ratio <0.70 shows airflow limitation.
- Give the bronchodilator by metered dose inhaler (MDI) through a spacer device or by nebuliser.
- Give short-acting beta-agonist, at a dose selected to be high on the dose–response curve (e.g., 200–400mcg salbutamol from MDI and spacer).

Repeat spirometry 15–30 minutes after bronchodilator is given and calculate reversibility.

FEV_1=forced expiratory flow in one second. FVC=forced vital capacity.

C4.1 Confirm or exclude asthma

If FEV_1 increases > 400 ml following bronchodilator, consider asthma, or coexisting asthma and COPD [evidence level III-2, strong recommendation]

Some patients may have coexisting COPD and asthma (Global Initiative for Asthma 2019). Asthma usually runs a more variable course and dates back to a younger age. Atopy is more common, and the smoking history is often relatively light (e.g., less than 15 pack-years). Airflow limitation in asthma is substantially, if not completely, reversible, either spontaneously or in response to treatment. By contrast, COPD tends to be progressive, with a late onset of symptoms and a heavier smoking history (usually >15 pack-years) and the airflow limitation is not completely reversible.

Long-standing or poorly controlled asthma can lead to chronic, irreversible airway narrowing even in non-smokers, thought to be due to airway remodelling resulting from uncontrolled airway wall inflammation with release of cytokines and mediators.

Patients with COPD and features of asthma should receive inhaled corticosteroid therapy (to treat the asthma component), as well as long-acting bronchodilators. LABA monotherapy should be avoided in patients who have a component of asthma (Global Initiative for Asthma 2019).

C5. Specialist referral

Further investigations may help a) confirm or exclude other conditions (either coexisting or with similar symptoms to COPD) and b) assess the severity of COPD [evidence level III-2, strong recommendation]

Referral to specialist respiratory services may be required [evidence level III-2, strong recommendation]

Confirmation of the diagnosis of COPD and differentiation from chronic asthma, other airway diseases or occupational exposures that may cause airway narrowing or hyper- responsiveness, or both, often requires specialised knowledge and investigations. Indications for which consultation with a respiratory medicine specialist may be considered are shown in **Box 6**.

Box 6:Indication for referral to specialist respiratory outpatient services

Reason	Purpose
Diagnostic uncertainty and exclusion of asthma	Establish diagnosis and optimise treatment. Check degree of reversibility of airflow Obstruction
Unusual symptoms such as haemoptysis	Investigate cause including exclusion of Malignancy
Rapid decline in FEV_1	Optimise management
Moderate or severe COPD	Optimise management
Onset of cor pulmonale	Confirm diagnosis and optimise treatment
Assessment of home oxygen therapy: ambulatory or long-term oxygen therapy	Optimise management, measure blood gases and prescribe oxygen therapy
Assessing the need for Pulmonary Rehabilitation	Optimise treatment and refer to specialist or community-based rehabilitation service
Bullous lung disease	Confirm diagnosis and refer to medical or surgical units for bullectomy
COPD <40 years of age	Establish diagnosis and exclude alpha1- antitrypsin deficiency
Assessment for lung transplantation or lung volume reduction surgery	Identify criteria for referral to transplant Centres
Frequent chest infections	Rule out co-existing bronchiectasis
Dysfunctional breathing	Establish diagnosis and refer for pharmacological and non-pharmacological management

FEV_1, forced expiratory volume in 1s; COPD, chronic obstructive pulmonary disease. Box adapted from British Thoracic Society Statement (British Thoracic Society 2008)

C5.1 Complex lung function tests

Other measurements of lung function such as static lung volumes and diffusing capacity of lungs for carbon monoxide assist in the assessment of patients with more complex respiratory disorders. Measurements such as inspiratory capacity (IC), which indicate the degree of hyperinflation and relate to exercise tolerance (O'Donnell 2001) and mortality (Casanova 2005) and forced oscillometry, have not yet found clinical application.

C5.2 Exercise testing

Cardiopulmonary exercise tests may be useful to differentiate between breathlessness resulting from cardiac or respiratory disease, and may help to identify other causes of exercise limitation (e.g., hyperventilation, musculoskeletal disorder). Exercise prescription and monitoring of outcomes from drug or rehabilitation therapies are additional uses for these tests. Walking tests (6-minute walking distance and shuttle tests) are also useful, and can indicate whether exercise oxygen desaturation is occurring.

C5.3 Sleep studies

Specialist referral is recommended for patients with COPD suspected of having a coexistent sleep disorder or with hypercapnia or pulmonary hypertension in the absence of daytime hypoxaemia, right heart failure or polycythaemia. Continuous overnight oximetry (with appropriate sampling frequency and averaging time) may be used to assess a need for overnight domiciliary oxygen therapy, and may be indicated in patients receiving long-term domiciliary oxygen therapy to assess whether hypoxaemia has been adequately corrected.

C5.4 Chest x-rays

A plain posteroanterior and lateral chest x-ray helps to exclude other conditions such as lung cancer. The chest x- ray is not accurate for the diagnosis of COPD (den Harder 2017) as hyperinflation is not specific and will not exclude a small lung nodule (<1cm).

C5.5 High resolution computed tomography

High resolution computed tomography (HRCT) scanning gives precise images of the lung parenchyma and mediastinal structures. The presence of emphysema and the size and number of bullae can be determined. This is necessary if bullectomy or lung reduction surgery is being contemplated. HRCT is also appropriate for detecting bronchiectasis. Vertical reconstructions can provide a virtual bronchogram.

Helical computed tomography (CT) scans with intravenous contrast should be used in other circumstances, such as for investigating and staging lung cancer.

CT pulmonary angiograms are useful for investigating possible pulmonary embolism, especially when the chest x- ray is abnormal.

C5.6 Ventilation and perfusion scans

The ventilation and perfusion (V/Q) scan may be difficult to interpret in COPD patients because regional lung ventilation may be compromised leading to matched defects. If pulmonary emboli are suspected, a CT pulmonary angiogram may be more useful. Quantitative regional V/Q scans are helpful in assessing whether patients are suitable for lung resection and lung volume reduction surgery.

C5.7 Transcutaneous oxygen saturation

Oximeters typically have an accuracy of plus or minus 2%, which is satisfactory for routine clinical purposes. They are more useful for monitoring trends than in single measurements. If continuous overnight oximetry is required, standard oximeters are not appropriate (See section C5.3). Oximetry does not provide any information about carbon dioxide status and is inaccurate in the presence of poor peripheral circulation (e.g., cold extremities, cardiac failure) and when readings are consistently below SpO_2 80%.

C5.8 Arterial blood gas measurement

Arterial blood gas analysis should be considered in all patients with severe disease, those being considered for domiciliary oxygen therapy (e.g., whose FEV_1 is <40% predicted or <1 L, whose oxygen saturation as measured by pulse oximetry [SpO_2] is <92%), those with pulmonary hypertension, and those with breathlessness out of proportion to their clinical status). Respiratory failure is defined as a PaO_2<60mmHg (8kPa) or $PaCO_2$ >50mmHg (6.7kPa). The latter is termed 'ventilatory failure' and is accompanied by either compensated (chronic) or uncompensated (acute) acidosis. Acute respiratory acidosis indicates a need for assisted ventilation.

C5.9 Sputum examination

Routine sputum culture in clinically stable patients with COPD is unhelpful and unnecessary. Sputum culture is recommended when an infection is not responding to antibiotic therapy or when a resistant organism is suspected.

C5.10 Haematology and biochemistry

Polycythaemia should be confirmed as being secondary to COPD by blood gas measurement that demonstrates hypoxaemia. The possibility of sleep apnoea or hypoventilation should be considered if polycythaemia is present but oxygen desaturation or hypoxaemia on arterial blood gas tests are absent when the patient is awake.

Hyperthyroidism and acidosis are associated with breathlessness. Hyperventilation states are associated with respiratory alkalosis. Hypothyroidism aggravates obstructive sleep apnoea. Harrison et al 2014 performed a multicentre prospective study of exacerbations of COPD requiring hospital admission in 1343 patients with spirometry confirmed COPD. The authors reported the novel finding of an association between thrombocytosis (>400/mm3 on admission) and mortality. Thrombocytosis (after controlling for confounders) was associated with an increased 1-year all-cause mortality and an increased in hospital mortality (OR 1.53 (95% CI 1.03 to 2.29, p=0.030) and OR 2.37 (95% CI 1.29 to 4.34, p=0.005)) respectively (Harrison 2014) [evidence level III-2].

The Thoracic Society of Australia and New Zealand Alpha1 Antitrypsin Deficiency Position Statement indicates that testing for alpha1 antitrypsin deficiency (AATD) should be considered in all patients with chronic airflow obstruction (Dummer 2020). The prevalence of severe homozygous AATD has been estimated at approximately 1 in 4,500 in European populations (Blanco 2006). Available data from 15 cohorts in Australia and New Zealand suggest that the prevalence of affected individuals is around 1 in 4,000 (de Serres 2002). Tobacco smoking is still the most important risk factor for COPD even in this group.

C5.11 Electrocardiography and echocardiography

Cardiovascular disease is common in patients with chronic obstructive pulmonary disease but is often under-recognised. Electrocardiography (ECG) may be useful to alert the clinician to its presence. In a retrospective Dutch study of patients entering pulmonary rehabilitation, ischaemic changes were present on ECG in 21% of all patients and in 14% of those without reported cardiovascular co-morbidity (Vanfleteren 2011). Electrocardiography is also indicated to confirm arrhythmias suspected on clinical grounds. Multifocal atrial tachycardia is a rare arrhythmia (prevalence < 0.32% of hospitalised patients) but over half the cases reported in the literature had underlying COPD (McCord 1998). Atrial fibrillation commonly develops when pulmonary artery pressure rises, leading to increased right atrial pressure.

Echocardiography is useful if cor pulmonale is suspected, when breathlessness is out of proportion to the degree of respiratory impairment or when ischaemic heart disease, pulmonary embolus or left heart failure are suspected. Patients with COPD may have poor quality images on transthoracic examination and transoesophageal echocardiography may be frequently needed.

Patients with COPD are prone to other conditions associated with cigarette smoking, including accelerated cardiovascular, cerebrovascular and peripheral vascular disease, and oropharyngeal, laryngeal and lung carcinoma. Conversely, there is a high prevalence of COPD among patients with ischaemic heart disease, peripheral vascular disease and cerebrovascular disease and smoking-related carcinomas (National Heart Lung and Blood Institute 1998). These patients should be screened for symptoms of COPD, and spirometry should be performed.

C5.12 Trials of Therapy

The evidence supporting the utility of specific diagnostic tests in COPD is typically not of the same strength as that for specific therapies reviewed in subsequent sections. The evidence base for tests used in the diagnosis and monitoring of several respiratory diseases at one specialist referral clinic was reviewed by Borrill et al (Borrill 2003). They were unable to identify any evidence to support the use of peak flow charts to assess treatment with inhaled steroids in patients with pre-diagnosed COPD. Studies were found that did not support the diagnostic use of trials of therapy with inhaled or oral steroids in COPD. There was no evidence to support the diagnostic use of trials of therapy with short or long-acting bronchodilators or oral theophyllines in COPD. However, it should be remembered that absence of evidence is not the same as evidence of absence of utility.

O: Optimise function

Assessment is the first step to optimising function [evidence level III-2, strong recommendation]

Optimise pharmacotherapy using a stepwise approach [evidence level I, strong recommendation]

THE PRINCIPAL GOALS OF THERAPY are to stop smoking, to optimise function through symptom relief with medications and pulmonary rehabilitation, and to prevent or treat aggravating factors and complications. Adherence to inhaled medications regimes is associated with reduced risk of death and admissions to hospital due to exacerbations in COPD (Vestbo 2009) [evidence level II].

Confirm goals of care

Addressing the goals of care is one of the most complex clinical issues in the management of COPD.

- **Active therapy:** In the early stages of the disease the goals of care must be to delay the progress of the disease by aggressive treatment of exacerbations in order that patient function is optimised, and their health is maintained. In this setting management of disease may provide the best symptom control. Should the goal of health maintenance not result in adequate symptom control then a palliative approach may also be required to augment active therapy. During this period of the patient's disease trajectory any change in therapy should be seen as an opportunity to review the goals of care in general terms with the patient. Optimal management of any individual patient with COPD must include careful management of comorbidities and anticipation of increased risks associated with those comorbidities in the presence of COPD.

- **Active therapy with treatment limitations:** The transition phase of health maintenance to functional deterioration despite maximal therapy is difficult to define. The burden of disease and care fluctuates, and it may be appropriate to encourage discussion about long term goals prognosis and attitudes to future treatment and care plans can be encouraged. The initiation of long-term oxygen therapy and functional deterioration have been found to be an important point at which patient's may be receptive to reviewing the goals of care, end of life care and treatment limitations.

- **Palliative and supportive care:** Functional deterioration in the presence of optimum treatment requires a reappraisal of the goals of care. Each exacerbation may be reversible until there is a suboptimal or no response to treatment. At this point the patient may enter their terminal phase and the goals of care may change rapidly to palliation with treatment limitations or palliation alone with withdrawal of active therapy. In this setting (unstable, deterioration or terminal care) the goals of care need to shift from active therapy to one of palliation. Should the patient recover despite a palliative approach then the goals of care may continue to be active management in preparation for the next crisis. A review of symptom management, end of life care issues, and advanced directives should take place to prepare for the next crisis.

- **Terminal care:** Terminal care plans may be appropriate for patients who elect to avoid active management. These plans need to be communicated to all services involved in the care of the patient so that there is a continuity of care. In this situation the goals of care should be clearly communicated and the advanced directive, terminal care plan and the location of care documented. Patients may elect to be treated palliatively in their terminal phase[2] by their respiratory physician owing to their long-standing relationship with the clinician. Terminal care does not always require specialist palliative care unless there are problems with symptom control or other complex needs. Hospice or specialist consultations should be available to patients should they be required.

O1. Inhaled bronchodilators

See **Appendix 1.** Use and doses of long-term inhaled bronchodilator and corticosteroids determined in response trials

O1.1 Short-acting bronchodilators

O1.1.1 Short-acting beta$_2$-agonists (SABA)

Regular short-acting beta$_2$-agonists improve lung function and daily breathlessness scores. A systematic review of randomised controlled trials (Ram 2003) found a significant increase in post-bronchodilator spirometry when compared to placebo; weighted mean difference = 140 ml (95% CI 40 to 250) for FEV$_1$ and 300 ml (95% CI 20 to 580) for forced vital capacity (FVC). There were also improvements in post-bronchodilator morning and evening PEF: weighted mean difference = 29.17 l/min (95% CI 0.25 to 58.09) for morning and 36.75 l/min (95% CI 2.57 to 70.94) for evening measurements. The relative risk of dropping out of the study was 0.49 (95% CI 0.33 to 0.73), giving a number needed to treat of 5 (95% CI 4 to 10) to prevent one treatment failure. There was no significant benefit on functional capacity, measured by walking tests, or symptoms other than breathlessness, although one randomised controlled trial has found a significant improvement in 6-minute walking distance and quality of life (Guyatt 1987). Short-acting beta$_2$-agonists are now usually prescribed for use as "rescue" medication, i.e. for relief of breathlessness, rather than for regular use.

O1.1.2 Short-acting muscarinic antagonists (SAMA)

Bronchodilators such as ipratropium, tiotropium, glycopyrronium, aclidinium and umeclidinium are not 'anticholinergics' since they are unable to antagonize the effects of acetylcholine on nicotinic receptors. They only block the muscarinic effects of acetylcholine. The word 'anticholinergic' suffers from pharmacodynamic approximation and should be replaced by 'antimuscarinic' (if we consider the involved receptor) or 'atropinic' (in relation to the pharmacodynamics effects of this drug class) (Montastruc 2010).

The duration of action of short-acting muscarinic antagonists (formerly known as anticholinergics) is greater than short-acting beta$_2$-agonists. A systematic review of randomised controlled trials comparing ipratropium bromide alone, or in combination with short-acting beta$_2$-agonists, against short-acting beta$_2$-agonists alone found significant benefits for regimens containing ipratropium bromide (Appleton 2006). Ipratropium bromide improved spirometry over short-acting beta$_2$-agonists alone, weighted mean difference = 30 ml (95% CI 0 to 60) for FEV$_1$ and 70 ml (95% CI 10 to 140) for forced vital capacity (FVC). Ipratropium bromide improved quality of life, with a statistically

[2] Terminal Phase is characterised by the following criteria:
1. Profound weakness
2. Essentially bedbound (ECOG 4)
3. Drowsy for extended periods
4. Disorientated to time with poor attention span
5. Disinterested in food or fluids
6. Difficulty swallowing medications

significant improvement in all domains of the Chronic Respiratory Disease Questionnaire (CRQ). These benefits occurred with fewer minor adverse drug effects, Number Needed to Harm (NNH) = 32 (95% CI 20 to 316). There was a lesser need to add or increase the dose of oral corticosteroids for participants receiving ipratropium bromide, with 15 (95% CI 12 to 28) people requiring treatment with ipratropium bromide to prevent one receiving additional oral corticosteroids.

However, some studies have found that ipratropium bromide is associated with an increased risk of adverse cardiovascular effects (Lee 2008, Singh 2008, Ogale 2010). A nested case-control study (Lee 2008) [evidence level III-2] found an increased risk of cardiovascular death associated with the prescription of ipratropium, OR 1.34 (95% CI 1.22 to 1.47). A meta-analysis of randomised controlled trials (Singh 2008) found an increased risk for a combined cardiovascular endpoint of cardiovascular death, myocardial infarction and stroke, estimated NNH for cardiovascular death 40 (95% CI 18 to 185) per year. The consistent finding across these studies suggests the cardiovascular adverse effects are likely to be real [evidence level I].

A Cochrane meta-analysis comparing treatment with tiotropium [HandiHaler or Respimat] with ipratropium bromide (via MDI) for patients with stable COPD found that tiotropium treatment, was associated with improved lung function, fewer hospital admissions (including those for exacerbations of COPD), fewer exacerbations of COPD and improved quality of life. There were both fewer serious adverse events and disease specific events in the tiotropium group, but no significant difference in deaths with ipratropium bromide when compared to tiotropium. Thus, tiotropium appears to be a reasonable choice (instead of ipratropium bromide) for patients with stable COPD (Cheyne 2015).

O1.1.3 Short-acting bronchodilator combinations

For combination therapy with ipratropium bromide and short-acting beta$_2$-agonists, there was no significant difference in pre-drug spirometry compared to ipratropium bromide alone (Appleton 2006). There was a significant benefit for the combination in post-drug spirometry measurements; weighted mean difference = 70 ml (95% CI 50 to 90) for FEV_1 and 120 ml (95% CI 80 to 160) for forced vital capacity (FVC). There was no significant difference between interventions for quality of life or adverse drug effects, but combination treatment decreased the need to add or increase oral corticosteroids compared to ipratropium bromide alone, Number Needed to Treat = 20 (95% CI 12 to 108).

In summary, short-acting bronchodilators, either beta$_2$-agonists or ipratropium bromide, significantly increase lung function measurements in COPD. Ipratropium bromide has a significantly greater effect on lung function compared to beta$_2$-agonists alone; in addition to improving quality of life and decreasing need for oral corticosteroid treatment. These benefits occurred with a decreased risk of adverse drug effects. Combining two classes of bronchodilator may provide added benefits without compounding adverse effects.

O1.2 Long-acting bronchodilators

Long-acting bronchodilators produce significant improvements in lung function, symptoms and quality of life (Braido 2013), as well as decreasing exacerbations. These benefits come at a cost of increased adverse effects, which are generally of mild to moderate severity.

O1.2.1 Long-acting muscarinic antagonists (LAMA)

Long-acting muscarinic antagonists (LAMAs) result in bronchodilation with a duration of action of 12 to 24 hours, depending on the agent. A number of LAMAs are available in Australia, which are delivered via a range of devices:

- aclidinium (Genuair)
- glycopyrronium (Breezhaler)
- tiotropium (HandiHaler, Respimat)
- umeclidinium (Ellipta)

Aclidinium: Aclidinium is a twice daily LAMA. A Cochrane systematic review of 12 RCTs (9,547 participants) showed that, compared to placebo, aclidinium resulted in marginal improvements in quality of life and FEV_1, and reduced the number of patients with exacerbations requiring hospitalisation (NNT 77, 95% CI 51 to 233) (Ni 2014) [evidence level I]. Aclidinium has also been shown to reduce the rate of moderate to severe exacerbations (OR 0.80) (Wedzicha 2016a) [evidence level I] without increasing major adverse cardiovascular events (Wise 2019) [evidence level II].

Glycopyrronium: Once daily glycopyrronium demonstrated significant improvement in spirometry and a reduction in the rate of moderate to severe exacerbations, but no difference in quality of life, compared with placebo (D'Urzo 2011, Kerwin 2012) [evidence level II]. In an RCT comparing glycopyrronium to tiotropium, there was no difference in FEV_1, dyspnoea, quality of life, exacerbation rate or adverse effects (Chapman 2014) [evidence level II].

Tiotropium: Once daily tiotropium resulted in improved quality of life, and reduced exacerbation rates (OR 0.78, 95% CI 0.70 to 0.87; NNT 16, 95% CI 10 to 36) compared to placebo, in a Cochrane systematic review of 22 studies (23,309 participants) (Karner 2014) [evidence level I]. Tiotropium improved FEV_1 (mean difference 119 mL, 95% CI 113 to 125), and there was no overall difference in mortality. In a 2-year RCT of 841 COPD patients with post-bronchodilator FEV_1 $\geq$50% predicted, tiotropium resulted in a significantly higher FEV_1 (mean difference of 157 ml, 95% CI 123 to 192) and reduced annual decline in post-bronchodilator FEV_1 (mean difference 22 ml per year, 95% CI 6 to 37), compared to placebo (Zhou 2017) [evidence level II]. However, there was a high withdrawal rate and 40% were current smokers.

Compared to ipratropium, tiotropium had beneficial effects for quality of life, dyspnoea and exacerbation rates (Yohannes 2011b) [evidence level I]. Compared to LABAs, tiotropium reduced exacerbation rates (Vogelmeier 2011, Decramer 2013) [evidence level II], whereas effects were heterogeneous for quality of life, compared to various LABAs (Chong 2012, Decramer 2013) [evidence level II].

Umeclidinium: Once-daily umeclidinium significantly improved lung function, dyspnoea and quality of life, compared with placebo (Trivedi 2014) [evidence level II]. Umeclidinium resulted in a greater improvement in FEV_1 than tiotropium, but there were no significant differences between umeclidinium and tiotropium for dyspnoea, St George's Respiratory Questionnaire (SGRQ) or COPD Assessment Test (CAT) scores (Feldman 2016) [evidence level II].

Adverse effects of LAMAs include dry mouth, constipation and urinary retention (Halpin 2015). A safety study showed similar rates of death and exacerbations with tiotropium HandiHaler and tiotropium Respimat (Wise 2013) [evidence level II].

Network meta-analyses of LAMAs: A network meta-analysis of LAMAs versus placebo showed that there were no statistically significant differences among LAMAs in preventing moderate-to-severe COPD exacerbations (Oba 2015) [evidence level I]. Tiotropium HandiHaler was the only LAMA formulation which reduced severe exacerbations (HR 0.73; 95% CrI 0.60– 0.86). Another network meta-analysis showed that current LAMAs have similar efficacy for change in FEV_1, SGRQ, dyspnoea and rescue medication use (Ismaila 2015) [evidence level I]. However, with few head-to-head

comparisons of LAMAs available, the choice of LAMA and inhaler device depends on patient and clinician preferences.

A meta-analysis of 9 studies of LAMA versus LABA inhalers (17,120 COPD patients, with tiotropium as the most common LAMA) showed that LAMAs had reduced exacerbation rates (RR 0.88, 95% CI 0.84 to 0.93) and exacerbation-related hospitalisations (RR 0.78, 95% CI 0.69 to 0.87), compared to LABAs (Maia 2017) [evidence level I].

O1.2.2 Long-acting beta$_2$-agonists (LABA)

Long-acting beta$_2$-agonists cause prolonged bronchodilatation with a duration of action of 12 to 24 hours. Indacaterol is available in Australia on PBS as a monocomponent LABA inhaler for the management of COPD. This and other LABAs (salmeterol, formoterol, vilanterol, olodaterol) are also available as combination LAMA/LABA, ICS/LABA or ICS/LABA/LAMA inhalers.

Indacaterol is an inhaled LABA that is given as a once daily maintenance therapy for COPD. Compared to placebo, indacaterol improves dyspnoea, FEV$_1$ and health-related quality (HRQoL) of life, and reduces exacerbations (Geake 2015) [evidence level I]. Compared with twice daily beta$_2$-agonists (salmeterol and formoterol) indacaterol did not lead to a clinically significant difference in FEV$_1$, dyspnoea or quality of life (Geake 2015).

The bronchodilator effects of indacaterol are at least as good as tiotropium (Donohue 2010). Once-daily treatment with indacaterol via Breezhaler (150 µg) or tiotropium bromide via HandiHaler (18 µg) in patients with severe COPD and a history of exacerbations gave equally effective and clinically relevant improvements in lung function, health status, and breathlessness. Patients receiving indacaterol had a 29% higher annual rate of exacerbations versus patients receiving tiotropium (Decramer 2013).

Comparison with LAMAs: A meta-analysis of 16 randomised, double-blinded controlled trials which included 22,872 patients with moderate to severe or very severe COPD with a treatment period ranging from 12 to 52 weeks found that LAMAs were associated with a lower risk of acute exacerbations (OR 0.84, 95% CI 0.74–0.90; P = 0.004) and lower incidence of adverse events (OR 0.92, 95% CI 0.86–0.98; P = 0.007) compared with LABAs (Chen 2017). There were no significant differences between LAMAs and LABAs in terms of changes in lung function, symptom score, health status and serious adverse events. LAMA may be preferable to LABA in patients with stable COPD, especially in those at risk of frequent exacerbations.

Adverse effects: A meta-analysis of 24 clinical trials (Xia 2015) of inhaled LABAs (salmeterol, formoterol, indacaterol, vilanterol, olodaterol, aformoterol) for COPD of any severity with at least 3 months follow-up (12,291 received a LABA and 7,784 received placebo) found that LABAs were associated with a lower rate of fatal cardiovascular events compared with placebo (RR 0.65, 95% CI 0.50 to 0.86, P = 0.002). This is contradictory to the findings of a meta-analysis of 33 trials lasting from 3 days to 1 year, in which beta$_2$-agonist treatment significantly increased the risk for a cardiovascular event (relative risk [RR], 2.54; 95% CI 1.59 to 4.05) compared to placebo (Salpeter 2004). The RR for sinus tachycardia alone was 3.06 (95% CI 1.70 to 5.50), and for all other events it was 1.66 (95% CI 0.76 to 3.6). Post hoc analysis of the 3-year TORCH dataset found that the probabilities of having a cardiovascular adverse event by 3 years were similar for placebo (24.2%), salmeterol (22.7%), fluticasone propionate (24.3%) and salmeterol-fluticasone propionate combination (20.8%) (Calverley 2010). Cardiac safety of LABAs is less clear when used inappropriately (e.g. overdosing) or in patients with COPD and substantial cardiovascular disease, prolonged QTc interval, or polypharmacy (Lahousse 2016a).

O1.2.3 Long-acting bronchodilator combinations (LAMA/LABA)

A number of LAMA/LABA fixed dose combinations in a single inhaler are available in Australia, which are delivered via a range of devices:

- aclidinium/formoterol (Genuair)
- glycopyrronium/indacaterol (Breezhaler)
- tiotropium/olodaterol (Respimat)
- umeclidinium/vilanterol (Ellipta)

***Aclidinium/formoterol**:* Twice daily aclidinium/formoterol had greater bronchodilation over placebo (mean FEV_1 up to 143 ml greater), and to a lesser extent, versus. formoterol (mean FEV_1 53 ml greater) or aclidinium (small differences at various timepoints) (Bateman 2015, D'Urzo 2014, Singh 2014b) [evidence level II]. There were some improvements in dyspnoea and health-related quality of life (HRQoL), measured by St George's Respiratory Questionnaire (SGRQ). Aclidinium/formoterol reduced the rate of moderate to severe exacerbations by 29%, when compared to placebo, but not when compared to aclidinium or formoterol alone (Bateman 2015). In a systematic review of seven trials (Ni 2018), the aclidinium/formoterol fixed dose combination (FDC) was found to improve dyspnoea and lung function compared to the monocomponents or placebo. Quality of life (SGRQ) was better with the combination compared to formoterol or placebo. There was no difference between the FDC and monotherapy or placebo for hospital admissions, mortality, and non-fatal adverse events. A lower risk of moderate exacerbations was observed with the FDC compared to formoterol but not with the FDC compared with aclidinium [evidence level I].

***Glycopyrronium/indacaterol**:* Once daily indacaterol/glycopyrronium had greater bronchodilation compared with glycopyrronium, indacaterol, tiotropium (Bateman 2013) or placebo (Bateman 2013, Dahl 2013, Wedzicha 2013) [evidence level II]. Moderate to severe exacerbations were reduced by 12% with indacaterol/glycopyrronium, compared to glycopyrronium (Wedzicha 2013). These benefits were supported by systematic reviews (Ulrik 2014, Rodrigo 2014) [evidence level I].

***Tiotropium/olodaterol**:* Once daily tiotropium/olodaterol significantly improved lung function, quality of life (SGRQ total score) and breathlessness (transition dyspnoea index), compared to tiotropium or olodaterol (Miravitlles 2017) [evidence level I]. However, patients taking tiotropium/olodaterol 5 µg/5 µg and tiotropium 5 µg (two puffs once daily via the Respimat device) had no significant differences in moderate and severe exacerbation rate (rate ratio [RR] 0·93, 99% CI 0·85–1·02;p=0·0498) and time to first moderate or severe event ([HR] 0·95, 99% CI 0·87–1·03; p=0·12) over a 52-week treatment period compared to tiotropium alone (Calverley 2018b) [evidence level II].

***Umeclidinium/vilanterol**:* Once-daily umeclidinium/vilanterol improved lung function and symptoms, when compared with placebo (Donohue 2013, Donohue 2014) [evidence level II]. Systematic reviews of umeclidinium/vilanterol have shown improved FEV_1, reduced dyspnoea and reduced rate of exacerbations, when compared with umeclidinium or vilanterol (Rodrigo 2015, Guo 2016a) [evidence level I].

Systematic reviews of LAMA/LABA combinations: A meta-analysis and systematic review of results of 8,641 participants in 22 double blinded RCTs comparing a once-daily LAMA/LABA combination with placebo demonstrated similar clinically and statistically significant differences with each of the inhalers with respect to St George's Respiratory Questionnaire (SGRQ) quality of life (4.1 units), and improvement in FEV_1 (200mls). Of the four once-daily LAMA/LABA combinations studied, only the combination of umeclidinium/vilanterol (using the Ellipta inhaler device) was evaluated with respect to the outcome of exacerbation rate, with an overall pooled rate reduction of 47% in three studies (Maqsood 2019) [evidence level I].

A systematic review of 24 studies (n=45,441 participants) found statistically significant reductions in hospital admissions (risk ratio 0.89, 95% CI 0.82 to 0.97) and exacerbations (risk ratio 0.80, 95% CI

0.69 to 0.92) with LAMA/LABA combination therapy, compared with LAMA or LABA monotherapy (Mammen 2020b) [evidence level I]. Reductions in dyspnoea and health-related quality of life did not reach MCID.

***Network meta-analyses of LAMA/LABA**:* Because head-to-head studies of all relevant treatment options may not be available, indirect comparisons of treatments using a technique comparing relative effects against a common comparator (network meta-analysis) offers a way of comparing the relative effects of treatment. A network meta-analysis was undertaken for dual combination inhalers compared with single-agent long-acting bronchodilators (Oba 2018) [evidence level I]. In the network meta-analysis, LAMA/LABA inhalers decreased the rate of moderate to severe exacerbations compared to ICS/LABA (HR 0.86, 95% credible interval (CrI) 0.76 to 0.99), LAMA (HR 0.87, 95% CrI 0.78 to 0.99), and LABA (HR 0.70, 95% CrI 0.61 to 0.80) in frequent exacerbators (moderate certainty of evidence), with LABA being the least beneficial. However, the evidence was not statistically significant in some of the pairwise meta-analyses between treatments.

***Comparisons of LAMA/LABA versus ICS/LABA**:* In the FLAME study, indacaterol /glycopyrronium once daily was compared to fluticasone/salmeterol twice daily in an RCT of 3,362 patients with moderate to severe COPD, who had a history of at least one exacerbation in the previous year (Wedzicha 2016b). Patients receiving indacaterol/glycopyrronium had a lower annual rate of exacerbations (rate ratio 0.89; 95% CI 0.83 to 0.96). Trough FEV_1 was 62 ml higher at 52 weeks and SGRQ was 1.8 points lower with indacaterol/glycopyrronium although these changes were of unclear clinical significance. The reduction of exacerbations was independent of baseline eosinophil count and use of inhaled corticosteroids at time of recruitment (Roche 2017).

A Cochrane systematic review of 19 studies (22,354 participants) found that LAMA/LABA and LABA/ICS had similar odds of having an exacerbation (OR 0.91, 95% CI 0.78 to 1.06; I^2 = 61%; 13 studies, 20,960 participants; moderate-certainty evidence) or a serious adverse event (OR 1.02, 95% CI 0.91 to 1.15; I^2 = 20%; 18 studies, 23,183 participants; high-certainty evidence) (Fukada 2023) [evidence level I]. Improvements in SGRQ and the odds of achieving a minimal clinically important difference of four or more points on the SGRQ were similar between groups (MD -0.57, 95% CI -1.36 to 0.21; I^2 = 78%; 9 studies, 14,437 participants; moderate-certainty evidence) and (OR 1.06, 95% CI 0.90 to 1.25; I^2 = 77%; 4 studies, 13,614 participants). However, participants receiving LAMA/LABA showed a greater improvement in trough FEV_1 (MD 0.07, 95% CI 0.05 to 0.08; I^2 = 73%; 12 studies, 14,681 participants; moderate-certainty evidence). LAMA/LABA decreased the odds of pneumonia compared with LABA+ICS from 5% to 3% (OR 0.61, 95% CI 0.52 to 0.72; I^2 = 0%; 14 studies, 21,829 participants; high-certainty evidence) but increased the odds of all-cause death from 1% to 1.4% (OR 1.35, 95% CI 1.05 to 1.75; I^2 = 0%; 15 studies, 21,510 participants) [evidence level I]. Combined LAMA/LABA inhalers hold similar benefits to LABA/ICS inhalers for exacerbations and quality of life for people with moderate to severe COPD but offer a larger improvement in FEV_1 and a lower risk of pneumonia. LAMA/LABA demonstrated statistically significant advantage over LABA/ICS for avoiding pneumonia and improving FEV_1 (though the clinical significance on FEV_1 remains uncertain). Other outcomes were similar. The choice between LAMA/LABA and LABA/ICS should be based on the individual's condition, including blood eosinophil count, history of pneumonia, and recent exacerbations. See **Appendix 5.** Table of Minimum Clinically Important Differences.

O1.3 Assessment of response and continuation of bronchodilator therapy

In some patients a response to bronchodilator therapy may require treatment for up to two months. Symptomatic and functional benefits can often be demonstrated in the absence of an increase in FEV_1. Other objective measurements, such as an increase in exercise capacity (e.g., as measured using a walking test such as the 6-minute walk test or the incremental or endurance shuttle walking test (Pepin 2007, Pepin 2005) or an increased inspiratory reserve capacity, may be useful indicators of physiological improvement.

Subjective measurements, such as quality of life, breathlessness and functional limitation (e.g. MRC Dyspnoea Scale), can determine the patient's perception of benefit. If there is no improvement:

- check inhaler technique;
- consider psychosocial issues and deconditioning; and
- exclude other causes of exercise impairment (consider specialist referral or a cardiopulmonary exercise test).

O2. Oral bronchodilators

O2.1 Methylxanthines

Theophylline is rarely used for COPD in Australia. A small, randomised placebo-controlled trial in China demonstrated that doses of 100mg twice daily reduced exacerbations compared with placebo (Zhou 2006). In this study, patients were not on inhaled corticosteroids or long-acting bronchodilators which limits the generalisability of the study findings. Devereux et al randomised 1,567 UK-based COPD patients with a history of exacerbations to theophylline or placebo. All patients were receiving inhaled corticosteroids and 80% of patients were on 'triple-therapy' (Devereux 2018). An RCT of low dose theophylline plus low dose oral prednisone, theophylline or placebo in 1,670 patients with COPD in China found no statistically significant differences in exacerbation rates, hospitalisations, FEV_1, SGRQ and CAT scores at 48 weeks (Jenkins 2020) [evidence level II].

A meta-analysis of 4 RCTs and 3 cohort studies (n=47,556) examined the addition of theophylline to inhaled corticosteroids. Of the 7 studies reviewed, 4 used an ICS/LABA combination, 2 used ICS alone and 1 trial did not specify. Theophylline was associated with a higher hospitalization rate (HR 1.12, 95% CI 1.10-1.15), and mortality (HR 1.19, 95% CI 1.14-1.25) (Shuai 2021) [evidence level I].

Based on the available evidence, theophylline cannot be recommended for patients with COPD.

O2.2 Phosphodiesterase type-4 inhibitors

Phosphodiesterase type-4 (PDE-4) inhibitors act by increasing intracellular concentrations of cyclic adenosine monophosphate (cAMP) to suppress inflammation and bronchoconstriction. A Cochrane Review analysed results from RCTs of roflumilast (20 trials, 17,627 patients) and cilomilast (14 trials, 6,457 patients) (Chong 2017) [evidence level I]. Compared to placebo, PDE-4 inhibitors improved FEV_1 (mean difference 51 ml, 95% CI 43 to 60, moderate quality evidence) and reduced exacerbation rates (OR 0.78, 95% CI 0.73 to 0.83, high quality evidence; NNTB 20, 95% CI 16 to 26), but had relatively small effects on quality of life and symptoms. Gastrointestinal adverse effects were more frequent with the PDE-4 inhibitors, and psychiatric adverse events such as insomnia and depressive mood symptoms were more frequent with roflumilast (OR 2.13, 95% CI 1.79 to 2.54). These oral agents are not currently available in Australia.

O3. Corticosteroids

O3.1 Oral corticosteroids

Long term use of systemic corticosteroids is not recommended (Postma 1988, Postma 1985, Decramer 1996, Decramer 1994, Decramer 1992) [evidence level I]. Indeed, caution in the long-term use of systemic corticosteroids is necessary because of limited efficacy and potential toxicity in elderly patients. Some patients with stable COPD show a significant response to oral corticosteroids (on spirometry or functional assessment). Therefore, a short course (two weeks) of prednisolone (20–50mg daily) may be tried with appropriate monitoring. Short courses of oral corticosteroids (<14 days) do not require tapering. A negative bronchodilator response does not predict a negative steroid response (Senderovitz 1999). If there is a response to oral steroids, continued treatment with inhaled corticosteroids is indicated, but these may fail to maintain the response (Senderovitz 1999, Vestbo 1999).

O3.2 Inhaled corticosteroids (ICS)

Exacerbations have a detrimental effect on quality of life, and patients with severe disease and frequent exacerbations have an accelerated decline in their quality of life (Miravitlles 2004).

A Cochrane systematic review (Yang 2023a) of studies of long-term (more than 6 months) ICS monotherapy compared to placebo, in people with stable COPD has found that ICS monotherapy likely reduces the rate of clinically relevant COPD exacerbations (0.05 exacerbations per participant per year, 95% CI −0.07 to −0.02; vs 0.88 exacerbations per participant per year, 95% CI 0.82 to 0.94), and probably slows the rate of decline of lung function (FEV_1) (MD 6.31 mL/year benefit, 95% CI 1.76 to 10.85), although the magnitude of this change is of unclear clinical relevance. ICS as monotherapy likely results in a small improvement in health-related quality of life measures without meeting the threshold for a clinically important difference (MD −1.22 units/year, 95% CI −1.8 3 to −0.60) but there is probably no reduction in all-cause mortality (OR) 0.94, 95% CI 0.84 to 1.07). The potential benefits of ICS as monotherapy must be weighed against the potential adverse events such as a likely increase in the risk of pneumonia (OR 1.38, 95% CI 1.02 to 1.88), increased risk of oropharyngeal candidiasis (OR 2.66, 95% CI 1.91 to 3.68) and hoarseness (OR 1.98, 95% CI 1.44 to 2.74) [evidence level I].

A nested case-control analysis of a new-user database cohort of 103,386 patients treated with inhaled corticosteroids in Quebec during 1999-2005 found that cessation of inhaled corticosteroids was associated with a 36% decrease in the rate of severe pneumonia events defined as hospitalisation or death from pneumonia during the study period (Suissa 2015). 14,020 patients had a serious pneumonia episode during 4.9 years of follow-up (incidence rate 2.8/100/year). The decreasing rate of serious pneumonia occurred rapidly, going from 20% reduction in the first month to 50% reduction by the fourth month after discontinuation. The risk reduction was more marked with cessation of fluticasone than cessation with budesonide.

Inhaled corticosteroids alone do not improve mortality, with pooled results from nine studies involving 8,390 participants showing an odds ratio of death of 0.98 (95% CI 0.83-1.16). The effect of inhaled corticosteroids on the rate of decline in lung function is inconsistent. Pooled results from studies of six months duration or longer, show either no significant difference in the rate of decline in post-bronchodilator FEV_1 (generic inverse variance analysis: weighted mean difference of 5.8 ml/year (95% CI -0.28-11.88, 2,333 participants) or a small statistically significant difference (pooled means analysis: 6.88 ml/year, 95% CI 1.80-11.96, 4823 participants, with the inclusion of the TORCH study (Calverley 2007, Yang 2023).

A comprehensive overview by Miravitlles et al (2021) of the risks associated with the use of ICS in patients with COPD found an increased risk of local disorders such as oral candidiasis and dysphonia

and infectious adverse events such as pneumonia [evidence level I]. The pooled analysis of 16 RCTs with n=33,725 participants showed that exposure to ICSs almost tripled the risk of oral candidiasis (RR 2.89, 95% CI 2.36–3.55; p<0.00001). The pooled analysis of nine RCTs with 22 841 participants showed that exposure to ICS increased the risk of dysphonia by 277% (RR 3.77, 95% CI 2.81–5.05; p<0.00001; I^2=0%). The pooled analysis of 19 RCTs with 66 485 participants showed that exposure to ICSs for ⩾1 year increased the risk of pneumonia by 41% (RR 1.41, 95% CI 1.23–1.61; p<0.00001; I^2=55%). An interaction was found between the risk of pneumonia and the type of ICS used, with the highest risk being associated with fluticasone (10 studies with 45870 participants), whereas exposure to budesonide (six studies with 13 479 participants) was not associated with an increased risk of pneumonia (Miravitlles 2021). A dose–response relationship was observed, indicating that lower doses of ICS should be used in patients with COPD whenever possible. The risks of diabetes, osteoporosis, bone fractures and eye disorders are less clear.

In people with COPD and diabetes mellitus, particular care should be taken not to exceed the recommended dose of corticosteroids as there is some evidence of a direct relationship between corticosteroid dose and glucose levels in such patients (Slatore 2009) [evidence level III-2]. In a large, real-world, retrospective, Swedish cohort study, patients with COPD (n = 9651) were more susceptible to bone fractures and osteoporosis than those of the same age and sex without COPD (Janson 2021). The treatment of COPD patients, especially with high-dose ICS (⩾640 µg/day), was associated with a higher risk of bone fractures and osteoporosis-related events (risk ratio 1.52 (95% CI 1.24–1.62). Screening of patients with COPD for osteoporosis and identifying those at high risk of fracture (those with comorbidities such as asthma, cardiovascular disease and depression), may be beneficial. In some patients, reducing the dose or discontinuation of ICS might be warranted [evidence level III-2). The treatment of people with COPD, especially with high-dose ICS (⩾640 µg/day), was associated with a higher risk of bone fractures and osteoporosis-related events (risk ratio 1.52 (95% CI 1.24–1.62). Screening of patients with COPD for osteoporosis and identifying those at high risk of fracture (those with comorbidities such as asthma, cardiovascular disease and depression), may be beneficial. In some patients, reducing the dose or discontinuation of ICS might be warranted [evidence level III-2).

Withdrawal of inhaled corticosteroids was not associated with any statistically significant increase in exacerbation rate in a systematic review of 4 RCTs in 901 patients (Nadeem 2011) (OR 1.11, 95% CI 0.84 to 1.46) [evidence level I]. The 12-month Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial, studied patients with severe COPD who were stable on triple therapy (tiotropium, fluticasone propionate and salmeterol). Staged withdrawal of fluticasone propionate over 12 weeks was compared to continuation of fluticasone propionate, plus salmeterol and tiotropium (Magnussen 2014). 2,495 COPD patients with FEV_1 <50% predicted and a history of at least one exacerbation in the last 12 months were studied. The hazard ratio for the first COPD exacerbation that was moderate or severe was 1.06 with ICS withdrawal (95% CI 0.94 to 1.19) which was below the upper limit of the non-inferiority margin for the primary outcomes of exacerbation of 1.20 [evidence level II]. The mean reduction in FEV_1 was 43 ml greater in the ICS withdrawal group at 52 weeks, which was statistically significant. At 52 weeks there was no statistically different significance in a mMRC dyspnoea score, and there was a small difference in change in SGRQ score, favouring ICS continuation. Although the authors concluded that in patients with severe COPD withdrawal of ICS in a tapered fashion was non-inferior to continuation of ICS, there were statistically significant reductions in FEV_1 and quality of life which may be clinically relevant to some patients.

In the 26 week SUNSET trial (Chapman 2018) abrupt withdrawal of ICS from long-term triple therapy (tiotropium AND fluticasone/salmeterol administered via separate inhalers) to a LABA/LAMA combination (indacaterol/glycopyrronium administered via Breezhaler) in COPD patients (mean FEV_1 57%) with no more than one moderate or severe exacerbation in the previous year led to a small but significant decrease in trough FEV_1 (26 ml; (95% CI −53 to 1 mL) with no differences in the rates of COPD exacerbations (0.52 versus 0.48, rate ratio 1.08; 95% CI 0.83 to 1.40) or the time to first moderate or severe COPD exacerbation (hazard ratio 1.11; 95% CI 0.85 to 1.46). Patients with high blood eosinophils (≥ 300 cells/µL) at baseline showed greater differences in lung function (a mean

decrease of 69 ml) and were at increased risk of exacerbations after ICS withdrawal (rate ratio 1.86; 95% CI 1.06 to 3.29). The incidence of adverse events was similar across both treatment arms.

In patients with COPD without evidence of asthma and with infrequent exacerbations, ICS withdrawal could be considered. Close follow-up is recommended following withdrawal. Post hoc analysis suggests ICS withdrawal should be approached cautiously in patients with COPD and elevated eosinophil counts.

Patients with COPD with FEV_1 50 to 80% predicted and no exacerbations in the past 12 months were able to be switched to indacaterol with no significant differences in FEV_1, dyspnoea score, SGRQ score or frequency of exacerbations over six months, providing reassurance that switching from salmeterol/fluticasone to indacaterol appeared to be safe in this group of milder COPD patients (Rossi 2014) [evidence level II].

In an RCT of 639 patients with COPD, the commencement of fluticasone propionate (250mcg bd) and salmeterol (50mcg bd) within 14 days of the index exacerbation, compared to salmeterol alone, was not associated with benefit in terms of incidence in moderate or severe exacerbations, over a 6-month follow-up, although a 100 mL FEV_1 benefit was demonstrated (Ohar 2014).

A systematic review of RCTs of ICS versus. non-ICS therapy for COPD showed an increased risk of TB associated with ICS use (Peto OR, 2.29; 95% CI 1.04-5.03), and no excess risk of influenza with ICS use (Peto OR, 1.24; 95% CI 0.94-1.63) (Dong 2014) [evidence level I]. The risk for TB was higher in endemic areas (NNH 909), compared to non-endemic areas (NNH 1,667). Limitations of the systematic review included: these outcomes were not the primary outcomes; limited number of trials reporting TB events; lack of chest x-ray at recruitment; varying definitions for TB infection; and differential withdrawal rate between ICS and non-ICS groups; and the authors recommended further investigation (Dong 2014).

A systematic review of case-control and cohort studies also found that ICS use may increase the odds of nontuberculous mycobacterial [NTM] infection in patients with chronic respiratory disease (OR = 3.93, 95% CI 2.12–7.27. High-dose ICS use (OR = 2.27, 95% CI 2.08–2.48) and fluticasone use (OR = 2.42, 95% CI 2.23–2.63) were in particular associated with increased odds of NTM infection. ICS use also increased the odds of TB infection at high-doses (OR = 1.70, 95% CI 1.56–1.86) and in COPD patients (OR = 1.45, 95% CI 1.29–1.63). When using ICS, clinicians should pay attention not only to TB infection but also to NTM infection and also the types and dose of ICS (You 2022) [evidence level III-2].

O3.3 Inhaled corticosteroids (ICS) versus long-acting beta$_2$-agonists (LABA)

A systematic review of inhaled corticosteroids versus. long-acting beta-agonists in COPD found similar benefits in exacerbation rates and mortality when comparing these treatments, but there was a higher rate of pneumonia with inhaled corticosteroids (Spencer 2011) [evidence level I]. There were small benefits in FEV_1 (for long-acting beta-agonists) and quality of life (for inhaled corticosteroids). Overall, the authors conclusions supported long-acting beta-agonists as part of frontline therapy for COPD, with regular inhaled corticosteroid therapy as an adjunct in patients experiencing frequent exacerbations (Spencer 2011).

O4. Combination therapies and biologic therapies

O4.1 Inhaled corticosteroids and long-acting beta$_2$-agonists in combination (ICS/LABA)

A systematic review of 19 randomised controlled trials involving 10,400 COPD patients of combined corticosteroids and long-acting beta$_2$-agonists in one inhaler (Nannini 2013a) [evidence level I] found that, compared with placebo, both fluticasone/salmeterol and budesonide/formoterol reduced the rate

of exacerbations (rate ratio 0.73; 95% CI 0.69 to 0.78). It was estimated that treatment with combined therapy would lead to a reduction of one exacerbation every two to four years. The three-year number needed to treat for an additional beneficial outcome (NNTB) with fluticasone/salmeterol to prevent one extra death was estimated at 42 (95% CI 24 to 775). Combined treatments improved health status to a small extent and improved lung function. Increased risk of pneumonia was observed with combined treatments compared with placebo (OR 1.62, 95% CI 1.36 to 1.94), with a three-year NNTH for one additional case of pneumonia estimated to be 17. However, exacerbations, hospitalisations or deaths did not increase. Overall, the authors concluded that there were no major differences between combined inhalers in terms of benefits, but the evidence was currently not strong enough to demonstrate that all are equivalent. Data from Kliber (Kliber 2010) [evidence level I] in 30,495 patients with COPD enrolled in trials of six months or greater duration found combination therapy, compared with placebo, was associated with a reduction in all-cause mortality, relative risk 0.80 (95% CI 0.69, 0.94).

Studies have found conflicting results when the different combination therapies were compared with the mono-components alone. A systematic review of 14 studies (Nannini 2012) (11,784 participants) found low quality evidence for reduced exacerbation rates (rate ratio 0.76; 95% CI 0.68 to 0.84) with ICS/LABA versus LABA alone [evidence level I]. There was no statistically significant difference in hospitalisations or mortality. ICS/LABA improved quality of life and FEV_1 to a small extent, compared to LABA alone. High attrition rates from the studies limited the confidence in the results, except the mortality result. Pneumonia was observed more commonly with ICS/LABA use (OR 1.55; 95% CI 1.20 to 2.01) with an annual risk of 4% on combination treatment, compared to 3% on LABA alone. A network meta-analysis of 21 clinical trials of ICS/LABA demonstrated that these combinations, except budesonide/formoterol and beclometasone/formoterol, reduced moderate-to severe exacerbations as compared with placebo and LABA; however, none of the combinations reduced severe exacerbations (Oba 2014) [evidence level I]. In 2012, Sharafkaneh et al reported that budesonide/formoterol 320/9 mg compared with formoterol alone prolonged the mean time to first exacerbation (277.9 days versus 249.8 days; p= 0.029). Higher pneumonia rates were noted with budesonide/formoterol 320/9 mg 6.4% compared with 2.7% for formoterol alone (Sharafkhaneh 2013). In a RCT of 26 weeks (Ferguson 2017) [evidence level II], twice daily budesonide/formoterol pMDI 320/9 mcg resulted in a 24% reduction in exacerbation rate (rate ratio 0.76, 95% CI 0.62 to 0.92; P = 0.006) and a 22% reduction in time to first exacerbation (hazard ratio 0.78; 95% CI 0.64 to 0.96; P = 0.0164) compared with twice daily formoterol DPI 9 mcg. The study did not show any important difference between the groups in their safety profile, including incidence of pneumonia (1% versus 0.5%).

A systematic review of 15 randomised controlled trials involving 7,814 COPD patients of combined corticosteroids and long-acting beta2-agonists in one inhaler versus inhaled steroids alone (Nannini 2013b) [evidence level I] found that, compared with inhaled steroids, exacerbation rates were significantly reduced with combination therapies (rate ratio 0.87, 95% CI 0.80 to 0.94). Mortality was lower with combination therapy (OR 0.78, 95% CI 0.64 to 0.94), mainly due to results from the TORCH study. There was a small improvement in lung function and health-related quality (HRQoL) of life. The authors concluded that combination ICS/LABA inhalers offer some clinical benefits in COPD compared with ICS alone, especially for reduction in exacerbations. The review did not support the use of ICS alone when LABAs are available.

Compared to placebo, combination therapy did not significantly increase other adverse events, but oral candidiasis was significantly more common, (NNH 16 [8-36], 1,436 participants). Combination therapy was not associated with more adverse effects compared to long-acting $beta_2$-agonists. Chen et al (Chen 2011) conducted a retrospective cohort study of Veterans Affairs (VA) patients with COPD who were admitted for pneumonia. Prior use of inhaled corticosteroids was associated with significantly reduced 30- and 90-day mortality and need for mechanical ventilation. The analysis adjusted for age, gender, race, marital status, primary care, classes of medications, smoking, comorbidities etc. However, the patients were 98% male, and the most common inhaled steroids were flunisolide and triamcinolone [evidence level III-2]. Studies by Calverley (Calverley 2007) and Kardos (Kardos 2007)

have found an increased rate of pneumonia (defined on clinical grounds) in the inhaled corticosteroid arms, and this was also found in the Rodrigo systematic review, NNH = 48 (95% CI 31, 85) (Rodrigo 2009). These results contrast with the reductions in exacerbation rates induced by these drugs. A nested case control study from Canada (Ernst 2007) [evidence level III-2] using databases linking hospitalisations and drug dispensing information also found an increased risk of pneumonia and hospitalisation from pneumonia in those prescribed and dispensed inhaled corticosteroids and that this appeared dose-related. In the two-year RCT of salmeterol/fluticasone versus. tiotropium (Wedzicha 2008), the number of *de novo* pneumonias not preceded by symptoms of exacerbations was similar between the two treatment groups (Calverley 2011). However, unresolved exacerbations preceding pneumonia were more common in the salmeterol/fluticasone-treated patients (32 exacerbations in 658 patients), compared to the tiotropium-treated group (7 exacerbations in 665 patients) [evidence level II]. Further prospective studies using objective pneumonia definitions may clarify the situation. Meantime, increased vigilance and patient education about prompt treatment of infections would seem prudent. A network meta-analysis of 71 RCTs of 73,062 patients with COPD showed that quality of life and lung function improved most with combination ICS/LABA inhalers, with LABA or LAMA inhalers next in efficacy, and ICS alone least effective (Kew 2014). Many of the patients in these studies had FEV_1 <50% predicted.

Fluticasone furoate/vilanterol is a new once daily ICS/LABA combination inhaled medicine. In short term studies of 12 weeks duration, fluticasone furoate/vilanterol had comparable lung function and quality of life effects as fluticasone propionate/salmeterol twice daily (Agusti 2014, Dransfield 2014). Longer term studies (6 months) have shown that fluticasone furoate/vilanterol improves lung function compared to fluticasone furoate alone or placebo, and was similar in effect to vilanterol (Kerwin 2013, Martinez 2013). Patients with higher blood eosinophil count gain greater benefit from treatment with fluticasone furoate to reduce exacerbation frequency than do those with a low eosinophil count. Reductions in exacerbations with fluticasone furoate and vilanterol, compared with vilanterol alone, were 24% in patients with baseline eosinophil counts of ≥ 2 to <4%, 32% for those with counts of 4 to < 6%, and 42% for those with eosinophil counts of ≥ 6%. In patients treated with vilanterol alone, exacerbation rates increased progressively with increasing eosinophil count percentage category (Pascoe 2015). However, prospective validation is required before routine clinical recommendations can be made.

In a 12-month study of patient with COPD with a history of exacerbations, fluticasone furoate/vilanterol reduced the rate of moderate to severe exacerbations by 20 to 30% compared to vilanterol alone, whereas the rate of pneumonia increased approximately 2-fold (Dransfield 2013). The study reported the event-based number needed to treat to prevent a moderate or severe exacerbation per year of 3.3 to 5.6 for the 3 doses of fluticasone furoate/vilanterol used, compared to vilanterol. In comparison, the event-based number needed to harm for pneumonia was 19 to 27 for fluticasone furoate/vilanterol, compared to vilanterol. 8 deaths from pneumonia were observed in the patients treated with fluticasone furoate/vilanterol (7 of whom were in the highest dose of 200/25 mcg), compared to no deaths from pneumonia in the vilanterol group. A higher number of fractures was observed in the fluticasone furoate/vilanterol groups. The study authors advised that clinicians should weigh up the benefit of reduced exacerbations with the risk of pneumonia when considering fluticasone furoate/vilanterol and recommended that the 100/25 mcg dose be the maximum dose used in future clinical trials.

The SUMMIT study randomised 16,590 patients with COPD with post-bronchodilator FEV_1 50 to 70% predicted, and history or increased risk of cardiovascular disease, to fluticasone furoate/vilanterol, fluticasone furoate, vilanterol or placebo (Vestbo 2016a). Median study exposure was 1.8 years in this event-driven RCT. No benefit for all-cause mortality was seen with any of the active treatments, compared to placebo [evidence level II]. Because this primary outcome was not reached, the secondary outcomes were considered to be descriptive. These included a clinically insignificant reduction (8 ml/year) in the rate of decline of FEV_1 with fluticasone furoate/vilanterol or fluticasone furoate versus. placebo (Calverley 2018a). Fluticasone furoate/vilanterol reduced the rate of

exacerbations treated with corticosteroids alone (61% reduction, 95% CI 51 to 69%) or with corticosteroids and antibiotics (45%, 95% CI 38 to 52%), but not those treated with antibiotics alone (-2%, 95% CI -15 to 9%) (Martinez 2016). Rates of pneumonia were similar between fluticasone furoate and placebo groups (Vestbo 2016a, Crim 2017).

Vestbo et al (Vestbo 2016b) performed an open label randomised trial in 75 UK general practices where 2,799 patients were randomised to a combination of fluticasone furoate 100 µg and vilanterol 25 µg or usual care. The trial design was unique in that patients in the control group were permitted to continue their current inhalers rather than all take the same treatment, the trial was performed in general practice and the majority of patients only had contact with study staff at baseline and at 12 months. The rate of moderate or severe exacerbations was 8.4% lower (95% CI 1.1 to 15.2) with fluticasone furoate–vilanterol therapy compared with usual care (P = 0.02). There was no increase in pneumonia.

Addition of fluticasone furoate to vilanterol increased the risk of pneumonia, particularly in patients with more severe airflow limitation ($FEV_1/FVC < 0.46$) and either BMI <19 (HR 7.8, 95% CI 4.7–13.0) or previous history of pneumonia (HR 4.8, 95% CI 3.0–7.7) (DiSantostefano 2014) [evidence level II]. Risk for pneumonia was significantly higher in all fluticasone furoate/vilanterol treatment groups (fluticasone furoate/vilanterol 50 mcg/25 mcg, 100 mcg/25 mcg and 200 mcg/25 mcg) compared with the vilanterol 25 mcg group when administered once daily in the morning. Factors associated with at least a twofold increase in risk of pneumonia were low BMI (<25 kg/m^2), 30% ≤ FEV_1<50% predicted, age >65 years, a prior exacerbation history, being a current smoker, and having a prior pneumonia event (Crim 2015).

O4.2 Inhaled corticosteroids and long-acting beta$_2$-agonists and long-acting antimuscarinics in combination (ICS/LABA/LAMA)

More data are becoming available on the efficacy of multiple inhaled medications to guide the best combination that will optimise patient's lung function, improve symptoms and prevent/ reduce exacerbations.

ICS/LABA plus LAMA: The GLISTEN three arm study compared the addition of glycopyrronium or tiotropium or placebo to salmeterol/fluticasone propionate. The addition of either of the LAMAs demonstrated statistically significant improvements to FEV_1 (101 ml at 12 weeks), a statistically but not clinically significant change in health status (2.15 units St George's Respiratory Questionnaire (SGRQ)) and reduced rescue medications (less than one puff per day) (Frith 2015).

A two-year double-blind, double dummy randomised controlled trial comparing tiotropium and combination therapy with fluticasone/salmeterol (500/50 µg bd) (Wedzicha 2008) found no difference in exacerbation rates between the groups (the primary aim of the study), but the combination therapy group achieved a small, statistically significant benefit in quality of life as well as the unexpected benefit of fewer deaths [evidence level II].

A Cochrane systematic review (Rojas-Reyes 2016) that compared tiotropium plus LABA/ICS combination therapy versus tiotropium found no significant difference in risk of hospital admission with the use of tiotropium + LABA/ICS (two studies; 961 participants; OR 0.84, 95% CI 0.53 to 1.33; I^2 = 0%); the quality of evidence for this outcome is low because of the risk of bias in included studies and imprecision of the estimates of effect [evidence level I].

Health-related quality of life (HRQoL) measured by SGRQ showed a statistically significant but not clinically significant improvement in total scores with the use of tiotropium plus LABA/ICS compared with tiotropium alone (mean difference (MD) -3.46, 95% CI -5.05 to -1.87; four studies; 1,446 participants). Statistically significant changes in FEV_1 with the use of tiotropium plus LABA/ICS compared with tiotropium plus placebo were observed (four studies; 1,678 participants; MD 0.06,

95% CI 0.04 to 0.08); however, the difference in treatment effect on FEV_1 was 60 mL and did not reach the MCID. Compared with the use of tiotropium alone, tiotropium plus LABA/ICS-based therapy does not seem to increase adverse effects. Evidence is insufficient to support the benefit of "triple" therapy for mortality or exacerbations (low-quality evidence). Not all people included in these studies had COPD that was severe enough to be recommended "triple" therapy according to current guidelines [evidence level I].

ICS/LABA/LAMA – single inhaler triple therapy

Beclometasone/formoterol/glycopyrronium: The TRINITY study evaluated the use of extra-fine beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide BDP/FF/GB (fixed triple) (n=1078) compared to tiotropium, with a free combination of BDP/FF in one inhaler (n=538) and tiotropium (n=1075) in a second inhaler as a control (Vestbo 2017). The rates of moderate to severe COPD exacerbations were 0·46 (0·41–0·51) per patient per year for fixed triple, 0·57 (0·52–0·63) for tiotropium, and 0·45 (0·39–0·52) for open triple. Extra-fine particle fixed triple was superior to tiotropium, with an adjusted rate ratio (RR) of 0·80 (95% CI 0·69–0·92; p=0·0025). The time to first severe exacerbation was prolonged with fixed triple compared with tiotropium (HR 0·70 [95% CI 0·52–0·95]; p=0·0208), and was similar for fixed triple and open triple (1·05 [0·70–1·56]; p=0·82). The adjusted mean changes from baseline in pre-dose FEV_1 at week 52 were 0·082 L (95% CI 0·065 to 0·100) for fixed triple, 0·021 L (0·003 to 0·039) for tiotropium and 0·085 L (0·061 to 0·110) for open triple. The incidence of adverse events (55 to 58%), including serious adverse events (13 to 15%) and pneumonia (1 to 2%) were similar across the three groups.

In the TRILOGY study, escalation to ICS/LABA/LAMA in a single inhaler, in patients already taking ICS/LABA, was tested in a 52-week RCT of 1,368 COPD patients who had FEV_1 <50% predicted, one or more exacerbations in the last 12 months, and significant dyspnoea and impact of COPD (Singh 2016a) [evidence level II]. Compared to ICS/LABA (beclometasone/formoterol), ICS/LABA/LAMA in a single MDI (beclometasone 100µg/formoterol 6 µg/glycopyrronium 12.5 µg, two inhalations twice daily) improved pre-dose FEV_1 by 0.081 L (95% CI 0.052-0.109) at week 26, with no difference in dyspnoea score. At week 52, beclometasone/formoterol/glycopyrronium was associated with a reduced rate of moderate-severe exacerbations (rate ratio 0.77, 95% CI 0.65-0.92) and increased proportion of patients having a beneficial improvement in SGRQ (rate ratio 1.33, 95% CI 1.06-1.66). In patients with severe COPD and frequent exacerbations, ICS/LABA/LAMA in a single inhaler may be more beneficial than ICS/LABA.

In the TRIBUTE study of COPD patients with severe airflow obstruction and frequent exacerbations, ICS/LABA/LAMA in a single MDI (beclometasone/formoterol/glycopyrronium, twice daily) was associated with reduced exacerbations over 52 weeks (rate ratio 0·85, 95% CI 0·72–0·99), compared to once daily LABA/LAMA (indacaterol/glycopyrronium) (Papi 2018) [evidence level II]. Pneumonia rates were similar.

Budesonide/formoterol/glycopyrronium: In patients with severe COPD and frequent exacerbations, ICS/LABA/LAMA may be more beneficial than dual therapies ICS/LABA and LAMA/LABA. In the 24-week KRONOS study, triple therapy (ICS/LABA/LAMA - budesonide/formoterol/glycopyrronium MDI) was compared with dual therapies (ICS/LABA - budesonide/formoterol as MDI or DPI, and LAMA/LABA MDI - glycopyrrolate/formoterol) (Ferguson 2018) [evidence level II]. Triple therapy improved lung function compared to budesonide/formoterol and glycopyrrolate/formoterol. The rate of moderate or severe exacerbations was lower in the triple therapy group.

In patients with moderate-to-very-severe COPD who are at risk of exacerbations, triple therapy with a budesonide–glycopyrrolate–formoterol combination MDI (ETHOS Trial) showed significant benefits over dual therapy with a LAMA–LABA or an ICS–LABA combination with respect to the annual rate of moderate or severe COPD exacerbations (Rabe 2020) [evidence level II]. The rate was significantly

lower with 320-µg–budesonide triple therapy than with glycopyrrolate–formoterol (24% lower: rate ratio 0.76; 95% CI 0.69 to 0.83; P<0.001) or budesonide–formoterol (13% lower: rate ratio 0.87; 95% CI 0.79 to 0.95; P=0.003). The rate was significantly lower also with 160-µg–budesonide triple therapy than with glycopyrrolate–formoterol (25% lower: rate ratio 0.75; 95% CI 0.69 to 0.83; P<0.001) or budesonide–formoterol (14% lower: rate ratio 0.86; 95% CI 0.79 to 0.95; P=0.002).

Triple therapy with a 320-µg dose of budesonide also resulted in a 46% lower all-cause mortality than glycopyrrolate–formoterol group [28 vs 49 deaths; hazard ratio 0.54; 95% CI 0.34 to 0.87].

The incidence of any adverse event was similar across the treatment groups (range 61.7 to 64.5%); the incidence of confirmed pneumonia was higher in the groups that included inhaled glucocorticoid (range 3.5 to 4.5%) than the glycopyrrolate–formoterol group (2.3%).

A network meta-analysis of ETHOS, KRONOS, IMPACT, and TRILOGY studies (n = 21,909) comparing triple ICS/LABA/LAMA FDC with dual LABA/LAMA and ICS/LBA FDCs administered via the same inhaler device in COPD patients (Calzetta 2020) found that regardless of the level of blood eosinophil count at baseline, the triple ICS/LABA/LAMA fixed dose combination (FDC) was the most effective treatment in reducing the risk of exacerbation, compared to LABA/LAMA FDC (RR 0.45, 95% CrI 0.32–0.61, P < 0.05) and ICS/LABA FDC (RR 0.73, 95% CI 0.54–0.99, P < 0.05) [evidence level I]. In patients with low level of blood eosinophil count at baseline, LABA/LAMA and ICS/LABA FDCs were equally effective in preventing exacerbations (RR 1.12, 95%CrI 0.83–1.35, P > 0.05). FDCs including an ICS were affected by an increased risk of pneumonia. No increased cardiovascular risk was detected in the FDCs that included two bronchodilators.

The combinations of both *beclometasone/formoterol/glycopyrronium* and *budesonide/formoterol/glycopyrronium* are now available in Australia and have been approved for listing as PBS subsidised medications.

Fluticasone furoate/umeclidinium/vilanterol*:* In a 24-week RCT of 1,810 patients with moderate to severe COPD, once daily fluticasone furoate/umeclidinium/vilanterol in a single inhaler was compared to twice daily budesonide/formoterol (Lipson 2017). Fluticasone furoate/umeclidinium/vilanterol improved FEV_1 (mean difference 171 ml, 95% CI 148 to 194) and SGRQ total score (mean difference -2.2 units, 95% CI -3.5 to -1.0), and reduced exacerbation rates (rate ratio 0.65, 95% CI 0.49 to 0.86), supporting some benefits of single inhaler triple therapy.

The IMPACT trial (n=10,355) compared triple therapy (ICS/LABA/LAMA - fluticasone furoate, umeclidinium and vilanterol) with dual therapies using the same molecules (ICS/LABA and LAMA/LABA), all administered once-daily via an Ellipta dry powder single-inhaler (Lipson 2018). This demonstrated a significantly lower rate of moderate or severe COPD exacerbations – 0.91 per year, as compared with 1.07 per year in the fluticasone furoate–vilanterol group (rate ratio with triple therapy, 0.85; 95% CI 0.80 to 0.90; 15% difference; p<0.001) and 1.21 per year in the umeclidinium–vilanterol group (rate ratio with triple therapy, 0.75; 95% CI 0.70 to 0.81; 25% difference; p<0.001). The annual rate of severe exacerbations (resulting in hospitalisation) in the triple therapy group was 0.13, as compared with 0.19 in the umeclidinium–vilanterol group (rate ratio 0.66; 95% CI 0.56 to 0.78; 34% difference; p<0.001). Overall, the adverse-event profile of triple therapy was similar to that of the dual therapy comparators. Incidence of pneumonia was higher in the ICS groups than in the umeclidinium–vilanterol group, and the risk of clinician-diagnosed pneumonia was also significantly higher with triple therapy than with umeclidinium–vilanterol (hazard ratio 1.53; 95% CI 1.22 to 1.92; p<0.001).

The difference in the mean change in trough FEV_1 between the triple therapy and fluticasone furoate–vilanterol groups was 97 ml (95% CI 85 to 109; p<0.001), and the difference between the triple

therapy and umeclidinium–vilanterol groups was 54 ml (95% CI 39 to 69; p<0.001). There were significant differences between the triple therapy group and the fluticasone furoate–vilanterol and umeclidinium–vilanterol groups in the mean change from baseline in the SGRQ total score (–1.8 [–2.4 to –1.1] and –1.8 [–2.6 to –1.0], respectively; both p<0.001) and in the percentage of patients who had a response as defined by a decrease in the SGRQ total score of at least 4 points (1.41 [1.29 to 1.55] and 1.41 [1.26 to 1.57], respectively; both p<0.001). ICS regimens also showed a possible signal toward lower all-cause mortality during treatment than umeclidinium–vilanterol.

In pre-specified secondary analyses of patients with eosinophil levels <150 cells/μL, the annual rate of moderate or severe exacerbations was 0.85 (95% CI 0.80 to 0.91) with triple therapy, 1.06 (95% CI 0.99 to 1.14) with fluticasone furoate–vilanterol and 0.97 (95% CI 0.88 to 1.07) with umeclidinium–vilanterol. Among patients with eosinophil levels of at least 150 cells per microlitre, the annual rate was 0.95 (95% CI 0.90 to 1.01) with triple therapy, 1.08 (95% CI 1.02 to 1.14) with fluticasone furoate–vilanterol, and 1.39 (95% CI 1.29 to 1.51) with umeclidinium–vilanterol.

The results described above are further supported by systematic reviews of RCTs assessing the effects of fixed and separate inhaled triple therapy versus dual therapy (of LABA and LAMA, LABA and ICS, or LAMA and ICS) or monotherapy (LAMA, LABA, or ICS) (Calzetta 2019, Cazzola 2018b, Zheng 2018, Mammen 2020a). In a meta-analysis of 13 RCTs including 15,519 patients with COPD (Calzetta 2019) [evidence level I], triple therapy was significantly more effective than the ICS/LABA combination in improving trough FEV_1, HRQoL and dyspnoea, and protecting against the risk of moderate or severe exacerbations, without compromising cardiovascular safety. The NNT for a ≥100-mL increase from baseline in trough FEV_1 of ICS/LABA/LAMA combination versus ICS/LABA combination was 3.97 (95% CI, 3.25-5.13) and for protection against the risk of a COPD exacerbation was 26.07 (95% CI, 16.79-152.70).

A network meta-analysis of 14 trials found that ICS/LABA/LAMA combination therapy significantly (p<0.001) reduced the risk of moderate or severe COPD exacerbation compared to LABA/LAMA combination therapy (relative effect 0.70, 95% CrI 0.53–0.94) and single long-acting bronchodilator therapy (relative effect 0.62, 95% CrI 0.48–0.80) (Cazzola 2018b). No significant difference was found for the risk of pneumonia when comparing ICS/LABA/LAMA combination therapy with LABA/LAMA combination therapy (relative effect 1.36, 95% CrI 0.84– 2.00) and single long-acting bronchodilator therapy (relative effect 1.31, 95% CrI 0.76–2.32). Females with COPD seemed to be at higher risk of pneumonia and the risk of pneumonia was greater when the value of FEV_1 was high at enrolment.

In a meta-analysis of 21 trials, triple therapy reduced moderate or severe exacerbations compared to LAMA/LABA (rate ratio 0.78, 95% CI 0.70 to 0.88) or ICS/LABA (rate ratio 0.77, 95% CI 0.66 to 0.91) (Zheng 2018) [evidence level I]. A meta-analysis of 11 studies found that triple therapy reduced the risk of exacerbations (relative risk 0.75, 95% CI 0.68 to 0.82) and increased the risk of pneumonia (relative risk 1.48, 95% CI 1.23 to 1.79) (Mammen 2020a).

A meta-analysis of two trials (Bremner 2018, Vestbo 2017) directly comparing fixed triple therapy with separate triple therapy found no statistically significant associations for all the outcomes, including exacerbations of COPD, lung function, adverse events and HRQoL (Zheng 2018).

A systematic review and Bayesian network meta-analysis of 219 trials involving 228,710 patients with stable COPD, comparing exacerbation, mortality, and adverse events among all regular inhaled drug classes, including ICS/LAMA/LABA, LAMA/LABA, ICS/LABA, LAMA, LABA, ICS, and placebo found that all drug classes showed significant benefits in reducing total exacerbations, compared to placebo (Lee 2019). Triple therapy was the most effective treatment in reducing total exacerbations (odds ratio [OR] = 0.57; 95% credible interval [CrI] 0.50 to 0.64; and all-cause mortality OR = 0.74, 95% CrI 0.59 to 0.93, P[OR>1] = 0.004 compared to placebo. However, ICS combinations had a high probability of pneumonia in comparison to placebo (OR 1.58 (1.26 to 2) for triple therapy and for ICS/LABA 1.59 (1.36 to 1.91). Different formulations of single inhaler triple therapy (ICS/LABA/LAMA) have similar efficacy for reducing exacerbations, as shown in two network meta-analyses (Bourdin 2021, Lee 2021) [evidence level I]. A

meta-analysis of 60 RCTs (103,034 patients) suggested that compared with inhaled therapy without ICS, inhaled therapy containing ICS (Peto OR 0.90; 95% CI 0.84-0.97), especially triple therapy (Peto OR, 0.73; 95% CI, 0.59-0.91) was associated with a reduction in all-cause mortality in patients with COPD. Further subgroup analyses revealed that treatment duration >6 months (Peto OR 0.90; 95% CI 0.83-0.97), medium-dose (Peto OR 0.71; 95% CI 0.56-0.91), and low-dose ICSs (Peto OR 0.88; 95% CI 0.79-0.97), and budesonide (Peto OR, 0.75; 95% CI 0.59-0.94) were involved in this association. Eosinophil counts ≥200/μL or percentage ≥2%, documented history of ≥2 moderate and/or severe exacerbations in the previous year, GOLD stage III or IV, age<65 years, and BMI ≥25 were significant predictors, among which eosinophil count ≥200/μL (Peto OR 0.58; 95% CI 0.36-0.95) was the strongest (Chen 2023) [evidence level I].

Reduction in mortality with triple therapy in the IMPACT and ETHOS studies was mainly observed in the first 3 months after randomization. As all the patients recruited for these two trials were frequent exacerbators, and a proportion had ICS ceased prior to randomisation, it is possible that withdrawal from ICS could have been a factor in the observed difference in mortality in those randomised to receive an ICS-containing preparation (Suissa, 2022). Therefore, not all patients with COPD will necessarily achieve a reduction in all-cause mortality as a consequence of ICS-containing triple therapy (Chen 2022) [evidence level I].

In summary, triple therapy results in a lower rate of moderate or severe COPD exacerbations, and better lung function and HRQoL than dual therapies. COPD subgroups whose all-cause mortality risk may be reduced with the inhaled therapy containing ICS include those with eosinophil counts ≥200/mL or ≥2%, documented history of ≥2 moderate and/or severe exacerbations in the previous year, GOLD stage III or IV, age<65 years old, and BMI ≥25. However, triple therapy could increase the risk of pneumonia, when compared with dual bronchodilator therapy. Therefore, triple therapy should be limited to patients with exacerbations and more severe COPD symptoms that cannot be adequately managed by dual therapy, and to patients with COPD phenotypes most likely to respond to the triple therapy. In patients with COPD already on ICS/LABA combination, the therapy can be improved without increase of cardiovascular adverse events when a LAMA is added to the combination. Triple therapy delivered in a single inhaler is convenient for patients and may improve adherence, but it is non-inferior to the use of multiple inhalers in terms of clinical efficacy.

Triple therapy prescribing has been increasing since 2016. Retrospective analysis of de-identified administrative data from the US between 2013 and 2018 found that almost three-quarters of patients with COPD who were prescribed triple therapy did not meet guideline recommendations pertaining to prior maintenance therapy and/or exacerbations. Relative to patients prescribed open triple therapy (multiple inhalers collectively containing ICS, LAMA, and LABA), those prescribed closed triple therapy (a fixed-dose single triple therapy inhaler containing fluticasone furoate/umeclidinium/vilanterol) were more likely not to have used ICS, LAMA or LABA and/or their combinations (i.e. maintenance inhaler naïve) and to have no evidence of at least 2 moderate or one severe exacerbation prior to initiating triple therapy. This guideline-discordant prescribing behaviour occurred more often among generalist-specialty prescribers than pulmonologists. Increasing prescriber awareness of guideline recommendations is warranted to counter the continuing overprescribing of triple therapy in individuals with COPD (Bhatt 2022) [evidence level III-2].

In Australia, for initiation of triple therapy (ICS/LABA/LAMA) subsidised through the PBS, the patient must have experienced at least one severe COPD exacerbation, which required hospitalisation, or two or more moderate exacerbations in the previous 12 months, with significant symptoms despite regular bronchodilator therapy with a long-acting muscarinic antagonist (LAMA) and a long-acting beta-2 agonist (LABA) or an inhaled corticosteroid (ICS) and a LABA; OR the patient must have been stabilised on a combination of a LAMA, LABA and an ICS for COPD.

O4.2.1 Eosinophil count and inhaled corticosteroids

There is significant interest in the use of blood eosinophil count as both a prognostic marker and to guide the use of inhaled corticosteroids in COPD.

In a US cohort study (Zeiger 2018), elevated blood eosinophils at baseline were independently associated with COPD exacerbations and COPD-related ED visits or hospitalisations during a year of follow-up. After adjusting for confounders, rate of future exacerbations were 25%, 48% and 76% greater for patients with eosinophils ≥ 300 cells/ mm^3 ≥ 400 cells/ mm^3 and ≥ 500 cells/ mm^3, respectively. Analysis of data from the COPD Gene and ECLIPSE longitudinal studies (Yun 2018) also found baseline blood eosinophils ≥ 300 cells/ mm^3 to be associated with increased exacerbation frequency. In a large group of patients (n=7,180) from the Danish Copenhagen General Population Study (Vedel-Krogh 2018), blood eosinophils ≥ 0.34 $x10^9$ cells/L in people whose FEV_1 was < 50% predicted were associated with a higher risk of hospitalisation for pneumonia compared with those with the same degree of airflow obstruction but a lower eosinophil count. In the Korean Obstructive Lung Disease cohort study, patients with COPD who had persistently high blood eosinophils (≥ 300 cells/ mm^3) had a better survival rate and improved symptoms and quality of life than those with persistently low eosinophil counts (<300 cells/ mm^3) while those with variable eosinophil counts had survival rates similar to those with persistently low counts (Shin 2018). In an Australian study by MacDonald et al (2019), low blood eosinophil counts (<50/uL) during admission for acute exacerbation of COPD were associated with bacterial infection, increased length of stay and a higher 12-month mortality, while just over half of exacerbations associated with higher eosinophil counts (>150/uL) also demonstrated evidence of infection, likely requiring antibiotic therapy (MacDonald 2019). A retrospective study from a single centre in China found no association between in hospital eosinophil count and in hospital mortality or length of stay, or exacerbation within one year of discharge (Yu 2021) [evidence level III-B].

Higher eosinophil counts have also been shown to be associated with a higher rate of lung function decline in individuals with and without COPD in the Canadian CANCOLD study, a prospective cohort study based on the Canadian COPD prevalence study (COLD). CANCOLD evaluated 6000 males and females ≥40 years, recruited through random sampling. The study included all subjects with COPD from the original COLD study and an equal number of age and sex-matched peers without COPD. A total of 1285 individuals had bloods drawn for eosinophil counts at 0 and 18 months as well as lung function tests, and high-resolution CT scans. Baseline eosinophil count of ≥ 300 cells/uL was an independent risk factor for accelerated decline in lung function in those with and without COPD, independent of exacerbations, and was related to the presence of gas trapping, airway wall thickening and reduction of total airway count base on CT (Tan 2021) [evidence level III-2].

In a post-hoc analysis of the FORWARD study, a double blind randomised controlled study which compared 48 weeks of treatment with extra fine beclomethasone dipropionate (BDP) plus formoterol furoate 100/6 ug two puffs bd with formoterol furoate (FF) 12 ug one puff bd in patients with COPD, patients with eosinophil counts ≥ 279.8 cells/μL experienced the highest exacerbation rate with FF and the greatest benefit from the BDP/FF combination (Siddiqui 2015). In a post-hoc review of data from WISDOM, patients with higher blood eosinophil counts were more likely to develop exacerbations after withdrawal of inhaled corticosteroids, with a significant treatment-by-subgroup interaction above an eosinophil count of 4% or greater or above 300 cells/μL (Watz 2016). Bafadhel et al used negative binomial regression analysis using splines to examine data from RCTs of budesonide/formoterol in patients with COPD, a history of exacerbations and available eosinophil counts (n=4,528) (Bafadhel 2018). They found a treatment effect interaction between the budesonide-formoterol combination as compared with formoterol alone and eosinophil count, with respect to exacerbations, lung function and health status. At eosinophil counts of 100/μL or more, a significant treatment effect was found for exacerbation reduction with budesonide/formoterol compared with formoterol alone (RR 0.75, 95% CI 0.57-0.99); p interaction =0.015).

Casanova et al examined the prevalence and stability of the finding of a blood eosinophil count ≥ 300 cells/μL and its relationship to outcomes over two years using hazard analysis in patients from the

CHAIN (patients with COPD and smokers without COPD) and BODE (patients with COPD only) cohorts (Casanova 2017). 15.8% of COPD patients in CHAIN and 12.3% of those in BODE had persistently elevated eosinophils during the period of follow-up (at least 3 measurements over two years). A similar eosinophil blood pattern was observed in controls. Exacerbation rates did not differ in patients with and without eosinophilia. All-cause mortality was lower in patients with high eosinophils compared with those with values <300 cells/μL−1 (15.8% versus 33.7%; p=0.026). In the SPIROMICS database of patients with COPD, smokers without COPD and 7% non-smokers, blood eosinophil count alone was not a reliable biomarker for COPD severity or exacerbations (Hastie 2017). Although there was a statistically significant relationship between blood and sputum eosinophils, blood eosinophil count did not reliably predict the level of sputum eosinophilia. Sputum eosinophils were available in a subset of just on 1,000 patients. The authors found that high sputum eosinophils, but not blood eosinophils, identified a subset of patients with more severe airflow obstruction, worse quality of life, more emphysema and gas trapping and more exacerbations. However, there were no differences in COPD Assessment Test (CAT) scores noted with either blood or sputum eosinophil stratification. In the prospective GLUCOLD study of patients with COPD using ICS or placebo during 30 months of follow up, neither baseline blood eosinophil levels nor baseline eosinophil levels in sputum, bronchoalveolar lavage (BAL) or bronchial biopsy predicted longitudinal changes in FEV_1 with or without ICS (Hartjes 2018).

Prospective studies that randomise patients based on eosinophil count are required to confirm these associations.

A meta-analysis by You et al (2020) compared outcomes of acute exacerbations of COPD (AECOPD) with and without eosinophilia (defined as an eosinophil count ≥2% or an absolute eosinophil count ≥0.34x109). Outcomes were better overall for eosinophilic AECOPD, with decreased hospital mortality (OR 0.59, 95% CI 0.31-0.95, p=0.03), decreased length of stay (OR 0.72,95% CI-1.44 to -0.00, p=0.05), higher FEV_1 (mean difference =0.14, 95% CI 0.08-0.2, p<0.00001) and a lower risk of arrhythmias 9 (OR 1.5, 95% CI 1.01-2.21, p=0.04). It was noted that there were more males among the non- eosinophilic group (OR 1.34, 95% CI 1.15-1.56, p=0.0002), but that steroid use did not differ between the groups (You 2020). The majority of studies in this meta-analysis were single centre and retrospective in design.

O4.3 Biologic therapies

Post hoc analyses of data from a number of studies involving patients with COPD have highlighted the blood eosinophil count as a potentially important biomarker of response to glucocorticoid treatment. Several studies have examined whether depleting eosinophils with interleukin-5 (IL-5) or IL-5 receptor antibodies could affect clinical outcomes in COPD. Pavord and colleagues compared the IL-5 inhibitor mepolizumab with placebo in patients with COPD in two 12-month randomised, controlled, parallel-group trials (METREX and METREO) (Pavord 2017). In METREX, the annual rate of moderate or severe exacerbations was significantly lower in the mepolizumab group than in the placebo group (1.4 versus. 1.71 per year; rate ratio, 0.82; 95% CI 0.68 to 0.98; P=0.04). The time to first exacerbation was also significantly longer in the mepolizumab group than in the placebo group, but there were no significant differences in outcomes when patients were not stratified according to eosinophilic phenotype. In contrast, no significant differences in exacerbation rates were detected in METREO. There was no significant between-group difference in the rate of exacerbations that led to an emergency department visit or hospitalisation or in measures of patients' symptoms in either trial.

A phase 2a trial of benralizumab, a humanized monoclonal antibody to IL-5 receptor alpha, did not demonstrate benefit in terms of exacerbations or quality of life in a group of patients with COPD who had at least one exacerbation in the preceding year and a sputum count of ≥ 3% in the preceding year; however the investigators felt that a prespecified subgroup analysis of patients with higher blood eosinophil counts supported further investigation of the effects of this drug in patients with COPD and eosinophilia (Brightling 2014). Nonetheless, large trials of benralizumab in patients with moderate

COPD and frequent exacerbations despite dual or triple therapy found no differences in annual rates of COPD exacerbations in patients treated with benralizumab compared with placebo, and no associations between baseline eosinophil counts and treatment effect (Criner 2019a). In a further pre-specified analysis of the combined GALATHEA and TERRANOVA studies of benralizumab (Criner 2019b), a variety of statistical techniques were used to identify "efficacy associated factors" in the two studies. These hypothesis-generating analyses were interpreted as suggesting that, in a subpopulation of patients with COPD who had frequent exacerbations during treatment with triple therapy and higher eosinophil counts might benefit from benralizumab 100 mg every 8 weeks.

A Cochrane Systematic review of randomised controlled trials by Donovan et al (2020) comparing anti-IL-5 therapy with placebo in adults (≥40 years old) with a diagnosis of COPD (as defined by GOLD 2020) and with frequent exacerbations included three studies each of mepolizumab (1530 participants) and benralizumab (4012 participants), both comparing anti-IL-5 therapy with placebo. No head-to-head comparison trials were identified. Mepolizumab 100 mg reduced the rate of moderate or severe exacerbations by 19% in those with an eosinophil count of at least 150/microlitre (RR 0.81, 95% CI 0.71 to 0.93; participants = 911; studies = 2, high-certainty evidence). In participants with lower eosinophils, mepolizumab 100 mg might reduce exacerbations (RR 0.92, 95% CI 0.82 to 1.03; participants = 1285; studies = 2, moderate-certainty evidence). Benralizumab 100 mg reduced the rate of severe exacerbations requiring hospitalisation in those with an eosinophil count of at least 220/microlitre (RR 0.63, 95% CI 0.49 to 0.81; participants = 1512; studies = 2, high-certainty evidence). Anti-IL-5 therapies appeared to be safe in individuals with COPD and were likely to reduce the rate of moderate and severe exacerbations in people with both COPD and higher levels of blood eosinophils. Lung function and health-related quality of life were not improved (Donovan 2020) [evidence level I].

Dupilumab is a monoclonal antibody which blocks the interleukin-4 receptor α for interleukin-4 and interleukin-13, inhibiting type 2 inflammation. In a multicentre, double-blind RCT (BOREAS trial), 939 patients with COPD with chronic bronchitis for at least 3 months and at least 2 moderate exacerbations or one severe exacerbation in the year prior to screening, blood eosinophil count >300 per µl, and using ICS/LABA/LAMA therapy were randomised to dupilumab 300 mg subcutaneous every 2 weeks for 52 weeks vs placebo. Patients with a clinical diagnosis of asthma were excluded. Mean FEV_1 was 51% predicted. Dupilumab reduced the rate of moderate or severe COPD exacerbations (rate ratio 0.70, 95% CI 0.58 to 0.86), improved prebronchodilator FEV_1 (mean difference 83 ml, 95% CI 42 to 125) and improved HRQL (SGRQ improvement exceeding the MCID, odds ratio 1.4, 95% CI 1.1 to 1.9) (Bhatt 2023) [evidence level II]. Adverse effects were similar. Although biologic therapy with dupilumab targeting type 2 inflammation has potentially beneficial effects in a select group of people with COPD and increased blood eosinophils, dupilumab is not indicated in Australia for COPD at this time, and cost-effectiveness has not been evaluated.

O5. Inhaler technique and adherence

Adherence and inhaler technique need to be checked on a regular basis [evidence level I, strong recommendation]

O5.1 Inhaler technique

Incorrect inhaler technique is common and is associated with worse outcomes. A systematic review of articles reporting direct observation of inhaler technique in COPD and asthma reported that the overall prevalence of optimal inhaler technique was only 31% (95% CI 28 to 35%), and that this pattern had not improved over 40 years. Common errors were identified, for the MDI these were poor coordination (45%; 95% CI 41 to 49%), inadequate speed and/or depth of inspiration (44%; 95% CI 40 to 47%), and the absence of post inhalation breath-hold (46%; 95% CI 42 to 49%). For the DPI, common errors included incorrect preparation in 29% (95% CI 26-33%), inadequate expiration before inhalation in 46% (95% CI 42 to 50%), and the absence of a post inhalation breath-hold in 37% (95% CI 33-40%) (Sanchis 2016). These data highlight the importance of inhalation technique education.

Inhaler devices must be explained and demonstrated for patients to achieve optimal benefit. It is necessary to check regularly that the patient has the correct inhaler technique as proficiency will wane with time. There is no evidence to guide the optimal frequency of reviewing inhaler technique. Inhaler

proficiency may wane with time so we recommend at least 6 monthly inhaler technique reviews, or after an exacerbation, or after a change in treatment.

Ensuring that patients are shown the correct inhaler technique requires the health professional to have an understanding of the devices. Unfortunately, large gaps remain in health professionals' knowledge and skill in this area. A systematic review that included 55 studies and evaluated health professionals performing 9,996 tests demonstrating their inhaler technique confirmed this (Plaza 2018) [evidence level I]. Inhaler technique was only considered correct in 15.5% of health professionals (95% CI 12-19.3) overall. Another finding of the review was that inhaler technique proficiency of health professionals has decreased over time. In studies between 1975 and 1995, overall proficiency was 20.5% (95% CI 14.9 to 26.8) compared to only 10.8% (95% CI 7.3-14.8) in the period between 1996 and 2014. These data highlight the necessity of health professionals to develop their knowledge and proficiency of inhaler device use.

A randomised cross over trial of 180 individuals hospitalized with COPD sought to understand the determinants of incorrect inhaler technique by assessment technique with 10 different inhaler placebo devices including: pressurised metered dose inhaler (pMDI), Aerolizer, Handihaler, Turbohaler, Discus, Breezhaler, Ellipta, Easyhaler, Diskhaler and Respimat without receiving any instructions. The strongest determinants of incorrect technique were: past-experience (OR 14.639, P<.001), type of device (OR 10.397 at P<.001, 4.267 at P=.007, 2.664 at P=.057, 8.666 at P=.001, 10.250 at P<.001, 0.613 at P=.212 and 0.265 at P<.001 for pMDI, Aerolizer, Handihaler, Turbohaler, Discus, Breezhaler and Ellipta, respectively), female gender (OR 0.310, P<.001), older age (OR 0.307, P<.001) and GOLD group (OR 2.289, P=.005) (Harb 2021) [evidence level II]. Inhaler technique is poor in COPD and determinants of technique are older age, female gender, severity of disease and the type of device. It is important to tailor the inhaler device to the patients' needs and preferences, as well as patient education and repeated review.

Elderly and frail patients, especially those with cognitive deficits, may have difficulty with some devices. Correct inhaler technique is essential for the optimal use of all inhaled medications (Melani 2011) [evidence level I] and is associated with fewer severe exacerbations. An observational study involving 2,935 patients with COPD, reported that in individuals who were treated for at least three months (n=2,760), the occurrence of prior (past three months) severe exacerbation was significantly associated with at least one observed critical error using prescribed inhalers (OR 1.86, 95% CI 1.14-3.04; p=0.0053) (Molimard 2017). Ease of operating and dose preparation were rated as being the most important inhaler features leading to higher patient satisfaction and fewer critical errors in a randomised, open-label, multicentre, cross-over study of two inhaler devices (van der Palen 2013) [evidence level II]. An Australian cross-sectional study found that the proportion of patients with COPD who made at least one error in inhaler technique ranged from 50 to 83%, depending on the device used (Sriram 2016). Similarly, a systematic review and meta-analysis of 72 studies involving asthma and COPD patients, reported that 50-100% of patients performed at least one handling error. The pooled summary results for pMDI estimated an overall error rate of 86.6% (95% CI 79.4-91.9) and for DPIs it was 60.9% (95% CI 39.3-79.0) (Chrystyn 2017) [evidence level I].

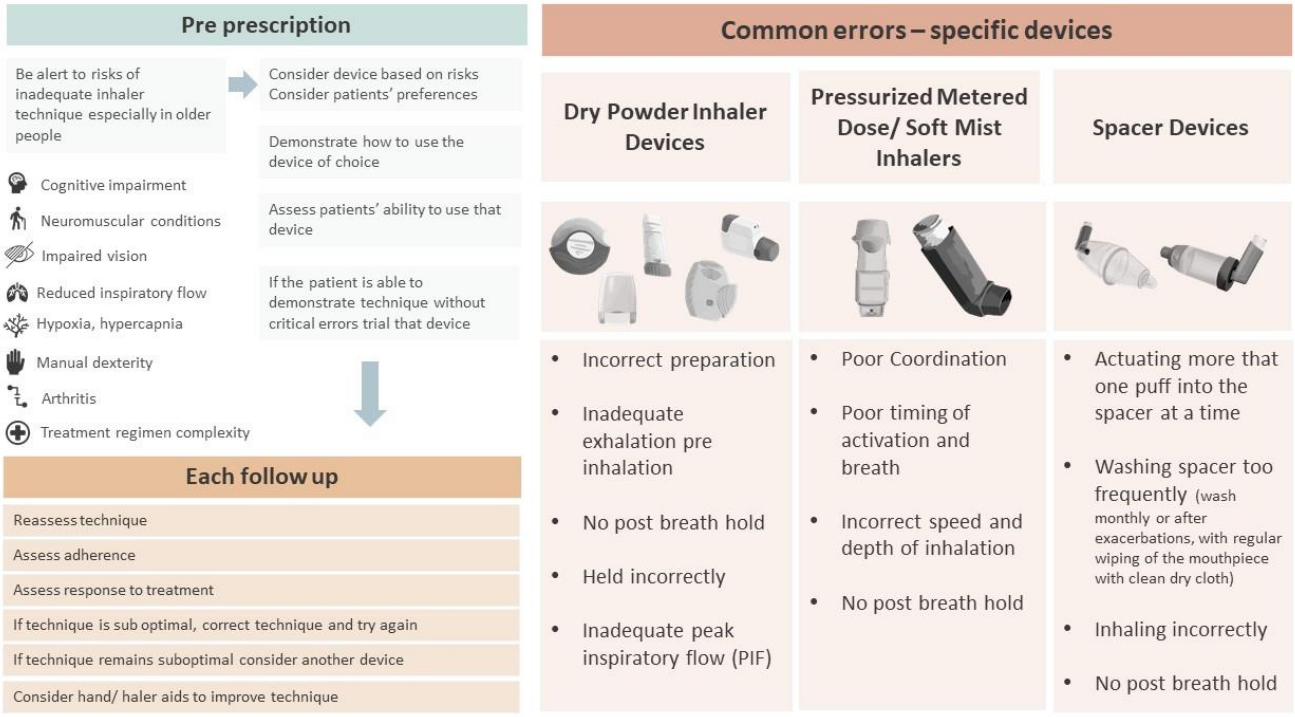
Consideration of cognitive impairment is important for the learning and retaining of inhaler technique (Baird 2017, Iamthanaporn 2023) [evidence level I]. Ongoing training for re-enforcement, or alternative inhaler device substitution, may be beneficial.

With the proliferation of new inhaler devices, inhaler device poly-pharmacy is becoming an increasing problem amongst COPD patients and has a negative impact on outcomes (Bosnic-Anticevich 2017). A study of 16,450 COPD patients compared exacerbation frequency and SABA use of patients who were using similar style inhalers e.g. all MDI to those that were prescribed devices that required a different technique. Those in the similar device cohort experienced fewer exacerbations (adjusted IRR 0.82, 95% CI 0.80 to 0.84; and used less SABA (adjusted OR 0.54, 95% CI 0.51-0.57), compared to the mixed device cohort. Adherence may also be improved when using single inhaler therapy compared

to multiple inhaler therapies. A GSK-led retrospective study using a large US claims database involving 9942 patients demonstrated that those who initiated triple therapy with single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) had significantly better adherence (46.5% vs. 22.3%; RR 2.08, 95% CI 1.85–2.30) and persistence (35.7% vs. 13.9%; HR 1.91, 95% CI 1.81–2.01, p<0.001) compared with patients who initiated multiple inhaler therapy (Mannino 2022) [evidence level III-2]. These data support the recommendation to minimise the number of different devices prescribed in COPD patients. Single combination inhaler devices have comparable efficacy to multiple inhaler devices, delivering the same medications and doses without any additional safety concerns. Retrospective and prospective studies have shown that using a single inhaler was associated with decreased healthcare resource utilisation and improved cost-effectiveness compared with multiple inhalers. However, due to the lack of long-term data, differences in outcome definitions and study designs, robust conclusions regarding the differences between single- and multiple inhaler users cannot be made (Zhang 2020) [Evidence level I].

An infographic highlighting important considerations for inhaler device prescription is included below.

Figure 5: Important considerations for inhaler device prescription



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Lung Foundation Australia has developed a series of inhaler device technique videos and factsheets for patients which provide step-by-step instructions on correct inhaler technique.

These are available at:

https://lungfoundation.com.au/resources/?user_category=32&search=inhaler%20device.

NPS Medicine Wise has also developed a checklist for inhaler device technique available at https://www.nps.org.au/assets/NPS-MedicineWise-Inhaler-Technique-v2-jg-120320-ACC.pdf

The National Asthma Council has produced a number of "how-to" videos which are available on their website at https://www.nationalasthma.org.au/living-with-asthma/how-to-videos. The Lung Foundation Australia resource, *Better Living With COPD: A Patient Guide* contains an inhalation devices

chapter which can be accessed at https://lungfoundation.com.au/wp-content/uploads/2018/09/Book-Better-Living-with-COPD-Dec2016.pdf.

The cost of inhaler devices varies between products. As there are no differences in patient outcomes for the different devices, the cheapest device the patient can use adequately should be prescribed as first line treatment (NHS Centre for Reviews and Dissemination 2003). The range of devices currently available, the products and dosage, as well as their advantages or disadvantages, are listed in **Appendix 2**. Brief counselling; monitoring and feedback about inhaler use through electronic medication delivery devices; and multi-component interventions consisting of self-management and care co-ordination delivered by pharmacists and primary care teams have been shown to improve medication adherence (Bryant 2013) [evidence level I].

Pharmacist-led interventions comprising information provision, motivating patients and taught necessary behavioural skills significantly improved medication adherence (1.41 [1.24 to 1.61], P<.00001) and correct inhalation technique (Risk Ratio 1.85, 95% CI 1.57 to 2.17), compared with the control group (Jia 2020) [evidence level I].

O5.2 Inhaler adherence

Bhattarai et al (2020) conducted a systematic review of 38 studies published from 2003 to 2019 that examined rates of medication adherence and reported on barriers and enablers to adherence. Rates of non-adherence ranged from 22% to 93%. The majority of studies identified the presence of depression and subjects' concern about the harmful effects of the medicine as barriers to adherence (Bhattarai 2020).

A systematic review comprising predominantly retrospective database studies which measured prescription refill adherence with one-to-two-year follow-up of patients with COPD found increased hospitalizations, mortality, poor quality of life and loss of productivity among non-adherent patients (van Boven 2014) [evidence level III-2]. Inhaler adherence and technique were found to be suboptimal in an observational study of use of an ICS/LABA combination inhaler fitted with an electronic audio recording device. Impaired lung function and cognition, as well as cough, predicted suboptimal adherence and technique (Sulaiman 2017).

A large retrospective study examined medication use data of patients with asthma and COPD from a digital health platform (smartphone App and electronic medication monitors). They compared adherence rates using a once daily controller regimen compared to twice daily. In 1791 patients with COPD, once daily was associated with higher median daily adherence than the twice daily regime 83.3% [IQR: 57.2 to 95.6] versus 64.7% [IQR: 32.8 to 88.9], p < .001). In COPD once daily regimen was also associated with an increased odds of achieving ≥80% adherence [1.73 (95% CI: 1.38-2.17, p < .001)]. Patients received electronic reminders via a mobile app if the medication was not taken, therefore inflating real life adherence rates. These data highlight the importance of identifying the regimen most likely to lead to improved adherence (De Keyser 2023) [evidence level III-I].

The National Asthma Council of Australia's Australian Asthma Management Handbook contains further information about adherence:
http://www.asthmahandbook.org.au/management/adherence.

O6. Non-pharmacological interventions

There is strong evidence for the benefits of regular exercise in individuals with COPD (McCarthy 2015, Ries 2003, Spruit 2013, Alison 2017) [evidence level I]. All individuals with COPD should be encouraged to engage in physical activity consistent with the recommendations for 'healthy' adults. The current Australian and New Zealand guidelines for physical activity for adults at:

www.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-phys-act-guidelines#apaadult and www.health.govt.nz/system/files/documents/publications/eating-activity-guidelines-for-new-zealand-adults-oct15_0.pdf recommend:

- Doing any physical activity is better than doing none;
- Be active on most, preferably all, days every week;
- Accumulate 150 to 300 minutes of moderate intensity physical activity or 75 to 150 minutes of vigorous intensity physical activity, or an equivalent combination of both moderate and vigorous activities, each week;
- Do muscle strengthening activities on at least 2 days each week.

Meeting current guidelines for physical activity is challenging for people with COPD due to exertional dyspnoea and symptoms of fatigue. A large cohort study of 2,398 individuals with COPD (mean age 52.1 [11.5] years, 52.1% male) recruited as part of Health Surveys in England and Scotland (Cheng 2018) provide data demonstrating a reduction in mortality at a level of physical activity significantly below that recommended by the current Australian and New Zealand guidelines for physical activity for adults. Please refer to the Department of Health's Australia's Physical Activity and Sedentary Behaviour Guidelines at: http://www.health.gov.au/internet/main/publishing.nsf/content/health-pubhlth-strateg-phys-act-guidelines and the Ministry of Health's Eating and Activity Guidelines for New Zealand Adults at: https://www.health.govt.nz/publication/eating-and-activity-guidelines-new-zealand-adults.

Specifically, compared to those who reported no physical activity, over a mean follow up period of 8.5 ± 3.9 years, individuals who reported a level of physical activity below at least half that recommended (i.e. 75 min/week of moderate or 32.5 min/week of vigorous physical activity or equivalent combination) had a reduced risk of all-cause (hazard ratio [HR] 0.75, 95% CI 0.56-1.00) and cardiovascular disease (CVD) mortality (HR 0.48, 95% CI 0.26-0.88). Individuals who met the physical activity guidelines demonstrated the greatest reductions in all-cause (HR 0.56, 95% CI 0.45-0.69), CVD (HR 0.48, 95% CI 0.32-0.71) and respiratory mortality risk (HR 0.40, 95% CI 0.24-0.67). Dose response associations with mortality risk were found for walking and sport/exercise but not for domestic physical activity. The majority of the study cohort (80.2%) had an FEV_1 >50% predicted limiting the generalisability of the findings. These findings provide further support for encouraging walking and structured exercise in people with COPD with the aim of reducing mortality risk.

O6.1 Pulmonary rehabilitation

Non-pharmacological strategies (such as pulmonary rehabilitation and regular exercise) should be provided to all patients with COPD [evidence level I, strong recommendation]

Pulmonary rehabilitation programs involve patient assessment, supervised exercise training, education, behaviour change, nutritional intervention and psychosocial support (Spruit 2013). The aim of pulmonary rehabilitation is to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours (Spruit 2013). Exercise training is considered to be the cornerstone of pulmonary rehabilitation (Spruit 2013).

The benefits of pulmonary rehabilitation include a reduction in symptoms (dyspnoea and fatigue), anxiety and depression, and improvements in health-related quality of life (HRQoL), peripheral muscle function and exercise capacity. Following pulmonary rehabilitation, participants have been shown to gain an enhanced sense of control over their condition (Bolton 2013, McCarthy 2015, Ries 2007, Alison 2017, Gordon 2019, Paneroni 2020) [evidence level I/II]. There is also evidence that pulmonary rehabilitation reduces hospitalisation for exacerbations of COPD (Moore 2016) [evidence level I]. A systematic review of 21 studies (Moore 2016) reported the effects of pulmonary

rehabilitation on subsequent hospitalisation for exacerbations of COPD. The meta-analysis included 18 studies (10 RCTs, five observational before and after studies, and three cohort studies) of which five studies were carried out in Australia or New Zealand. Data from the RCTs, and from the five observational studies that compared hospital admissions in the 12 months before and following pulmonary rehabilitation, favoured rehabilitation (RCTs: mean [95% CI] number of hospitalisations/patient-year 0.62 [0.33 to 1.16] PR group versus. 0.97 [0.67 to 1.40] control group; before and after studies mean [95% CI] number of hospitalisations/patient-year 0.47 [0.28 to 0.79] pre-PR versus. 1.24 [0.66 to 2.34] post-PR). Results of the cohort studies did not support this finding. Pooled analysis of the three cohort studies showed a higher rate of hospitalisation (mean [95% CI] number of hospitalisations/patient-year in the PR group 0.28 [0.25 to 0.32]) compared to the reference group (0.18 [0.11 to 0.32]); however, this finding was influenced predominantly by the results from one study. Pulmonary rehabilitation has also been shown to be cost-effective (Griffiths 2001) [evidence level II].

Most research has been undertaken with hospital-based programs which may use exercise machines such as treadmills, stationary cycles, arm and rowing ergometers for aerobic training, and weight machines for resistance training, but there is also evidence of benefit from pulmonary rehabilitation provided to in-patients, and in community and home settings where programs involve regular face-to-face contact to facilitate exercise participation and exercise progression (McCarthy 2015, Ries 2007, Spruit 2013, Alison 2017). Travel and transport are consistently identified as barriers to participants undertaking programs that include supervised exercise training (Keating 2011). A systematic review and meta-analysis compared exercise training programs (ETPs) delivered in patients' homes (7 trials, n=319) or community settings (3 trials n=129) with out-patient (10 trials, n=486) ETPs in people with stable COPD (Wuytack 2018). Trials selected for this review were ETPs of at least 4 weeks duration with or without additional components often included in pulmonary rehabilitation programs such as patient education and nutritional support. Programs were equally effective for improving quality of life and exercise capacity irrespective of the setting (Wuytack 2018) [evidence level I]. A systematic review and meta-analysis of 15 RCTs comparing home-based pulmonary rehabilitation of at least 4 weeks duration to usual care or centre-based pulmonary rehabilitation, demonstrated that home-based pulmonary rehabilitation is as effective as centre-based pulmonary rehabilitation in improving functional exercise capacity and quality of life compared to usual care (Uzzaman 2022) [evidence level I]. A systematic review and meta-analysis of 19 RCTs comparing the effect of minimal equipment programs with usual care or with exercise equipment-based programs, demonstrated that pulmonary rehabilitation programs using minimal equipment elicit clinically significant improvements in 6-minute walk distance and health-related quality of life and are comparable with exercise equipment-based programs for improving 6-minute walk distance and upper limb and lower limb strength (Cheng 2023)) [evidence level I]. These systematic review findings are important because providing programs in community and home-based settings where access to gymnasiums and equipment is limited may enable greater access to pulmonary rehabilitation and overcome some of the barriers to program uptake and completion.

Pulmonary rehabilitation should be offered to patients with COPD who are limited by shortness of breath on exertion and can be relevant for people with any long-term respiratory disorder characterised by dyspnoea (Ries 2007, Spruit 2013, Alison 2017). Patients with COPD, of all mMRC grades, gain significant benefit from rehabilitation (Evans 2009, Altenburg 2012, Rugbjerg 2015). However, those with the most severe dyspnoea, i.e. those who are breathless at rest or on minimal activity (mMRC grade 3 and 4) are more likely to have difficulties attending out-patient programs for reasons that include problems with transportation (Sabit 2008). Exacerbations of COPD are also an indication for referral to pulmonary rehabilitation (Spruit 2013) and every effort should be made to encourage patients to resume their rehabilitation program as early as possible following an exacerbation (see section X3.6 Pulmonary rehabilitation).

Telerehabilitation may enable people with high symptom burden or travel restrictions to access pulmonary rehabilitation. Telerehabilitation is the delivery of rehabilitation services at a distance using information and communication technology (Kairy 2009). Communication between the health

professional and the patient in their home may utilise telephone (including text messaging), internet or videoconferencing technologies (Hwang 2015).

In an Australian randomised controlled study comparing an initial 8 week, twice weekly, supervised home-based pulmonary video-conferenced telerehabilitation program compared to a centre-based pulmonary rehabilitation program, there were no significant differences between the groups for any outcome at either 8 weeks or 12 months follow-up, and both groups achieved meaningful improvement in dyspnoea and exercise capacity at the end of rehabilitation (Cox 2022) [evidence level II]. In a Cochrane review including 15 studies, there was no difference between telerehabilitation and in-person pulmonary rehabilitation for exercise capacity measured by 6-minute walking distance (6MWD) (mean difference (MD) 0.06m, 95% CI -10.82m to 10.94m), quality of life measured by the St George's Respiratory Questionnaire (MD -1.26, 95% CI -3.97 to 1.45), or breathlessness measured by the Chronic Respiratory Disease Questionnaire dyspnoea domain score (MD 0.13, 95% CI -0.13 to 0.40). Telerehabilitation was associated with higher completion rates compared to in-person pulmonary rehabilitation (93% vs 70%). Ongoing maintenance telerehabilitation was associated with a greater 6MWD by 78.1m (95% CI 49.6m-106.6m) (Cox 2021) [evidence level I]. Long-term telerehabilitation consisting of two years of unsupervised exercise at home on a treadmill and strength training, plus either supervised exercise sessions once/week for 8 weeks or supervised exercise sessions once/week for 8 weeks followed by once/month for the two year duration of the study, reduced the rate of hospitalisations and ED presentations compared to standard care (Zanaboni, 2023) [evidence level II].

Exercise programs alone have clear benefits (McCarthy 2015) while the benefits of education or psychosocial support without exercise training are less well documented (Ries 2007, Spruit 2013, Alison 2017). There are few robust studies that have attempted to evaluate the role of disease specific education within a pulmonary rehabilitation program in addition to exercise training. An RCT, carried out in Australia, of 267 people with COPD failed to show any additional benefit with the combination of an 8-week pulmonary rehabilitation program comprising exercise training and disease specific education with a self-management focus, compared to exercise training alone. The outcomes assessed in this study included disease specific and generic HRQoL, functional exercise capacity, dyspnoea, health behaviours, self-efficacy and healthcare utilisation (respiratory-related hospital admissions, physician consultations and prescriptions) (Blackstock 2014). Further, a sub-analysis undertaken within the Cochrane Review of pulmonary rehabilitation for people with COPD showed no significant differences in the magnitude of improvement in HRQoL between programs that delivered exercise training alone (31 trials) when compared to those that delivered exercise training combined with any form of education and/or psychosocial support (34 trials) (McCarthy 2015).

Some patients who experience marked oxygen desaturation on exertion may benefit from ambulatory oxygen during exercise training and activities of daily living (see section **P10 Oxygen therapy**).

The duration of pulmonary rehabilitation programs reported in the literature ranges from 4 weeks to 18 months. Many programs within Australia and New Zealand are of 8 weeks duration, with patients attending two supervised group sessions each week supplemented by an unsupervised home exercise program (Alison 2017) consistent with the recommendations reported in pulmonary rehabilitation statements (Spruit 2013) and international guidelines (Bolton 2013, Marciniuk 2010, Ries 2007). It is unclear as to whether greater or more sustained benefits occur following programs of longer duration because there are no RCTs that directly compare the outcomes of 8-week programs with those of longer programs.

The improvements in functional exercise capacity and HRQoL begin to decline by 12 months following completion of a pulmonary rehabilitation program (Brooks 2002, Ries 2003). For this reason, within Australia, patients may be offered supervised exercise training at a lower frequency (≤1 session per week) than the initial pulmonary rehabilitation program (unpublished data Lung Foundation Australia, 2015). Several studies have investigated maintenance strategies aimed at preserving the benefits in exercise capacity and HRQoL (Spruit 2013, Alison 2017); however, more research is needed before

any specific strategy can be recommended. A Cochrane review of 21 studies comparing supervised maintenance pulmonary rehabilitation programs with usual care showed an improvement in health-related quality of life at 6-12 months (Chronic Respiratory Disease Questionnaire total score mean difference (MD) 0.54 points, 95% CI 0.04-1.03, n=258, 4 studies, which exceeds the minimal important difference of 0.5 points). It is uncertain whether supervised maintenance programs improve 6-minute walk distance (MD 26 meters, 95% CI -1.04 - 52.84, n=639, 10 studies) (Malaguti 2021). Unsupervised home-based exercise for 12 months has been shown to improve 1 minute sit-to-stand performance compared to usual care, had no effect on dyspnoea, but was well accepted by people with COPD (Frei 2022) [evidence level III-2]. Whilst the optimal model for supervised maintenance exercise programs is still unclear, some form of regular exercise should be encouraged following completion of a pulmonary rehabilitation program to sustain the benefits gained (Alison 2017). There is some evidence (n=2 RCT) that repeating a course of pulmonary rehabilitation within 12 months following an initial program may be beneficial (Burge 2022) [evidence level I].

A list of pulmonary rehabilitation programs known to Lung Foundation Australia can be accessed at Pulmonary Rehabilitation - Lung Foundation Australia. The individual contact details can be obtained by calling the Lung Foundation's Information and Support Centre (free-call 1800 654 301). An online toolkit is available to assist health professionals to implement a Pulmonary Rehabilitation Program. See www.pulmonaryrehab.com.au.

O6.2 Exercise training

Exercise is defined as physical activity that is planned, structured and repetitive, and undertaken with the aim of improving or maintaining physical fitness and for health benefits (Garber 2011). Exercise training (whole body endurance training and strength training) is considered to be the essential component of pulmonary rehabilitation (Ries 2007, Spruit 2013, Alison 2017). Numerous RCTs in people with moderate to severe COPD have shown decreased symptoms (dyspnoea and fatigue), increased maximal and functional exercise capacity and improved health-related quality of life (HRQoL), emotional function and the individuals' self-control over their condition following exercise training alone (McCarthy 2015, Ries 2007, Spruit 2013, Alison 2017, Paneroni 2020) [evidence level I]. Improvements in muscle strength and self-efficacy have also been reported (Bolton 2013, Ries 2007) [evidence level II]. Exercise training may confer a significant but small increase in physical activity (Mantoani 2016) [evidence level I].

Recommendations for exercise training in people with COPD are based on those for healthy adults (Garber 2011, Spruit 2013). However, since many individuals with COPD are unlikely to be able to achieve the recommendation for moderate to vigorous intensity exercise involving large muscle groups sustained for prolonged periods (i.e. 20-60 minutes) (Garber 2011) some modifications to these recommendations are required. Specifically, for people with COPD to accumulate the recommended dose (≥ 150 minutes per week of moderate intensity exercise, involving large muscle groups and accumulated over ≥ 5 days) they frequently need to undertake periods of exercise interspersed with rest periods in order to manage their dyspnoea. It is important to reassure patients that breathlessness on activity is not harmful and a degree of breathlessness is necessary in order to gain the benefits of exercise. When commencing an exercise program most individuals will need to gradually build up to the recommended weekly dose of exercise. Walking (ground-based or treadmill) and or stationary cycling are the forms of endurance exercise most commonly employed in exercise training programs for people with COPD (Spruit 2013) with ground-based walking having the advantage that it requires no equipment and can translate into improvements in walking capacity (Wootton 2014). Strength training is also recommended on at least 2 days each week interspersed with at least one rest day (Garber 2011). A systematic review and meta-analysis (de Lima 2020) including 3 studies and 145 participants suggests elastic resistance training may be an alternative to conventional resistance training using weight machines for improving knee extensor muscle strength due to similar effects [evidence level I]. In order to gain the most benefit from an exercise program it is likely that many individuals with COPD will require supervision from a health professional who has a knowledge of lung pathology and exercise prescription for people with chronic lung disease.

There is evidence from a multicentre, RCT (n=143) carried out in Australia that provides some support for the use of supervised ground-based walking training as the sole modality of exercise training in people with moderate to severe COPD (Wootton 2014). This trial demonstrated significant benefits in HRQoL and endurance walking capacity favouring the walking training group [evidence level II] however some of the benefits were of a lesser magnitude than reported following a comprehensive pulmonary rehabilitation program. Supervised walking training in isolation has a therapeutic role where access to pulmonary rehabilitation programs is limited or when specialised exercise equipment is unavailable.

In an Australian study of telerehabilitation comparing 8 weeks of group exercise training thrice weekly, compared to usual medical management involving pharmacotherapy and an action plan, the endurance shuttle walk test improved significantly in the trained group compared with usual care: 340 seconds (95% CO 153-526, p<0.001) (MCID 180 seconds). However, there were no significant differences in quality of life or physical activity measured as steps walked per day between the two groups (Tsai 2017) [evidence level II], despite the control group not receiving an exercise intervention.

Most of the evidence for the benefits from exercise training has been gained from supervised programs that involved land-based exercise training, however a Cochrane Review provides limited

evidence from RCTs conducted in a small number of patients with COPD that water-based exercise may confer short-term benefits in exercise capacity and quality of life (McNamara 2013b) [evidence level I]. The Australian study included in this Cochrane Review specifically recruited individuals with COPD who had concurrent physical comorbidities such as obesity or significant musculoskeletal problems that limited the ability to participate in a land-based exercise program (McNamara 2013a). Thus, supervised water-based exercise training may provide an alternative for people with COPD whose comorbidities preclude land-based exercise training or when pulmonary rehabilitation programs are unavailable.

Unsupervised exercise training using a formal prescription of frequency, intensity, time and type can significantly improve disease-specific quality of life in people with COPD, but not exercise capacity (Taylor 2021) [evidence level I]. Supervised exercise training is required to improve exercise capacity.

O6.3 Inspiratory Muscle Training

Inspiratory muscle training (IMT), performed in isolation using a threshold loading device or target-flow resistive device at loads equal to or greater than 30% of an individual's maximum inspiratory pressure generated against an occluded airway (PImax) has been shown to produce short-term gains in inspiratory muscle strength and endurance, reduce dyspnoea, improve functional exercise capacity (6 or 12 minute walk distance) and confer small gains in health-related quality of life (HRQoL) in patients with COPD (Ammous 2023) [evidence level I]. Although IMT used in isolation is beneficial, it does not appear to have any added benefits in terms of dyspnoea, functional exercise capacity or quality of life when combined with whole body exercise training in people with COPD (Ammous 2023) [evidence level I]. For this reason, IMT is not a replacement for whole body exercise training and is not recommended as a routine component of a pulmonary rehabilitation program (Spruit 2013).

O6.4 Neuromuscular electrical stimulation

Neuromuscular electrical stimulation (NMES) uses an intermittent electrical current to elicit a contraction of a superficial peripheral muscle. The main aim of NMES is to improve muscle power or endurance. In people with COPD, NMES is generally applied to the thigh muscles. NMES is associated with a very low ventilatory load and thus dyspnoea in contrast to whole body exercise training.

The findings of a Cochrane Review (Hill 2018) showed that NMES applied in isolation improved peripheral muscle force (SMD 0.34, 95% CI 0.02 to 0.65, 6 trials, n=159) and endurance (SMD 1.36, 95% CI 0.59 to 2.12, 2 trials, n=35) and 6-minute walk distance (39.26m, 95% CI 16.31 to 62.22, 2 trials, n=76) [evidence level I]. These trials applied NMES over a 4 to 8-week period, 4 to 7 days a week and for sessions lasting 30-60 minutes applied once or twice daily. The findings of studies that applied NMES in addition to conventional exercise training compared to conventional exercise training alone (6 trials) showed no additional gain in muscle performance. The quality of the evidence in this review was rated as low. The main clinical applications for NMES are for patients unable to engage in whole body exercise training, for example due to very severe dyspnoea including patients with an exacerbation and those awaiting transplantation.

O6.5 Physical activity and sedentary behaviour

Physical activity is defined as any bodily movement generated by skeletal muscle that results in energy expenditure above resting levels and is often classified as light, moderate or vigorous intensity according to the energy level required (Garber 2011). In its broadest form, physical activity encompasses exercise (physical activity) that is planned, structured and repetitive, undertaken with the aim of improving or maintaining physical fitness and for health benefits), sports, and physical activity done as part of daily living, work, leisure and transportation.

It is well-established that people with COPD participate in low levels of physical activity during daily life. Data from meta-analyses indicate that, on average, people with COPD participate in 57% of the total duration of physical activity undertaken by healthy controls (Vorrink 2011). Reductions in physical activity commence early in the COPD disease trajectory (Waschki 2015). Over time, levels of physical activity substantially decline across all severity stages of COPD and this decline is accompanied by deterioration in lung function and health status (Waschki 2015). Levels of physical activity are reduced further during hospitalisation for an exacerbation of COPD (Pitta 2006). An Australian study assessed physical activity in 50 individuals during hospitalisation for an exacerbation of COPD, and at 1- and 6-weeks following discharge (Tsai 2016). Although there was a significant improvement in physical activity at one week following discharge when compared to activity levels during admission, the level of physical activity at 6 weeks post-discharge showed no further significant improvement (Tsai 2016).

Low levels of physical activity are associated with increased mortality and exacerbations in people with COPD (Gimeno-Santos 2014) [evidence level I]. In one cohort study of 341 patients hospitalised for the first time with a COPD exacerbation, regular physical activity was related to a higher diffusing capacity of lung for carbon monoxide (D_LCO) test, expiratory muscle strength, exercise capacity (6-minute walk distance (6MWD) and VO_2 peak) as well as to lower levels of systemic inflammation, after adjusting for confounders (Garcia-Aymerich 2009) [evidence level III-2]. In a population-based sample of 2,386 individuals with COPD who were followed for a mean of 12 years, those who performed some level of regular physical activity had a significantly lower risk of COPD admissions or mortality than sedentary individuals (Garcia-Aymerich 2006) [evidence level III-2].

Regular physical activity is recommended for all individuals with COPD (Garcia-Aymerich 2009). In the absence of instruction from a health professional (i.e. physiotherapist, exercise physiologist), individuals with COPD should be encouraged to be physically activity (i.e. engage in at least moderate PA for 30 minutes on 5 days each week, e.g. walking) and participate in activities of daily living that require the use of muscle strength (e.g. lifting, squatting to complete tasks such as gardening) as well as doing activities such as bowls, golf, swimming and Tai Chi that they enjoy.

There is some evidence that interventions comprising physical activity counselling, especially when combined with coaching, can produce modest increases in physical activity in people with COPD however the quality of the evidence was rated as very low (Mantoani 2016) [evidence level I].

A randomised controlled trial carried out in Spain in people with moderate COPD (predominantly male) showed a significant increase in physical activity (mean difference 947 steps/day (95% CI 184 to 1731)) at the 12-month follow-up (per protocol analysis) in a group that received a multicomponent Urban Training intervention compared to a group that received usual care (Arbillaga-Etxarri 2018). Key components of the intervention included behavioural techniques and motivational interviewing, maps of validated walking trails of different intensities, pedometer and calendar to record physical activity, text messages every 2 weeks and option to participate in a monthly supervised walking group. No between group differences were seen in any of the secondary outcomes that included 6MWD, QoL and severe exacerbations.

Supervised exercise training alone or within the context of a pulmonary rehabilitation program has been shown to produce significant but small increases in physical activity, however the benefits are inconsistent and overall the quality of the evidence was rated very low (Mantoani 2016) [evidence

level I]. A systematic review and meta-analysis (Lahham 2016) found that activity counselling, when added to pulmonary rehabilitation, increased physical activity as measured by daily step count, and that this was both significant and exceeded the minimum important difference for daily step count (mean difference 1,452 daily steps, 95% CI 549 to 2,356). Physical activity promotion with a wearable activity monitor-based intervention (i.e., pedometer or accelerometer incorporated as a tool to monitor and provide feedback on step-count throughout the intervention), improved steps per day (median (IQR) 1153 (791-3199) steps per day) compared with usual care in a systematic review and meta-analysis (Reilly 2023) [evidence level I]. Further studies are needed, but physical activity counselling in the context of a pulmonary rehabilitation program shows promise in terms of increasing physical activity in daily life.

In addition to low levels of physical activity, there is growing recognition that people with COPD spend a large proportion of their waking hours in sedentary behaviours, (Hunt 2014) defined as those behaviours which are undertaken in a sitting or reclined posture and have low energy requirements (e.g. watching television, reading, playing cards, sitting at a computer) (Sedentary Behaviour Research Network 2012). People with COPD who accumulate the greatest sedentary time during daily life are more likely to live with someone else and be characterised by more frequent exacerbations, lower exercise capacity, long-term oxygen use, lower motivation for exercise, and the presence of physical comorbidities such as obesity, musculoskeletal or neurological conditions (Hartman 2013, McNamara 2014).

In the general population, data from several large longitudinal studies have reported the deleterious health consequences (e.g. both all-cause and cardiovascular mortality) of increased sedentary time (Dunstan 2010, Thorp 2011) [evidence level I]. Sedentary behaviour defined as more > 8.5 hrs/ day spent in sedentary behaviour in a cohort of 101 Brazilian patients with COPD was an independent risk factor for mortality (Furlanetto 2017) [evidence level III]. Furthermore, data collected in 76,688 people from Japan, who were followed for 19.4 years show that, when compared with men who watched television for < 2 hours/day, men who watched television for ≥ 4 hours/day had an increased risk of COPD-related mortality (HR 1.63; 95% CI 1.04 to 2.55). However, this relationship was not observed in females (HR 0.84; 95% CI 0.29 to 2.48) (Ukawa 2015). Data collected in 223 people with COPD as part of the National Health and Nutrition Examination Survey (NHANES), showed modest positive associations between sedentary time and markers of cardiometabolic risk such as waist circumference and fasting glucose levels (Park 2014).

Given that people with COPD accumulate large amounts of sedentary time and this may have deleterious health consequences, reducing sedentary time would seem to be an appropriate lifestyle goal in this population. Compared with the goal of increasing physical activity, particularly moderate or vigorous intensity physical activity, the goal of reducing sedentary time by increasing light intensity physical activity is likely to be more feasible in those with marked reductions in exercise capacity who are limited by dyspnoea during activities of daily living (Cavalheri 2016, Hill 2015). Of note, in people with COPD, greater participation in light intensity physical activity, such as slow walking, has been reported to reduce the risk of respiratory-related hospitalisations (Donaire-Gonzalez 2015). There is a need to identify approaches that are effective at reducing sedentary time in people with COPD, and most importantly, whether any reduction in sedentary time impacts health outcomes in this population.

The table in **Appendix 4** provides some strategies aimed at avoiding prolonged sedentary time.

O6.6 Education and self-management

There is limited evidence that education alone can improve self-management skills, mood or health-related quality of life (HRQoL). Education is often included with exercise training as part of a comprehensive pulmonary rehabilitation program (Ries 2007) [evidence level III-2]. Delivering COPD-specific information in a didactic style is unlikely to be beneficial and therefore is not recommended (Blackstock 2007). Providing information and tools to enhance self-management in an interactive

session is more effective than didactic teaching (Lorig 1999, Blackstock 2007).

A systematic review of self-management education for COPD (Schrijver 2022) concluded that self-management education is associated with improvements in HRQoL measured by the SGRQ, compared to usual care (mean difference -2.86 95% CI -4.87 to -0.85). This difference did not meet the MCID of 4 units however. The intervention group was also at a lower risk of at least one respiratory hospital admission, albeit the difference was small (OR 0.75 95% CI 0.57 to 0.98). This translates into a Number Needed to Treat of 15 (95% CI 8-399) to prevent one respiratory related hospital admission over a follow up period of 9.75 months. There were also improvements in exercise capacity (6MWD), anxiety and depression, and antibiotic courses. However, because of the heterogeneity in interventions, study populations, follow-up time and outcome measures, data are insufficient to formulate clear recommendations regarding the format and content of self-management education programs for individuals with COPD. Several more studies have not shown any benefit from self-management interventions (Bucknall 2012, Bischoff 2012). One study found excess mortality in the self-management group (Fan 2012). However, in the 2022 Cochrane review by Schrijver et al the mortality meta- analyses, which included Fan et al (2021), showed no difference in respiratory related mortality risk (risk difference RD 0.01 95%CI -0.02 to 0.04), or all-cause mortality risk (risk difference RD 0.01 95%CI -0.03 to 0.01) between intervention and usual care.

The single most important intervention is assistance with smoking cessation. Good nutrition; task optimisation for more severely disabled patients; access to community resources; help with control of anxiety, panic or depression; instruction on effective use of medications and therapeutic devices (including oxygen where necessary); relationships; end-of-life issues; continence; safety for flying; and other issues may be addressed (Spruit 2013, Morgan 2001).

O6.6.1 Psychosocial support

Support groups may provide people with COPD and their carers with emotional support, social interaction, and new knowledge and coping strategies, although studies specifically evaluating the benefits of these groups for improving quality of life and psychological well-being are yet to be conducted. Pulmonary rehabilitation provides a good opportunity to initiate support group attendance.

Lung support groups may provide patients and carers with emotional support, social interaction, and other social outlets, and help them gain new knowledge and coping strategies. A list of Patient Support Group names and locations can be accessed via Lung Foundation Australia's website at https://lungfoundation.com.au/patients-carers/get-support/support-groups/. Contact details can be obtained from Lung Foundation Australia's Information and Support Centre (free-call 1800 654 301). In New Zealand, Asthma and Respiratory Foundation NZ list Pulmonary Rehabilitation and Support Groups on their website: https://www.asthmafoundation.org.nz/about-us/support-groups, free-call 0800 100 506. Asthma New Zealand list COPD Support Groups and the 'Find your local group' directory: https://www.asthma.org.nz/pages/copd-support-groups, free-call 0800 227 328.

People with COPD are vulnerable to developing symptoms of anxiety and depression, which then worsen quality of life and disability (Xu 2008, Eisner 2010b) [evidence level III-2]. Pulmonary rehabilitation has been associated with short-term reductions in anxious and depressive symptoms (Coventry 2013, Yohannes 2017, Gordon 2019). Additional intervention by mental health specialists, such as high-intensity cognitive behavioural therapy interventions, will be required for clinically significant symptoms of anxiety or depression (Yohannes 2017, Williams 2020).

O6.7 Breathing exercises

A variety of breathing exercises are used in people with COPD. The aim of these exercises is to reduce dyspnoea by altering respiratory muscle recruitment, reducing lung hyperinflation, improving the functioning of the respiratory muscles and optimising thoraco-abdominal motion.

A Cochrane Review of 16 studies involving a total of 1233 individuals with stable COPD (Holland 2012) evaluated the effects of a variety of breathing exercises alone, or together with other interventions, on the primary outcome measures of dyspnoea, exercise capacity and health-related quality of life (HRQoL). The review found some evidence that breathing exercises (pursed lip breathing, diaphragmatic breathing, yoga involving pranayama timed breathing techniques) performed for between 4 and 15 weeks when compared to no breathing exercises improved exercise capacity as measured by 6-minute walking distance [evidence level I/II] but had inconsistent effects on dyspnoea or HRQoL. Mixed results were found when breathing exercises were compared with other techniques, namely inspiratory or expiratory muscle training, or whole-body exercise training, or when combined with another intervention. Computerised ventilation feedback was less effective than exercise training for improving exercise endurance [evidence level III-2] and when combined with exercise training did not confer any additional benefits in dyspnoea compared to exercise training alone [evidence level III-2]. No significant adverse effects were reported in the studies. A major limitation of the studies was that assessor blinding could only be determined in two studies. In a systematic review of 15 randomised control trials (1098 people with COPD), daily pursed lip breathing combined with deep breathing (2-5 times a day for 5-30 minutes) compared to usual care, showed statistically significant improved pulmonary function (FEV_1, FVC, FEV_1/FVC) and 6-minute walk distance (mean difference 29m, 95% CI 19-38, $p<0.001$) compared to control (Yang 2022) [evidence level I].

Breathing exercises practiced daily may have a role to improve exercise capacity in people with COPD who are unable to undertake exercise training, and their use during daily living activities can be beneficial for breathlessness management by reducing respiratory rate at rest and shortening time taken to recover from breathlessness.

O6.8 Chest physiotherapy (Airway clearance techniques)

Airway clearance techniques (ACTs) are only indicated for patients with COPD who have evidence of sputum. This is likely to include individuals who have the clinical features of chronic bronchitis, those with co-existent bronchiectasis and some patients during an exacerbation.

The aims of ACTs in patients with COPD are to assist sputum clearance in an attempt to reduce symptoms and paroxysmal coughing, slow the decline in lung function, reduce exacerbation frequency and hasten the recovery from exacerbations.

A variety of techniques are available that vary in terms of ease of learning and equipment-related cost. These include the active cycle of breathing techniques (ACBT), (a cycle of breathing control, thoracic expansion exercises and the forced expiration technique), positive expiratory pressure (PEP) therapy (e.g. Astra PEP® or Pari PEP®), devices that combine PEP and an oscillatory vibration of the air within the airways (e.g. Flutter®, Acapella® or Aerobika®) and autogenic drainage (AD). Autogenic drainage is a more complex technique that is based on the principle of achieving the highest possible airflow in different generations of bronchi, while preventing early airway closure, via the use of controlled tidal breathing. Conventional chest physiotherapy (defined as any combination of gravity-assisted drainage, percussion, vibrations and directed coughing /huffing) is now used less commonly. Short-acting inhaled bronchodilators prior to treatment may assist with sputum clearance in some patients. The Bronchiectasis Toolbox is an online resource which provides guidance for healthcare professionals and people living with chronic lung disease which describes and demonstrates airway clearance techniques (https://bronchiectasis.com.au/physiotherapy).

A Cochrane systematic review (Osadnik 2012) of 19 studies of ACTs in patients with stable COPD found evidence from single studies suggesting that ACTs may reduce the need for hospital admission and improve health-related quality of life (HRQoL) [evidence level II]. It is possible that ACTs may also enhance sputum clearance and exercise tolerance, and reduce the longer-term need for antibiotics [evidence level II] although further research is required. The trials included in the review were generally of small sample size and the ability to pool data for meta-analyses was limited due to

heterogeneity of outcome measures and inadequate reporting from cross-over studies.

It is unlikely that one ACT is appropriate or superior for all patients with COPD. The choice of technique depends on the patient's condition (e.g. extent of airflow limitation, severity of dyspnoea), sputum volume and consistency, the effects of the different techniques on lung volumes, expiratory flow and dynamic airway compression, presence of co-morbid conditions such as bronchiectasis, cognitive status of the patient and acceptability of the technique to the patient especially where long-term treatment is required (Holland 2006). Furthermore, the level of expertise of the therapist and availability and cost of ACT devices are also factors affecting the choice of ACT prescribed.

A randomised controlled trial of oscillating positive expiratory pressure (OPEP) using the Acapella device plus ACBT compared to ACBT alone in patients with COPD who frequently produce sputum demonstrated significant improvements in cough-related QOL, genericQOL, and reduced fatigue (Alghamdi 2022). In clinical practice, screening of patients who produce sputum on most days (i.e. COPD with a sputum producing phenotype), can identify patients where the Acapella™, and perhaps similar OPEP devices, can have a positive impact [evidence level II].

Patients with evidence of chronic sputum production should be referred to a physiotherapist for assessment and education regarding the most appropriate ACTs for each individual based on their clinical features.

O6.9 Smoking cessation

While smoking cessation has long been known to reduce the rate of decline of lung function (see section P1.1), there is evidence it also has short-term benefits on lung function and quality of life. In a randomised controlled trial of varenicline (Tashkin 2011b) participants who continuously abstained from smoking compared to those who relapsed, had higher post-bronchodilator FEV_1 at weeks 12 (mean 121.8 ml versus. 37.9 ml, $p<0.007$) and 24 (mean 58.4 ml versus. -19.1 ml, $p=0.07$) when compared to baseline measurements, although the difference at the latter time point was not statistically significant. Similarly, those who abstained, when compared to those who relapsed, had a greater improvement in the total clinical COPD questionnaire score at 12 weeks (mean -1.04 versus. -0.53, $p<0.0001$), and this significant benefit was also seen at 24 and 52 weeks. Benefits at all time points were also found for the domain scores of respiratory symptoms, functional status and mental state. Refer to P1.1 for additional information regarding smoking cessation.

O6.10 Nutrition

Nutritional management of COPD is complex, as both malnutrition and obesity are highly prevalent, and both contribute to patient morbidity and mortality risk. In addition, poor eating habits, sedentary lifestyle, smoking and corticosteroid use can lead to poor nutritional status in COPD, with deficiencies in various nutrients such as vitamins and minerals, fatty acids and amino acids. The randomised controlled trials (RCTs) that have been conducted with the aim of achieving a healthy weight, improving nutritional status and functional outcomes in COPD are discussed below.

Malnutrition: Malnutrition is an independent predictor of mortality and healthcare use in COPD patients (Hoong 2017) [evidence level III-2]. Low body weight and/or low-fat free mass (FFM) is common in COPD, particularly in those patients with severe disease and those who are socially deprived (Collins 2018), due to an inadequate nutritional intake compared to energy expenditure. Energy intake may be reduced due to breathlessness during eating, hyperinflation of lungs causing pressure on the stomach and loss of appetite induced by drugs (Sridhar 2006). At the same time, energy demands may be increased due to factors such as the energy costs of breathing, the metabolic costs of respiratory tract infections, increased nutrient-induced thermogenesis and catabolic effects of systemic inflammation (Sridhar 2006, Akner 2016). As a result, low BMI and loss of FFM are common in COPD patients and this increases COPD mortality risk, being inversely associated with respiratory and peripheral muscle function, exercise capacity and health status (Vestbo 2006, Schols 2005). Two

meta-analyses have shown that high calorie nutritional support has small, yet beneficial effects in COPD, particularly in those who are undernourished. A systematic review which included 13 RCTs of nutritional support included a meta-analysis that showed a pooled increase in mean weight, which was greatest in undernourished patients [1.94 (95% CI 1.43-2.45) kg]. There were also increases in grip strength 5.3% ($p < 0.05$) and small effects on fat free mass and skin fold thickness (Collins 2012) [evidence level I]. In a follow-up meta-analysis which focused on functional outcomes, nutritional support led to improvements in inspiratory muscle and expiratory muscle strength (Collins 2013) [evidence level I]. A Cochrane Review updated in 2012 also demonstrated in a meta-analysis of data from 17 RCTs, that nutritional therapy resulted in body weight gain in undernourished patients [1.65 (95% CI 0.14-3.16) kg] and improved FFM index and exercise tolerance (6-minute walk distance (6MWD)) in all patients. Importantly, the increase in 6MWD reached the minimum clinically important difference in severe COPD patients (Ferreira 2012) [evidence level I]. Hence high calorie nutritional supplements should be considered in COPD, particularly those who are malnourished and/or have severe disease. Importantly, those with undernutrition are most likely to benefit from nutrition therapy before an undernutrition state is established (Akner 2016).

Obesity: At the other end of the spectrum, obesity is becoming increasingly prevalent in COPD. Obesity complicates COPD management and in addition to the negative metabolic consequences, is associated with decreased expiratory reserve volume (ERV) and functional residual capacity (FRC), increased use of inhaled medications, increased dyspnoea and fatigue, decreased heath related quality of life and decreased weight bearing exercise capacity (Cecere 2011, Ramachandran 2008, Ora 2009). Despite these negative effects, obesity has been associated with reduced mortality risk in severe COPD, (Landbo 1999, Guo 2016b) which may be due to a reduction in static lung volumes (Casanova 2005) and /or the increase in FFM (Poulain 2008) that occurs in obesity due to over-nutrition and increased weight bearing. A meta-analysis of 17 studies evaluated the dose-response relationship between BMI and mortality. Compared to healthy weight COPD individuals, the RR for death in the underweight was 1.40 (95% CI 1.20-1.63; p=0.0001), whereas the risk of death was reduced in those in that were overweight (RR 0.80, 95% CI 0.67-0.96; p=0.0001) and obese (RR 0.77, 95% CI 0.62-0.95; p=0.0162). There was a nonlinear relationship between mortality and BMI categories. Those with a BMI <21.75 kg/m^2 had the greatest risk of dying. Once BMI exceeded 32 kg/m^2 the protective effect of high BMI was no longer evident (Guo 2016b).

No weight loss RCTs have been conducted in COPD to date, however, a recent pre-post study has demonstrated the potential benefits of weight loss. In this uncontrolled trial, dietary energy restriction coupled with resistance exercise training led to clinically significant improvements in BMI, exercise tolerance and health status, while preserving FFM (McDonald 2016b) [evidence level III]. Definitive RCTs are needed in this area in order to formulate clinical guidelines for managing obese COPD patients.

Other nutritional interventions: A number of large observational cohort studies have demonstrated that a healthy dietary pattern (including fruit, vegetables, fish and wholegrains) protects against lung function decline and COPD onset, while an unhealthy eating pattern (including refined grains, cured and red meats, desserts and French fries) has the opposite effect (Varraso 2015, Varraso 2007a, Varraso 2007b). Nutritional interventions targeting specific foods or nutrients in COPD are limited and to date, the level of evidence supporting these interventions is level II or less.

Fruit and vegetables: Fruit and vegetables are recognised as being part of a healthy diet as they are low in energy, yet dense in nutrients such as vitamins and minerals, fibre and phytochemicals. In a cohort study in 44,335 men followed for 13.2 years, high fruit and vegetable intake was associated with reduced risk of COPD. Current and ex-smokers with a high (≥ 5 serves per day) versus low (< 2 serves per day) had 40% and 34% lower COPD risk (Kaluza 2017) [evidence level III]. Two RCTs manipulating fruit and vegetable intake have been conducted in COPD. A 12-week study in 81 COPD patients showed no effect of a high fruit and vegetable intake on FEV_1, systemic inflammation or airway oxidative stress (Baldrick 2012) [evidence level III]. However, a 3-year study in 120 COPD

patients revealed an improvement in lung function in the high fruit and vegetable group compared to the control group (Keranis 2010) [evidence level III], suggesting that longer term fruit and vegetable intake provides a therapeutic effect.

Vitamin E: Vitamin E is a nutrient with antioxidant and anti-inflammatory properties. The ability for vitamin E to reduce biomarkers of oxidative stress in COPD has been demonstrated in one RCT (Daga 2003), but not another (Wu 2007) [evidence level II]. In a large-scale RCT (Women's Health Study, n=38597), the risk of developing chronic lung disease over a 10-year supplementation period was reduced by 10% in women using vitamin E supplements (600 IU on alternate days), suggesting benefit of long-term supplementation (Agler 2011) [evidence level III].

Omega-3 fatty acids: Omega-3 fatty acids have been demonstrated to have diverse anti-inflammatory effects. Two RCTs have examined the effect of omega-3 polyunsaturated fatty acids (PUFA) in COPD. One RCT randomised 32 COPD patients to supplementation with 0.6g omega-3PUFA per day combined with low intensity exercise or a control group for 12 weeks. They reported an improvement in weight, exercise capacity, quality of life and inflammation in the omega-3PUFA/ exercise group compared to controls (Sugawara 2010) [evidence level II]. The other study compared the effects of 8 weeks supplementation with 2.6g omega-3PUFA/day versus a placebo in 102 COPD patients undergoing pulmonary rehabilitation. They reported an increase in exercise capacity in the omega-3PUFA group compared to the placebo group, but there were no effects on muscle strength, FEV_1 or inflammation (Broekhuizen 2005) [evidence level II]. Hence omega-3PUFA supplementation may be a useful adjunct to COPD rehabilitation programs [evidence level II].

Vitamin D/ calcium: Vitamin D regulates calcium homeostasis and bone metabolism, as well as having roles in immune function, inflammation, airway remodelling and muscle strength. Vitamin D is frequently deficient in COPD due to factors including the use of oral corticosteroids, smoking, poor diet and reduced exposure to sunlight due to physical limitations. Vitamin D deficiency was associated with lower lung function and more rapid decline in FEV_1 among smokers in a cohort of elderly men followed for 20 years (Lange 2012) [evidence level III]. In another cohort of 18,507 participants, lung function decline was faster, and COPD risk increased, in individuals with the lowest vitamin D levels (Afzal 2014). Corresponding with low vitamin D levels, osteoporosis is highly prevalent in COPD; in 658 COPD patients in the TORCH study, 23% were osteoporotic and 43% osteopenic (Ferguson 2009). While there are no COPD-specific treatment guidelines for osteoporosis, standard treatment guidelines apply, with patients using corticosteroids requiring treatment according to the guidelines for management of corticosteroid-induced osteoporosis, including daily calcium intake of 1200-1500 mg/day and vitamin D doses of 800-1000 IU per day (Grossman 2010).

A meta-analysis of individual patient data from three RCTs of 468 patients (Jolliffe 2019) was conducted to determine whether vitamin D supplementation reduced exacerbations of COPD. The authors reported that vitamin D supplementation did not reduce overall moderate or severe exacerbations, (adjusted IRR 0.94, 95% CI 0.78 to 1.13; p=0.52; n=469 in three studies, one step IPD meta-analysis), and results were similar for the two-step analysis. There were however, protective effects of vitamin D supplementation in patients considered vitamin D deficient, [those with a baseline 25-hydroxyvitamin D level of <25 nmol/l (1.23 versus 2.10 events per person per year, aIRR 0.55, 95% CI 0.36 to 0.84 n=87 in three studies; within sub-group p=0.006] but not in those with baseline 25-hydroxyvitamin D levels ≥25 nmol/l (2.01 versus 1.94 events per person per year, p=0.71, aIRR 1.04, 95% CI 0.85 to 1.27; p for interaction=0.015, n=382,) [evidence level I].

In people with COPD, vitamin D deficiency should be considered, and supplementation is recommended in deficient patients, particularly those with a 25-hydroxyvitamin D level <25 nmol/l.

Amino Acids: Amino acids are the building blocks of protein and hence an integral component of muscle tissue. Various types of amino acids and their derivatives have been assessed in intervention trials in COPD. In a 12-week RCT in 88 COPD out-patients, those who received essential amino acid supplementation had an improvement in FFM, muscle strength, physical performance and St George

Respiratory Questionnaire (SGRQ) compared to placebo (Dal Negro 2010) [evidence level II]. Another RCT in 28 COPD patients examined outcomes following 12 weeks pulmonary rehabilitation, in patients with or without essential amino acid supplementation, including 5g/day branched chain amino acids. Body weight and FFM increased in the supplemented group compared to controls (Baldi 2010) [evidence level III]. Whey protein, rich in the amino acid cysteine and other essential amino acids, was trialled in a 16-week RCT in COPD patients who were undergoing exercise training for the last 8 weeks of the intervention. This resulted in increased exercise capacity and quality of life compared to placebo, but no changes in inflammation (Laviolette 2010) [evidence level II]. In a 6-week RCT in 16 COPD patients, the amino acid derivative L-carnitine was administered concurrent with pulmonary rehabilitation and resulted in improved exercise tolerance and inspiratory muscle strength compared to the placebo group (Borghi-Silva 2006) [evidence level II]. Conversely, the amino acid derivative creatine, has been shown in meta-analyses to have no effect on muscle strength, exercise tolerance or SGRQ in COPD (Al-Ghimlas 2010) [evidence level I]. In summary, based on level II evidence, essential amino acids, whey protein and L-carnitine may be beneficial in COPD, particularly when combined with exercise training.

Anabolic steroids: While anabolic steroids are not diet-derived, they have a potential role in FFM accretion. A recent systematic review and meta-analysis reported that in COPD patients, 8-26 weeks intervention with anabolic steroids led to improvements in body weight, FFM and SGRQ, while there was no improvement in lung function, handgrip strength or 6-minute walk distance (6MWD) (Pan 2014) [evidence level I]. Hence some specific benefits are apparent, although possible adverse effects also need to be considered.

In summary, level I evidence exists for the use of high calorie nutritional supplementation in COPD, to achieve body weight gain, improve FFM index and exercise tolerance (6MWD), with results most significant for patients who are undernourished. Benefits have been demonstrated for healthy eating patterns, increasing fruit and vegetable intake and supplementing with n-3 PUFA, vitamin E, vitamin D, essential amino acids, whey protein and L-carnitine in COPD, particularly when the supplements are used in combination with a pulmonary rehabilitation program. However, level I evidence supporting the use of these other interventions does not yet exist and further research is needed to confirm efficacy.

Eating strategies

For all COPD patients, a key goal of nutritional management is to eat a balanced diet and to achieve and maintain a healthy weight. Healthy eating means choosing a variety of foods from each of the five food groups every day, in suitable proportions including: vegetables and legumes/beans; fruit; grain foods, mostly wholegrain varieties, such as breads, cereals, rice and pasta; lean meats and poultry, fish, eggs, tofu, nuts and legumes; and dairy products such as milk, yoghurt and cheese. At the same time, foods that are high in saturated fat, sugar and sodium, such as highly processed and takeaway foods, should be limited.

To prevent dyspnoea while eating, various strategies as shown in **Box 7** have been recommended:

Box 7: Eating strategies which may prevent dyspnoea

- Clear the airways of mucus before eating
- If supplemental oxygen is used, make sure this is worn while eating
- Avoid eating large meals, instead eat small nutritious meals and snacks more frequently
- Avoid drinking with meals
- Eat slowly
- Choose softer foods that are easier to chew and swallow, e.g. mashed potato, soups, bananas
- Limit foods that can cause bloating, e.g. beans, onions, cauliflower, soft drinks
- Rest for at least 15-20 minutes after eating in an upright position
- In patients who are underweight, protein and calorie intake can be boosted using high energy, nutrient-rich foods that are easily accessible, such as milk powder, cheese, cream, custard, peanut butter and milkshakes or a nutritionally complete oral supplement (e.g. Sustagen)

- Referral to a dietitian for individual advice may be beneficial

Other tips to avoid aspiration can be found in **O7.6 Aspiration.**

O6.11 Complementary therapies

A systematic review by Guo (Guo 2006) concluded there was no clear evidence supporting the effectiveness of herbal medicines for treating COPD.

Tai Chi is a systematic callisthenic exercise that involves a series of slow and rhythmic circular motions moving from one form to another. The styles of Tai Chi are differentiated by the varying forms or postures, order of movement sequences, focus on muscle work, pace of movement and angle of knee flexion during practice. Tai Chi is most commonly performed in a semi-squat position and is recognised as an exercise of moderate intensity.

A Cochrane Review (Ngai 2016) in people with mild to very severe stable COPD included eight RCTs that compared Tai Chi to usual care. One trial was undertaken in Australia (Leung 2013). The findings provided very low to moderate quality evidence that when compared to usual care, Tai Chi improved functional exercise capacity (6MWD) (6 trials, n=318,) mean difference 29.64m (95% CI 10.52 to 48.77m) and lung function (FEV_1) (4 trials, n=258), mean difference 0.11L (0.02 to 0.20L) [evidence level I]. There were no significant differences between Tai Chi and usual care in dyspnoea or quality of life. No adverse events were reported. Tai Chi has also been shown to result in a significant improvement in body sway and functional balance in patients with COPD (see O7.5 Falls in COPD). Tai Chi did not show superiority when carried out in addition to breathing exercises (3 trials) or pulmonary rehabilitation (1 trial) when compared with these interventions alone.

Tai Chi can be carried out in a wide range of settings and does not require equipment or a large space. For these reasons, Tai Chi may be a potential treatment option when a pulmonary rehabilitation program is not available or if a patient declines referral.

There is some evidence that acupuncture may reduce exertional dyspnoea and improve exercise tolerance in people with moderate to severe COPD [evidence level II]. One placebo-controlled double blinded randomised trial (n=68), carried out in Japan (Suzuki 2012), compared acupuncture applied once a week for 12 weeks and sham acupuncture. Eleven standardised acupuncture points, including those close to the respiratory accessory muscles, were used with treatment lasting 50 minutes each session. Compared to sham acupuncture, real acupuncture reduced dyspnoea at the end of a 6-minute walk test (6MWT) by -3.58 points (95% CI -4.27 to -2.90) on the Borg 0-10 dyspnoea scale and improved 6-minute walk distance (6MWD) by 46 metres in the treatment group when compared to the sham acupuncture group. A possible mechanism proposed for the benefits was an improvement in rib cage mobility and accessory muscle function due to suppressed electromyogram activity of the accessory muscles by the acupuncture. A well designed randomised controlled trial, including sham acupuncture, with blinding of all involved apart from the acupuncturists themselves, demonstrated an 80-metre improvement in 6-minute walk distance as well as improvements in quality of life (Feng 2016). The effect of the lack of blinding of the acupuncturist is uncertain. Further studies are required to evaluate the effects of acupuncture and to determine whether any longer-term benefits of treatment occur.

A meta-analysis of 28 RCTs that included 2130 stable COPD patients using acupuncture therapy (AT) alone or combined with other treatments found that the AT group compared to the control group had significant improvements in FVC (WMD = 0.29 L, 95% CI: 0.22–0.36, P < .001), FEV_1 (WMD = 0.33 L, 95% CI: 0.23–0.43, P < .001), FEV_1% (WMD = 3.30%, 95% CI: 3.30–4.64, P < .001), FEV_1/FVC (WMD = 5.45%, 95% CI: 4.41–6.49, P < .001), 6MWD (WMD = 45.48 m, 95% CI: 28.21–62.16, P < .001) and SGRQ (WMD = −7.79, 95% CI: −12.34 to −3.24, P < .001) (Fan 2023) [evidence level I]. However, subgroup analyses stratified by comparison model (AT combined with other treatments vs

other treatments, AT alone vs sham AT) and treatment duration (≥8 weeks, <8 weeks) showed little between-subgroup differences. Small sample sizes, high risk of bias and unclear definitions of COPD used in individual studies are threats to external validity of the above findings and applications of these to Australian populations should be with caution.

O7. Comorbidities

Comorbid conditions are common in patients with COPD [evidence level III-2, strong recommendation]

Optimal management of any individual patient with COPD should include identification and management of comorbidities and anticipation of increased risks associated with those comorbidities in the presence of COPD (Gershon 2015). An American population based, nationally representative survey of almost 15,000 people demonstrated that patients with self-reported COPD have significantly higher prevalence of important medical co-morbidities (Schnell 2012). Higher prevalence of cardiac disease, stroke, diabetes, depression, poly-pharmacy and mobility problems were reported. The concept of multimorbidity has been increasingly discussed in primary care. Multimorbidity refers to co-occurrence of two or more chronic medical conditions that may or may not directly interact with each other within the same individual. Multimorbidity is the norm rather than the exception in older primary care patients (Mercer 2009). Managing patients with multimorbidity effectively involves taking a patient-centred approach to balancing multiple, and at times competing, priorities. Some of the common comorbidities experienced by people with COPD (e.g. obesity, anxiety, depression, osteoporosis and metabolic disease) are associated with poorer physical performance as measured by the distance walked on the 6-minute walk test (6MWT) (Li 2014). Both comorbid chronic respiratory conditions and comorbid psychiatric disorders have been found to be associated with a higher risk of frequent (≥ 2 per year) exacerbations (Westerik 2017).

O7.1 Increased risks from comorbidities in the presence of COPD

Using a large dataset generated from 311 general practices in the UK, Feary et al (Feary 2010) found COPD was associated with increased risks of cardiovascular disease (OR 4.98, 95% CI 4.85 to 5.81), stroke (OR 3.34, 95% CI 3.21 to 3.48) and diabetes mellitus (OR 2.04, 95% CI 1.97 to 2.12). In the follow-up analyses, after adjusting for confounding by sex and smoking status and stratifying for age, the greatest increase in the rate of acute arteriovascular events was found in the youngest age groups. Further supporting these findings, a prospective study examining in hospital mortality in patients with acute ST segment elevation myocardial infarction found that COPD was a strong independent risk factor for death (6.3% versus. 3.4% p=0.006) (Wakabayashi 2010). The most common comorbidities differ between men and women. Specifically, women are more likely to demonstrate anxiety and depression than men (Aryal 2014) [evidence level III-2]. In a cohort study in Spain, COPD was associated with an increased number of comorbidities, occurring at an earlier age (on average 10 to 20 years earlier) compared to non-COPD controls (Divo 2018), suggesting accelerated ageing [evidence level III-2]. A retrospective cohort study of COPD admissions in over 2,000 male US army veterans found that comorbidity was associated with a higher 30-day readmission and mortality rate and with lower rates of corticosteroid and antibiotic use whilst in hospital (Spece 2018).

A population-based cohort study in Ontario, Canada using linked datasets and including all patients aged 35 years or older living in Ontario who underwent intermediate to high-risk elective non-cardiac surgeries from April 2005 to March 2019, found that patients with COPD had lower survival and greater health care costs in the year after scheduled surgery than patients without COPD. Within 30 days after surgery, patients with COPD were more likely to die (n=5873, 3.4%) than those without (n=9429, 1.2%) (Sankar 2023) [evidence level III-2]. Perioperative patient care should include comprehensive assessment and treatment tailored not only to COPD, but also to management of concomitant conditions and surgical disease.

O7.2 Cardiac disease

COPD patients possess an increased burden of cardiovascular disease (CVD), cardiac arrhythmia and heart failure when compared to the normal population. Chen's systematic review and meta-analysis pooled the results from 29 datasets and reported that COPD patients were more likely to be diagnosed with cardiovascular disease (ischaemic heart disease, dysrhythmia, heart failure, pulmonary circulatory disorders and arterial diseases) than controls (OR 2.46, 95% CI 2.02 to 3.00, p<0.0001). This result was mainly driven by angina (OR 8.16) (Chen 2015) [evidence level III-2]. Feary's of 1,204,100 patients who were followed for a median of 895 days in the primary care setting, also demonstrated an association of COPD with increased rates of first myocardial infarction (MI) (HR 10.34, 95% CI 3.28 to 32.6), and stroke (HR 3.44, 95% CI 0.85 to 13.84), stratified by age and adjusted for gender and smoking status (Feary 2010) [evidence level III-2]. Subsequently, subanalysis of the Canadian Cohort Obstructive Lung Disease (CanCOLD) data (n=1561) has demonstrated a higher prevalence (adjusted OR 1.55 (1.04-2.31), p=0.033) and incidence (HR 2.09 (1.10-3.98, p=0.024)) of CVD (defined as ischaemic heart disease or heart failure) in those with COPD ((Krishnan 2023) [evidence level III-2).

CVD is an important cause of mortality and hospital presentations in COPD, even affecting those with mild disease. In addition to the high individual prevalence's of COPD and CVD, these conditions share conventional risk factors of advanced age, smoking, low socioeconomic status (SES) and sedentary lifestyle. Systemic inflammation, autonomic dysregulation, hypoxia, acidosis and haemodynamic derangements are likely to also contribute (Fuschillo 2012). Independent of smoking and other risk factors, impaired lung function per se is a major risk factor for CVD and arrhythmia (on par with hypercholesterolaemia), with the relationship being strongest for fatal CV events (Hole 1996, Agarwal 2012) [evidence level III-2]. Arterial stiffness has been proposed as one potential mechanism for this excess of CVD as it strongly predicts CVD events and mortality. In COPD, arterial stiffness increases during exacerbation and is associated with COPD severity (measured as airflow limitation or degree of emphysema), inflammation, oxidative stress and sympathetic nervous system (SNS) tone. COPD also predicted lipid core (OR 2, 95% CI 1.25 to 3.69, p=0.0058), plaque component vulnerable to rupture (Lahousse 2013) [evidence level III-2], which increases risk of acute CVD events.

One review (Vivodtzev 2014) [evidence III-2] demonstrates results across multiple studies showing increased arterial stiffness (n=18), endothelial dysfunction (n=4) and carotid intima-media thickness (n=3) in COPD patients compared to controls. Several trials showed a gradated effect, with an increase in COPD patients compared with non-COPD smokers, and in smokers compared with healthy non-smokers. This group also summarised preliminary data suggesting that current therapeutic interventions may impact on increased arterial stiffness; included studies reported a statistically significant improvement in arterial stiffness after standard pulmonary rehabilitation, after treatment with combination ICS/LABA or LAMA, and possible improvement with supplemental oxygen.

Konecny's group sought to explore cardiac arrhythmia as a potential source of the excess CVD mortality in COPD in a retrospective record review of 7,441 participants who underwent 24-hour Holter monitoring and spirometry during the course of clinical assessment. The 3,121 (49%) COPD patients demonstrated more arrhythmias than those without COPD; atrial fibrillation/flutter were identified in 23.3% versus 11% (p<0.0001), and non-sustained ventricular tachycardia in 13% versus 5.9% (p<0.0001). Both results remained statistically significant after adjustment for multiple confounders (Konecny 2014) [evidence level III-2]. The study population was a highly select group, which potentially limits the broad application of the results. However, the study reports a "COPD dose effect", based on spirometry criteria, which adds weight to its conclusions.

Medications used in the treatment of COPD also have potential to impact cardiac morbidity and mortality, due to intrinsic effects on chronotropy and muscle action potentials or due to side effects such as hypokalaemia. Medications implicated include methylxanthines, beta-agonist and antimuscarinic bronchodilators. Macrolide antibiotics, which in chronic dosing have been shown to reduce respiratory exacerbations, have been added to the list, due to an association with QT

prolongation and bradycardia. Randomised controlled trials (RCT) of chronically dosed azithromycin have not demonstrated adverse cardiac effects in the clinical setting, particularly when known drug interactions are avoided. Likewise, for most inhaled bronchodilators, when used at therapeutic dose in stable COPD, adverse cardiovascular effects are rare. However, a systematic review and meta-analysis of RCTs in patients with moderate to severe COPD using inhaled LAMA combined with LABA (Yang 2023b) [evidence level I) reported an excess of major adverse CV events (MACE) (LAMA/LABA 1.2% vs 0.9% control, RR 1.24, 95% CI 1.06-1.44; triple therapy 1.5% vs 1.3% control, RR 1.27, 95% CI 1.03-1.58). This finding should be considered in conjunction with the existing evidence base (see O1.2.3 LAMA/LABA) for the efficacy of such medication to prevent COPD exacerbations, improve symptoms and quality of life in well-designed prospective RCTs powered to measure these outcomes. Similarly, the challenges of accurate MACE adjudication, inconsistency in the definitions of MACE across trials and the reduced reliability of data extraction processes from safety reporting should be borne in mind. Importantly, none of the individual trials identified was powered or designed to investigate CV outcomes. Hence, whilst these results provide grounds for careful individualised cardiovascular risk evaluation for patients with COPD, they do not necessitate change to current treatment recommendations. Despite being common clinical practice, there is even less evidence about the safety of high dose, combined bronchodilator therapy in the setting of exacerbation of COPD.

Markers of cardiac involvement during an exacerbation of COPD may be an important determinant of short-term prognosis. In a study of 250 consecutive admissions with an exacerbation of COPD and no evidence of acute cardiac disease over 12 months, elevated NT-pro BNP >220 pmol/L and troponin T >0.03 were present in 27% and 16.7% of patients and predicted 30-day mortality (OR 9, 95% CI 3.1-26.2) and (OR 6.3, 95% CI 2.4 – 16.5), respectively, after adjustment for other mortality predictors. Elevated troponin T level lost significance with both cardiac biomarkers included in the model, although the mortality association was additive for patients in whom both biomarker levels were elevated (Chang 2011) [evidence level III-2]. Another prospective cohort study (Hoiseth 2012, Li 2020) [evidence level III-2] reported results for 99 COPD patients with 217 exacerbations and a median follow up duration of 1.9 years and found NT-pro BNP to be an independent risk factor for mortality after an exacerbation of COPD. Dividing NT-pro BNP levels into tertiles, mortality rates were 8.6, 35 and 62 per 100 patient years (age-adjusted log-rank p<0.0001) and, compared to the lowest tertile, adjusted HR for death were 2.4 (95% CI 0.95 to 6.0) and 3.2 (95% CI 1.3 to 8.1) in the intermediate and highest tertiles, respectively.

High sensitivity troponin (hs-Tn) levels have now been associated with increased mortality in prospective cohort studies in stable COPD (Neukamm 2016, Waschki 2019) [evidence level III-2]. In a well characterised cohort of 2085 COPD patients, Waschki and colleagues report baseline hs-Tn level to be independently associated with all-cause mortality at three years, whether considered as a continuous variable [log hs-TnI, HR 1.28 (95%CI, 1.01 to 1.62)] or dichotomised at 6ng/L [HR 1.63 (95%CI, 1.10 to 2.42)] (as hs-TnI levels greater than 6ng/L identify individuals in the general population who are at high risk of death during follow-up) (Waschki 2019). Similarly, in a population with stable COPD and cardiovascular risk or disease, high sensitivity troponin I levels were associated with increased cardiac events [adjusted HR 3.7 (1.3 to 10.1) p=0.012] and mortality [HR 20.1 (2.4 to 165.2), p= 0.005]. This effect was seen at troponin I >5ng/L; well below the threshold for diagnosis of coronary events (Adamson 2018) [evidence level III-2].

Post hoc analysis of the SUMMIT cohort data (Kunisaki 2018) confirms a significantly increased risk of CVD events, especially within 30 days following a COPD exacerbation. The study population was selected for CVD or CVD risk factors but does represent the "real patients" seen in clinical practice. The authors make a good case for heightened vigilance for CVD events in the immediate post-exacerbation period.

Preliminary research suggests that cardiac pathology contributes to a proportion of exacerbations of COPD. A small study (Bhatt 2012) [evidence level III-2] investigated a potential role for arrhythmia in an exacerbation; comparing ECG indices during an exacerbation with stable state. They reported

that P wave duration was more variable during exacerbation. Moreover, "frequent exacerbator patients" (defined as two or more exacerbations of COPD within 12 months) had increases in ECG P-R interval during stable state compared with "infrequent exacerbators". Although methodology was not robust, the results probably justify further research into this issue. In addition, Abusaid et al proposed a contributory role for diastolic dysfunction (DD) in an exacerbation of COPD (Abusaid 2009) [evidence level III-2]. Their retrospective single centre cohort study reported that diastolic dysfunction was associated with prolonged length of hospital stay (4.02 versus 3.24 days, p=0.005) and increased frequency of hospitalisation for an exacerbation (1.28 versus 0.67 per patient year, p=0.0067) in the absence of traditional precipitating factors.

Donaldson et al (Donaldson 2010) sought to quantify the increased risk of cardiac adverse events associated with an exacerbation of COPD. Using self-controlled case series methodology, they identified 25,857 COPD patients and their cardiac adverse events (524 myocardial infarctions (MI) in 426 patients and 633 ischaemic strokes in 482 patients) using health care database diagnostic codes and defining an exacerbation by receipt of systemic corticosteroid course (at minimum daily dose) and/or specified antibiotics. Comparing cardiac adverse events incidence during the period immediately after an exacerbation with that in stable state and adjusting for seasonality, they demonstrated increased risk for MI (RR 2.27, 95% CI 1.1 to 4.7) in the five days following exacerbation onset, if combined antibiotics and steroids were required and increased risk for stroke (RR 1.26, 95% CI 1.0 to 1.6) for 49 days, for an exacerbation requiring antibiotics only [evidence level III-2].

Two studies have attempted to evaluate the extra morbidity burden conferred by heart disease in COPD [evidence level III-2]. De Miguel Diez (de Miguel-Diez 2010) recruited patients meeting diagnostic criteria for stable COPD from the Spanish primary health care setting and assessed chronic morbidity and health resource utilisation according to the presence of ICD-9 codes for heart disease. Of 9,390 COPD patients, 18.8% had documented heart disease. Compared to patients without heart disease this group had worse lung function, worse quality of life (QoL), required more respiratory medications, consumed more health resources and generated greater expenses - differences which were all statistically significant. The authors identified admission duration as a major contributor to increased costs in these patients [evidence level III-2]. In the study by Patel's group (Patel 2012), data from the London Cohort (1995 – 2009), comprising prospectively collected exacerbation data via symptom diaries from 386 patients with COPD (as defined by spirometry) and at least 12 months' diary data. Health status assessment occurred whilst in stable phase and comparison was made regarding frequency and duration of an exacerbation of COPD between patients with and without ischaemic heart disease (IHD). The 16% of the cohort with IHD scored worse on QOL assessment (St George Respiratory questionnaire (SGRQ)), MRC dyspnoea scale and 6-minute walk distance. There was no difference in frequency of respiratory exacerbations or the need for antibiotics and systemic corticosteroid therapy. However, patients with IHD recovered more slowly and so endured more days with increased levels of symptoms. The patients did not differ in COPD treatments received, but the authors provided no information on treatments received for IHD [evidence III–2].

Conversely, two studies have looked at the impact of COPD on outcomes after first MI (Bursi 2010, Andell 2014) [evidence level III–2]. Prevalence of clinically diagnosed COPD in these studies was 12% and 6%, respectively. In Bursi's American cohort, COPD prevalence increased significantly over time, and was associated with increased mortality (adjusted HR 1.3, 95% CI 1.1 to 1.54), independent of age, traditional indicators of poor prognosis and comorbidities. Likewise, Andell's group reported worse outcomes for COPD patients in their Swedish cohort: one year mortality [HR 1.14 (1.07 – 1.21)], and development of heart failure [HR 1.35 (1.24 – 1.47)]. Bursi's group found that the association of COPD with survival remained unchanged over time, despite an overall decline in mortality after MI (seen with improvements in medical care). The difference in clinical presentation and therapeutic interventions received reported by Andell's group, may partially explain the discrepant outcomes seen in COPD patients (COPD patients were more likely to present with atypical symptoms, less likely to

undergo percutaneous revascularisation procedures or to receive secondary prevention medications).

O7.2.1 Heart failure

The diagnosis of heart failure coexisting with COPD is complicated by symptom overlap and the technical challenges of echocardiography in COPD. The natriuretic peptides, including BNP and NT-pro BNP, can assist in identifying heart failure in the setting of acute breathlessness, but do not exclude comorbid COPD, and currently have an unclear diagnostic role in stable disease. The prevalence of heart failure in COPD patients is estimated at 20 to 32%. For the converse situation in heart failure, COPD prevalence has been previously quoted as 10 to 33%. A prospective multicentre sub study of patients admitted with heart failure (Iversen 2008) [evidence level III-2] confirmed COPD in 35% of participants using spirometry. Self-reported COPD diagnosis had poor sensitivity to identify these individuals. Prevalence of COPD was higher in those heart failure patients with preserved left ventricular ejection fraction (LVEF), but was also substantial in those with reduced LVEF (41% versus 31%, p = 0.03). Potential mechanisms contributing to the high rates of heart failure in COPD include coronary artery disease (CAD), hyperinflation, sympathetic nervous system and renin-angiotensin system activation, pulmonary hypertension and right heart dysfunction. A study by Labaki et al found levels of the natriuretic peptide, NT-proBNP to be an independent risk factor for COPD exacerbations (Labaki 2018).

Barr and colleagues investigated a subgroup from the Multi-ethnic Study of Atherosclerosis (MESA): a multi-centre, prospective, cross-sectional study of CVD. The group initially reported a linear relationship between extent of emphysema and impairment of left ventricular filling, reduction of stroke volume and of cardiac output, without a threshold effect, in "healthy" patients prospectively assessed for cardiac disease with magnetic resonance imaging (MRI) (Barr 2010) [evidence level III-2]. The same association was not present for LVEF. Smoking status was an effect modifier, with a greater effect seen for current smokers. Similar relationships were obtained for measures of airflow limitation. Mechanisms have been further explored (Stone 2016) in a randomised crossover trial of combination ICS/LABA (fluticasone furoate/vilanterol) versus placebo in patients with at least moderate COPD and bronchodilator-responsive gas trapping. Compared with placebo, active treatment was associated with significantly reduced residual volume -429 ml, 95% CI 2.74-8.91, improved right and left ventricular filling indices and cardiac index. In COPD, heart failure adversely impacts on morbidity and prognosis. A prospective cohort study (Boudestein 2009) [evidence level III-2] further clarifies this relationship; Boudestein's group sought to quantify heart failure and its prognostic implications in 405 Dutch general practice patients identified as having COPD. Extensive diagnostic testing revealed occult heart failure in 20.5%; half of which half was systolic, half diastolic and none was cor pulmonale. Similar proportions were found in the subset of 244 patients meeting GOLD criteria for COPD. Not unexpectedly, comorbid heart failure proved a strong predictor of all-cause mortality over the mean follow up duration of 4.2 years for the whole cohort (adjusted HR 2.1, 95% CI 1.2-3.6, p=0.01) and for "GOLD COPD patients" (adjusted HR 2.0, 95% CI 1.0-3.7, p=0.04).

Since COPD and heart failure present with similar symptoms and frequently do coexist, the clinical implication is that the opportunity for intervention will be missed unless both diagnoses are specifically sought using careful clinical assessment in conjunction with appropriately directed investigations.

O7.2.2 Safety of beta-blockers

Beta-blockers have well established survival benefits in heart failure and after myocardial infarction and have been long used in coronary artery disease and hypertension but have been considered contra-indicated in patients with COPD. A Cochrane systematic review identified 20 RCTs of cardio-selective beta-blockers which examined lung function and respiratory symptoms in 278 patients with COPD (Salpeter 2005, Salpeter 2002) [evidence level I]. Eleven studies were of single dose and nine were of prolonged treatment (mean 3.7 weeks, range two days to 12 weeks). The beta blockers included atenolol, metoprolol, bisoprolol, practolol, celiprolol and acebutolol and were used at

therapeutic doses. There was no significant overall change in FEV_1, respiratory symptoms or the response to inhaled $beta_2$ agonists. The authors concluded that cardio-selective beta-blockers were safe and should not be withheld, even in patients with severe airflow limitation. However, even with pooled data, the absolute patient numbers were small and failed to represent minority groups such as females and the elderly. The longest duration included trial was 12 weeks, and so the meta-analysis provides little guidance about long-term safety and potential morbidity of prolonged beta-blocker use in COPD.

Despite a paucity of evidence to suggest harm, beta-blockers are still under-utilised in COPD for guideline-based indications such as heart failure with reduced ejection fraction (HFrEF) (Lipworth 2016) [evidence level III-2]. Australian data from a COPD cohort hospitalised for a COPD exacerbation also reflects this (Neef 2016) [evidence level III-2] as does a similar New Zealand study (Parkin 2020) [both evidence level III-2]. In contrast, Parkin et al report much higher prescription rates for other medications used to reduce cardiovascular risk, such as aspirin and hydroxymethylglutaryl-CoA reductase inhibitors (statins).

A number of observational studies also lend confidence to beta-blocker prescribing in COPD patients. In Du et al's meta-analysis (Du 2016) of 15 cohort studies with follow up ranging from one to 7.2 years beta-blocker treatment was associated with reduced mortality (RR 0.72, 95% CI 0.63 to 0.83) and exacerbation risk (RR 0.63, 95% CI 0.57 to 0.71). Despite significant heterogeneity, sensitivity analysis did not change the outcome [evidence level III-2]. Moreover, beta-blocker treatment did not diminish the beneficial effects of inhaled treatments on post bronchodilator FEV_1 or COPD exacerbations (Dransfield 2018). However, a prospective randomised trial of metoprolol to prevent exacerbations in moderate to severe COPD (Dransfield 2019) reported no benefit (adjusted HR 1.12, 95% CI 0.88 to 1.42), after early termination for futility and potential safety concerns about increased respiratory symptoms and severe exacerbations (adjusted HR 1.91, 95% CI 1.29 to 2.83) in the active treatment group. It is important to note that patients with heart failure and recent intervention for ischaemic heart disease were excluded. Due to the study's selection criteria, these results should only apply to patients who have no therapeutic indication for beta-blockers. Prospective data for COPD patients with cardiac disease are still needed.

O7.2.3 Stroke

The Rotterdam cohort study of 13,115 participants, studied for up to 22 years, included 1,566 patients with COPD, who had a 20% higher incidence of stroke during the study, particularly following an exacerbation of COPD. However, this association was no longer significant after adjusting for smoking, which indicates that smoking is a common risk factor for both conditions. The risk may have been higher, but COPD patients appear to be dying due to cardiovascular disease first, or early attention to cardiovascular disease attenuates the risk of stroke (Portegies 2016). In a 2017 meta-analysis that included eight longitudinal observation studies, patients with COPD had a significantly increased stroke risk compared to controls (HR 1.30, 95% CI 1.18 to 1.42) (Kim 2018).

O7.2.4 Statins

Despite historic cohort studies suggesting a potential benefit of statins in COPD, a meta-analysis of eight randomised controlled trials including 1,323 predominantly male patients with COPD showed no change to mortality, exacerbation rates, lung function or quality of life with statin therapy compared to placebo [evidence level I] (Walsh 2019). Several of the larger trials included in this meta-analysis excluded patients with a conventional indication for statin therapy. Based on this data there is no evidence to prescribe statins in patients with COPD outside of conventional indications.

O7.2.5 Coronary revascularisation procedures

Patients with COPD are at increased risk of death and complications following cardiac surgery [evidence level III-2]. A study identified 1169 patients undergoing coronary artery bypass grafts and/

or valve replacement at one US centre who had preoperative lung function tests (Adabag 2010). Operative mortality was 2% in those with no or mild airflow limitation, compared to 6.7% among those with moderate or severe airflow limitation ($FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ predicted). Postoperative mortality was 3.2 (95% CI 1.6-6.2) fold higher among those with moderate or severe airflow limitation and 4.9 (2.3-10.8) fold higher among those with diffusing capacity < 50% predicted. These patients were also more likely to require mechanical ventilation for > 48 hours and stayed longer in intensive care and hospital than those with normal lung function.

COPD and COPD severity as defined by spirometry were also associated with increased mortality (OR 1.79, 95% CI 1.63 to 1.96), cardiac mortality (OR 1.57, 95% CI 1.35 to 1.81) and post-discharge MI (OR 1.3, 95% CI 1.14 to 1.47) after percutaneous coronary intervention in multivariate analysis, despite equivalent procedural success and complication rates (Konecny 2010) [evidence level III-2]. In this study, data prospectively collected for 14,346 patients (2001 COPD and 12345 non-COPD) from a single centre between January 1995 and August 2008 were subjected to retrospective cross-sectional analysis. COPD patients were identified by ICD – 9 diagnostic codes and did possess significantly more manifestations of CVD, including heart failure, than the control group. Unfortunately, preoperative lung function data was only available in 60% of the COPD group.

O7.3 Osteoporosis

Patients with COPD are at increased risk for fracture due to the disease itself, the use of high dose corticosteroids and coexisting risk factors such as hypogonadism (induced by corticosteroid therapy itself in high doses in men and women), immobilisation reduced muscle mass and other factors. These patients may have reduced bone mineral density (BMD) due to a reduction in bone formation and perhaps increased bone resorption, the latter being primarily due to the underlying disease itself.

A systematic review of 58 studies of heterogeneous quality limited by largely cross-sectional designs (8,753 patients with COPD) found a mean prevalence of 38% (95% CI 34-43) for osteoporosis in patients with COPD, with increasing odds ratios for osteoporosis associated with lower BMI and sarcopenia (Chen 2019), indicating that people with COPD are at special risk of osteoporotic fracture. The overall OR for osteoporosis in COPD was 2.83 (95% CI 2.00-4.03) with particular risk (OR 4.26, 95% CI 1.07- 16.99) for those with BMI of < 18.5 kg/m2. Although there is conflicting evidence as to the strength of a causative relationship, oral or inhaled high dose corticosteroids, coexisting risk factors such as hypogonadism (induced by corticosteroid therapy itself in high doses in men and women), physical inactivity, repeated periods of immobilisation from hospital admissions, and low dairy food intake may be potential contributory risk factors. Assessment of vitamin D status, and other risk factors such as coexisting illnesses that may influence the skeleton (e.g. primary hyperparathyroidism) may also be required, with bone densitometry to investigate further.

Patients with vertebral compression fractures, visualised on a lateral chest x-ray, have been demonstrated to have more frequent admissions, longer length of hospital stay, and increased mortality in the two years after admission (Pascual-Guardia 2017) [evidence level III-2]. A meta-analysis by Kakoullis et al (2021) included 27 studies with a range of study designs, with 7662 participants and defined osteoporosis as a T-score of -2.5 SD where available. Participants with osteoporosis and or vertebral compression fractures were found to be older (3.17 years, 95% CI 2.14-4.19), lower BMI -3.15 (95% CI -4.41 to -1.88) and more likely to be female, which are recognised general population risk factors. These participants had a mortality OR of 2.40 (95% CI 1.24-4.64) and lower FEV_1 -0.41L (95% CI -0.59 to -0.24) with a lower FEV_1/FVC ratio. The authors note that it is likely that osteoporosis is a marker of severity of COPD or patient frailty, with surrogate associations with the outcomes demonstrated, rather than a direct cause of increased airflow obstruction or death (Kakoullis 2021) [evidence level I]. Pro-active screening and preventative treatment of osteoporosis are recommended.

A large systematic review and meta-analysis to determine the fracture risk of people with COPD who were using ICS (Peng 2023) [evidence level I]. Included in the review were 44 RCTs involving 87,594

patients. Meta-analysis showed that there was a significantly increased risk of fracture risk in people with inhalers containing ICS compared to inhalers without ICS (RR, 1.19; 95% CI 1.04 to 1.37; p = 0.010), and the risk was great in people using dual bronchodilator/ICS inhalers (RR 1.30; 95% CI 1.10 to 1.53; p = 0.002) and triple therapy (RR 1.49; 95% CI, 1.03 to 2.17; p = 0.04). Other factors that were associated with increased risk, identified in subgroup analyses were treatment duration ≥ 12 months, budesonide therapy, fluticasone furoate therapy, older age, and disease severity (Peng 2023) [evidence level I]. Being aware of these findings in addition to a patient's other risk factors for osteoporosis should underpin clinical decision-making relating to bone mineral density screening.

Guidelines on the currently recommended screening, prevention and treatments of osteoporosis, including corticosteroid-induced osteoporosis are available elsewhere including the eTG guidelines on Osteoporosis and minimal trauma fractures: https://tgldcdp.tg.org.au/guideLine?guidelinePage=Bone+and+Metabolism&frompage=etgcomplete.

O7.4 Frailty in COPD

Frailty is a loss of resilience which means people affected may be physically or mentally vulnerable and less able to recover quickly after illness or a stressful event (Clegg 2013). A consequence is that people who have frailty have decreased function, health status and require additional health and social care (Roe 2017).

Frailty can be assessed in a number of ways including a phenotypic approach or by noting the accumulation of deficits. The phenotypic approach is defined by the presence of three or more of the following five criteria: unintentional weight loss, self-reported exhaustion, weakness, slow gait speed, and low energy expenditure (Fried 2001). Alternatively, the accumulation of deficits approach is based counting the number of symptoms, diseases, conditions, and disability, which are used to calculate a frailty index (Rockwood 2005), with higher scores indicating more frailty.

Frailty affects older people and particularly those with chronic conditions such as COPD. Although there is no unified definition of frailty, a number of studies have demonstrated increased frailty in COPD using different measurement tools including those based on phenotypes (Lahousse 2016b) or accumulation of deficits (Gale 2018). A systematic review of frailty in COPD including 27 studies demonstrated from pooled data that 19% of patients were frail and 56% were pre-frail (Marengoni 2018). Overall, patients with COPD have double the risk of becoming frail and frailty has been associated with poorer lung function and reduced health status, increased length of stay following exacerbations (Bernabeu-Mora 2017) and increased mortality (Galizia 2011). An additional meta-analysis (Hanlon 2023) [evidence level I] on frailty, again highlighted the high prevalence of frailty in people with COPD, according to a range of frailty measures, associated with a clinically significantly increased risk of adverse outcomes. Proactive identification of frailty can identify candidates for targeted intervention such as pulmonary rehabilitation, with evidence of frailty reduction in at least one study when participants completed a programme (Maddocks, 2016).

The mechanism underlying increased frailty in COPD is likely to be multifactorial. COPD affects older adults in whom other health conditions are more prevalent. In addition, COPD is associated with inflammation that affects multiple body systems (Vanfleteren 2013), increased exacerbations, as well as lifestyle factors such as smoking and reduced physical activity (GOLD 2023), all of which may increase risk of frailty.

Although frailty can be difficult to manage, there is evidence from systematic reviews that exercise can be beneficial for physical functioning, cognitive and psychological wellbeing in frail older adults (Silva 2017). In addition, in older adults with frailty, multifactorial interventions including exercise and nutritional support can minimise physical decline and can be cost effective for health care providers (Apostolo 2018). In frail patients with COPD hospitalised for an acute exacerbation, exercise resulted in improvements in strength and balance (Torres-Sanchez 2017). Frail patients with COPD have also been shown to benefit from pulmonary rehabilitation with improvements in breathlessness, exercise

performance, physical activity level and health status (Maddocks 2016). However, frail patients were twice as likely to not complete pulmonary rehabilitation. Given that smoking is a predictor of frailty (Kojima 2015) and patients with frequent exacerbations have increased risk of frailty (Lahousse 2016b), smoking cessation as well as minimisation of exacerbations are additional key therapeutic targets in COPD.

In a retrospective cohort study using publicly available Health and Retirement Study data frailty prevalence measures such as BODE and Fried indices, were substantially higher in COPD than in those without COPD. Prevalence of frailty among those aged 50–64 years using the Fried index was 7.5%, and 11.0% for age ≥65. These measures identified patients with increased risk of poor outcomes including more than doubling of mortality, as well as increased hospital admissions and nursing home placement over the following 2 years (Roberts 2022) [evidence level III]. A study of 1,162 participants with COPD and 3,465 participants without COPD by Lee et al (2022) also supported the use of a bundle of physical frailty measurements in addition to lung function and dyspnoea scores in multidimensional evaluation of COPD. The addition of frailty measures highlighted the associations with the inability to perform daily tasks and mortality [evidence level III-2].

In summary, frailty is common in COPD and associated with poorer health outcomes, hospital admissions and failure to complete pulmonary rehabilitation. Measuring frailty is useful in COPD and may identify vulnerable patients and allow earlier interventions such as comprehensive medical or geriatric review and pulmonary rehabilitation to minimise the development and impact of frailty on patients and carers as well as health and social care services.

O7.5 Falls in COPD

Accidental falls are an important and underestimated problem in people with COPD. As in older adult populations, falls in people with COPD are associated with increased injury-related mortality and risk for hip fractures, which impose a substantial economic burden on health care systems worldwide (Berry 2008).

Chronic obstructive pulmonary disease was the second most prevalent condition among patients presenting to emergency departments with hip fractures (Johal 2009). A higher risk of hip fractures has been found in patients with COPD in comparison to a matched non-COPD sample (hazard ratio 1.78, $p<0.001$). In addition, patients who used inhaled bronchodilators and inhaled corticosteroids (n=10,362) had an even higher falls risk (HR 2.04, 95% CI 1.72-2.41, $p<0.001$) in comparison to those not using inhalers (n= 5,877, HR 1.63, 95% CI 1.40-1.89, $p<0.001$) (Huang 2016). Importantly, one study with robust methodology suggests that a history of falls in the six months prior to hospital admission is the strongest predictor of all-cause mortality in patients with severe COPD (odds ratio 3.05, 95% CI 1.40-6.66, $p<0.005$) (Yohannes 2016). A systematic review (Oliveira 2021) has reported a falls incidence rate in COPD of 1.17 to 1.49 falls/person-year. In a large 4-year follow-up cohort study, the incidence rate of falls in patients aged ≥35 years who had a new diagnosis of COPD was higher compared with a matched cohort of non-COPD patients in primary care. Patients with COPD were 55% more likely to have a fall compared to people without COPD (adjusted HR 1.55, 95% CI 1.50- 1.59) (Hakamy 2018).

The risk factors for falls identified in the COPD population are similar to those in older adults: advanced age, previous fall history, female gender, increased number of medications and comorbidities (Roig 2011). Risk factors specifically related to the physical and psychosocial effects of COPD include muscle weakness, impaired postural balance, use of supplemental oxygen, increased 'fear of falling' and heavy smoking history (Oliveira 2015, Beauchamp 2009). Of these, polypharmacy (use of ≥ 5 medications) is particularly important in those with multiple comorbidities, and was identified as a falls risk factor in two prospective studies in people with COPD (Oliveira 2015, Roig 2011). The relationship between medication type and falls risk is well established in older adults (Park 2015). Particularly the use of the falls risk increasing drugs (FRID's) including sedatives, hypnotics, antidepressants and benzodiazepines (Park 2015). Of note, patients with COPD were 47% more likely

to have a fall than non-COPD patients when adjusting for smoking status, use of antidepressants and diuretics (adjusted HR (aHR) 1.47, 95% CI 1.43-1.51) (Hakamy 2018). The adverse effects of systemic corticosteroids on muscle strength (Decramer 1994) and consequently balance (Beauchamp 2012) could also indirectly contribute to increased risk of falling in COPD.

The fact that COPD, consistent with many other chronic diseases, is associated with frailty and increased falls risk suggests that these patients may benefit from generic falls prevention programs designed for older adults. In addition, the findings of specific risk factors for falls in patients with COPD highlights the need for specific preventive interventions in this patient population. The importance of balance training has been increasingly recognised in COPD as an important fall's prevention strategy. For instance, Tai Chi exercises, which are characterised by posture alignment, weight shifting and circular movements that incorporate elements of muscle endurance and strengthening, balance, relaxation and breathing, have demonstrated significant improvement in body sway and functional balance in patients with COPD (Leung 2013). The benefits of specific balance training added to a 6-week conventional pulmonary rehabilitation program have also been documented in a RCT (Beauchamp 2013). Specific balance training including progressive stance tasks, transition, gait and functional strengthening exercises was superior to PR alone in improving functional balance in patients with COPD (Beauchamp 2013).

Given the higher fall frequency and prevalence of hip fractures in people with COPD, falls prevention programs targeting modifiable risk factors should be considered for this patient population.

O7.6 Sleep-related breathing disorders

COPD has adverse effects on sleep quality, resulting in poor sleep efficiency, delayed sleep onset, multiple wakening's with fragmentation of sleep architecture, and a high arousal index. Arousals are caused by hypoxia, hypercapnia, nocturnal cough and the pharmacological effects of methylxanthines and b-adrenergic agents (Phillipson 1986). Intranasal oxygen administration has been shown to improve sleep architecture and efficiency, as well as oxygen saturation during sleep (Meecham Jones 1995).

Indications for full diagnostic polysomnography in patients with COPD include persistent snoring, witnessed apnoea's, choking episodes and excessive daytime sleepiness. In patients with daytime hypercapnia, monitoring of nocturnal transcutaneous carbon dioxide levels should be considered to assess nocturnal hypoventilation. Patients with COPD with a stable wakeful PaO_2 of more than 55mmHg (7.3kPa) who have pulmonary hypertension, right heart failure or polycythaemia should also be studied. Overnight pulse oximetry is also useful in patients with COPD in whom long-term domiciliary oxygen therapy is indicated (stable PaO_2 <55mmHg, or 7.3kPa) to determine an appropriate oxygen flow rate during sleep.

The overlap syndrome: The combination of COPD and obstructive sleep apnoea (OSA) is known as the "overlap syndrome" (McNicholas 2009) [evidence level III-2]. The prevalence of COPD in unselected patients with OSA is about 10%, while about 20% of patients with COPD also have OSA (Chaouat 1995). Patients with COPD who also have OSA have a higher prevalence of pulmonary hypertension and right ventricular failure than those without OSA (Chaouat 1995). Findings of a systematic literature review suggest that COPD patients with overlapping OSA have higher mortality and more frequent exacerbations of their disease than COPD patients without OSA (Shawon 2017). Continuous positive airway pressure (CPAP) treatment reduced mortality and exacerbation rates (Marin 2010) [evidence level III-2]. While oxygen administration may diminish the degree of oxygen desaturation, it may increase the frequency and severity of hypoventilation and lead to carbon dioxide retention.

As in other patients with OSA, weight reduction, alcohol avoidance and improvement of nasal patency are useful in those with COPD. Nasal CPAP is the best method for maintaining patency of the upper airway and may obviate the need for nocturnal oxygen. If nasal CPAP is not effective, then nocturnal

bi-level positive airway pressure ventilation should be considered, although the benefits of this in chronic stable COPD remain to be established. The role of other OSA treatments, such as mandibular advancement splinting, remains to be evaluated in the overlap syndrome.

O7.7 Aspiration

Aspiration of food and liquid is common in those with COPD, up to 70% of adults with COPD and dysphagia (difficulty swallowing) aspirate (Good-Fratturelli 2000). Aspiration in those with COPD is thought to be due to the disrupted coordination of the exhale-swallow-exhale respiratory cycle during swallowing, cricopharyngeal muscle dysfunction, and changes in lung volume (Gross 2009, Zheng 2016). Silent aspiration has also been reported in those with COPD, which can complicate dysphagia detection and management (Zheng 2016).

The prevalence of dysphagia in patients with COPD has been reported between 17% to 42% depending on the method of assessment and disease severity (Ghannouchi 2016, Gonzalez Lindh 2017, Kertscher 2015).

Dysphagia in COPD is thought to be due to the disrupted coordination of the exhale-swallow-exhale respiratory cycle during swallowing (Gross 2009). This incoordination may place individuals with COPD at a higher risk of aspiration, which may in turn contribute to COPD exacerbations (Gross 2009, Terada 2010) [evidence level III-2].

Dysphagia and aspiration risk can be determined by a speech pathologist with an adequate history from patients and their partners or carers, clinical swallow examination and patient self-report scales (Regan 2017). Instrumental swallowing assessments – videofluoroscopy and fibreoptic endoscopic evaluation of swallowing (FEES) can be used to confirm aspiration (Ghannouchi 2016).

Further research characterising dysphagia in COPD has identified additional impairments in swallow physiology including reduced tongue control, delayed pharyngeal swallow, reduced tongue base retraction, impaired hyolaryngeal excursion, cricopharyngeal dysfunction, impaired laryngopharyngeal sensitivity and slower bolus transit (Regan 2017).

Management for dysphagia and aspiration will be provided on an individual basis by a speech pathologist and may involve the following (McKinstry 2010):

- Rehabilitation exercises
- Swallowing – breathing retraining (compensatory swallowing techniques)
- Texture modification of diet and fluids
- Postural strategies
- Safe swallowing strategies

O7.8 Gastro-oesophageal reflux disease (GORD)

In patients with COPD, hyperinflation, coughing and the increased negative intrathoracic pressures of inspiration may predispose to reflux, especially during recumbency and sleep. Microaspiration of oesophageal secretions (possible including refluxed gastric content) is a risk, especially with coexistent snoring or OSA. Reflux and microaspiration exacerbate cough, bronchial inflammation and airway narrowing. A nested case control study performed on a large primary care dataset found a modest increased risk of gastro-oesophageal reflux in patients with a pre-existing diagnosis of COPD (RR 1.46, 95% CI 1.19-1.78) (Garcia Rodriguez 2008) although higher relative risks have been reported in other studies and Sakae et al reported a RR of 13.06 (95% CI 3.64-46.87) in their systematic review and meta-analysis of exacerbations of COPD and symptoms of GORD. In a large cross-sectional study of patients with a wide range of COPD severity, forming part of the US COPD Gene Study, 29% of patients reported a diagnosis of physician-diagnosed GORD (Martinez 2014). In this study, GORD symptoms were associated with worse health-related quality of life (HRQoL) (St George's Respiratory

Questionnaire (SGRQ)), increased dyspnoea and more frequent exacerbations. Two of these three associations persisted after adjusting for the use of proton pump inhibitors (PPI) (although the latter was associated with an improvement in HRQoL). It is noted that PPI use in the general population is associated with a higher frequency of pneumonia (Gulmez 2007, Eurich 2010). Nonetheless, other studies have suggested PPI use is associated with a reduction in exacerbations in GORD-sufferers (Sakae 2013, Sasaki 2009). In the study by Martinez et al, patients with GORD were more likely to be female, to have symptoms of chronic bronchitis and to have a higher prevalence of cardiovascular disease. Over two years of follow-up the presence of GORD symptoms was associated with more frequent exacerbations which was not altered by PPI use. In another prospective cohort study, gastro-oesophageal reflux symptoms were associated with an increased risk of exacerbation (Terada 2008). Prospective data from users of inhaled medications in the COPD Gene cohort has shown that GORD is a common risk factor for COPD exacerbations across all medication groups except for those using only short-acting bronchodilator medications. Female gender was an independent risk factor across all groups (Busch 2016).

Further large prospective studies would seem to be required to clarify the relationships between GORD, its treatment and COPD exacerbations. Diagnosis may be confirmed by 24-hour monitoring of oesophageal pH, modified barium swallow or gastroscopy. However, a therapeutic trial of therapy with H_2-receptor antagonists or a proton-pump inhibitor may obviate the need for invasive investigations. Lifestyle changes, including stopping smoking, limiting food intake within 4 hours of bed-time, reduced intake of caffeine and alcohol, weight loss and exercise, will also help. Elevation of the head of the bed is also recommended.

O7.9 Lung cancer

Lung cancer is a serious health problem in Australia (Cancer Council Australia 2004). In 2007, in Australia, lung cancer was the fourth most commonly diagnosed cancer in both males and females (excluding basal and squamous cell carcinoma of the skin), with a total of 9.703 diagnosed (AIHW & Cancer Australia 2011). Lung cancer is the leading cause of cancer deaths for both sexes. The occurrence of lung cancer was strongly related to age, with 84% of new lung cancers in males and 80% in females diagnosed in those aged 60 and over. Smoking is the largest single cause of lung cancer, responsible for 90% of lung cancers in males and 65% of lung cancers in females in Australia. Between 1982 and 2007, the incidence rate of lung cancer decreased in males by 32%, but increased in females by 72%, reflecting historical differences in smoking behaviour.

The risk of lung cancer in people who have pre-existing lung disease has been studied using case-control studies, which found an increased risk of lung cancer in people with bronchitis and emphysema, even after correcting for the smoking history. A cohort study of 2,507 patients with COPD followed for 60 months found an incidence of lung cancer of 16.7 per 1000 patient years. The most frequent histological type was squamous cell (44%) followed by adenocarcinoma (38%) and small cell (12%). A diagnosis of lung cancer was associated with less severe GOLD stage, older age, lower BMI and a diffusing capacity of lung for carbon monoxide (D_LCO) test <80% predicted (de Torres 2011).

A much larger cohort study performed record linkage of Danish national hospital and cancer registries. The investigators identified 236,494 patients admitted for COPD between 1980 and 2008, who were followed for median of 3.5 years. During the first year of follow-up, the Standardised Incidence Ratio (SIR) for any cancer was 3.1 (95% CI 3.0-3.2), and lung cancer 8.5 (95% CI 8.2-8.8). The cumulative risks for lung cancer in this COPD cohort after 1, 5 and 10 years were 1.8% (95% CI 1.7- 1.9%), 3.6% (95% CI 3.6-3.7%) and 4.9% (4.9%-5.0%) respectively (Kornum 2012) [evidence level III-2].

During the longitudinal follow-up of the COPDGene Study [an average follow-up of 5.7 years (+/- 1.87 years)], a total of 169 subjects diagnosed with lung cancer were matched (for age, race, sex, smoking status, average smoking pack-years and years since quitting smoking) against 671 control

subjects with no reported lung cancer diagnosis. Characteristics associated with a future risk of lung cancer included airflow obstruction as measured by FEV_1/FVC, history of exacerbations in the previous year and the presence of visual emphysema. The results were similar when percentage predicted FEV_1 was used as the measure of airflow obstruction (Carr 2018).

Research has suggested a mechanism for the association, through identification of single-nucleotide polymorphisms (SNPs) on chromosome 15 in the nicotinic acetylcholine receptor subunit genes (CHRNA3 and CHRNA5) that are associated with smoking behaviour and with an increased risk of lung cancer and COPD (Bierut 2010). The SNPs on chromosome 15 appear to have an independent effect on disease risk, as if you incorporate the smoking history into the statistical analyses, the genetic variants continue to contribute to lung cancer risk above and beyond the smoking behaviour (Bierut 2010).

O7.10 Bronchiectasis

Bronchiectasis is characterised by dilated, thick-walled bronchi that fail to clear airway secretions, leading to a chronic productive cough, persistent bacterial infection and infective exacerbations. In milder COPD patients, bronchiectasis may be an incidental, subclinical finding on CT chest, as observed in the ECLIPSE study where the prevalence of bronchiectasis was 4% (Agusti 2010). In contrast, patients with moderate to severe COPD have a higher prevalence of bronchiectasis of 30 to 60% (O'Brien 2000, Patel 2004, Whitters 2013).

The presence of bronchiectasis influences the rate of respiratory infections and other adverse outcomes in COPD. A meta-analysis of observational studies totalling 5,329 patients with COPD showed that 30% had coexisting bronchiectasis, which increased the risk of exacerbations (OR 2.0), potentially pathogenic microorganisms in sputum (OR 4.1), severe airway obstruction (OR 1.3) and mortality (OR 2.0) (Du 2016).

These studies emphasise the clinical importance of coexisting bronchiectasis in some patients with COPD. A high-resolution CT chest scan should be considered in patients with COPD who have chronic bronchitis or frequent respiratory infections, to identify clinically important bronchiectasis which can then be managed in addition to the COPD (Chang 2015, Hurst 2015).

O7.11 Combined pulmonary fibrosis and emphysema

Combined pulmonary fibrosis and emphysema (CPFE) is a syndrome defined by clustering of pulmonary fibrosis and emphysema in a patient (Cottin 2022). Spirometry is frequently normal due to opposing effects of hyperinflation from emphysema and restriction from fibrosis. Gas transfer, however, is usually severely impaired due to the additive effect of dual pathology (Jankowich 2012, Papaioannou 2016). Cigarette smoking is a major risk factor. CPFE occurs predominantly in males (up to 9:1 male:female ratio). In non-smokers, CPFE has been described in people with occupational dust exposure and genetic mutations (Jankowich 2012, Papaioannou 2016).

CPFE has a higher mortality than that of emphysema alone. Prognosis has been shown to follow the course of patients with idiopathic pulmonary fibrosis (IPF) i.e. median survival between 2.1 and 8.5 years, or 5-year survival between 38% and 55% (Cottin 2017, Jankowich 2012, Papaioannou 2016). Even in patients who do not fulfil criteria for IPF, the presence of interstitial features in addition to emphysema carries a significantly higher mortality (Ash 2018).

In most cases, high resolution computed tomography (HRCT), spirometry and diffusing capacity of lung for carbon monoxide (D_LCO) test are adequate to diagnose CPFE. The prevalence of lung cancer is higher in CPFE than COPD. Therefore, more vigilant follow up of pulmonary nodules is recommended, though no specific screening guideline has been developed for CPFE (Jankowich 2012, Papaioannou

2016).

Currently, no specific treatment exists for CPFE. Post-hoc data from nintedanib trials (INPULSIS (Richeldi 2014) and INPULSIS-ON (Crestani 2019), which included patients with concurrent emphysema, showed attenuation of rate of decline in forced vital capacity (FVC) in IPF with emphysema, similar to IPF without emphysema. An observational cohort study of real-world patients who were commenced on pirfenidone also showed similar rate of progression between CPFE and IPF without emphysema (Oltmanns 2014). Hence, antifibrotic therapy can be considered in CPFE, where presence of IPF is confirmed. Early referral for lung transplantation should be considered in patients with rapidly declining lung function.

O7.12 Alcohol and sedatives

Patients with COPD have impaired gas exchange and an exaggerated fall in Po_2 with recumbency and sleep onset (Meecham Jones 1995, Chaouat 1995). Excessive use of alcohol and sedatives exacerbates this and predisposes to sleep-disordered breathing.

Heavy cigarette smoking is associated with misuse of other substances in many individuals. Nicotine, caffeine and alcohol also predispose to gastro-oesophageal reflux.

In a population-based cohort of 130,979 community-dwelling older adults with COPD, new opioid users were associated with significantly increased risk of emergency room visits for COPD or pneumonia (HR 1.14, 95% CI 1.00–1.29, p=0.04). Opioid use was also associated with significantly increased risk for COPD or pneumonia-related mortality (HR 2.16, 95% CI 1.61–2.88) and all-cause mortality (HR 1.76, 95% CI 1.57–1.98), but significantly decreased outpatient exacerbations (HR 0.88, 95% CI 0.83–0.94, p=0.0002). New opioid use and, in particular, use of the generally more potent opioid-only agents, was associated with increased adverse respiratory outcomes and mortality. A careful, individualised approach needs to be taken when administering opioids to older adults with COPD, given the potential for adverse respiratory outcomes (Vozoris 2016).

O7.13 Testosterone deficiencies and supplementation

Observational studies in COPD patients have revealed reduced total testosterone levels compared with matched controls [WMD -3.21nmol/L (95% CI -5.18 to -1.23)] (Atlantis 2013). The clinical significance of this finding is unclear. Although testosterone supplementation therapy has been shown to increase peak muscle strength and peak workload achieved in patients with COPD (not necessarily with testosterone deficiency) maximal oxygen uptake and health-related quality of life (HRQoL) were not improved. More data are awaited to determine whether screening patients with COPD for testosterone deficiency is clinically necessary and whether supplementation in deficient patients can induce any clinically relevant benefits.

O7.14 Cognitive impairment

Cognitive dysfunction has been described in people with COPD as in other chronic diseases such as cardiac failure and diabetes. The frequency of cognitive dysfunction varies depending upon the battery of neuropsychological tests used, with the domains most influenced being memory and attention. In a population cohort of community dwelling elderly (age 70-89) with normal cognition, those who had a diagnosis of COPD at baseline (based on medical record data), had an 83% increased risk of incident non-amnesic mild cognitive impairment (hazard ratio 1.83, 95% CI 1.04-3.23) over 5 years (Singh 2014a). Cognitive function in patients admitted to hospital with an exacerbation of COPD was more impaired than in patients with stable COPD which in turn was worse than in a matched control group (Dodd 2013) [evidence level III-2].

In a meta-analysis of 655 patients with stable COPD and 394 control participants, cognitive function was associated with severity of COPD only in those with severe to very severe disease (Schou 2012).

Baird et al performed a systemic review of 13 studies of the effect of cognitive impairment on self-management in COPD and demonstrated high degrees of inhaler incompetency with cognitive impairment, although dry powder inhalers are easier to learn to use (Baird 2017). As memory and attention, as well as speed, co-ordination and learning ability were shown to be reduced, it may be important to consider level of cognitive impairment when assessing capacity for self-management.

Potential aggregate anticholinergic effects of concurrent oral and inhaled medications should be considered in patients with cognitive impairment.

O7.15 Anaemia

Anaemia is a relatively uncommon comorbidity of COPD (Schnell 2012, Barnes 2009, Yohannes 2011a, Almagro 2012), either attributable to erythropoietin resistance (Markoulaki 2011) or inflammation (Markoulaki 2011, Rutten 2013, Boutou 2012), which may impair functional performance (Cote 2007a, Krishnan 2006, Boutou 2011) and health status (Krishnan 2006, Boutou 2011), contribute to worse survival (Haja Mydin 2013, Kollert 2013, Martinez-Rivera 2012, Boutou 2013, Cui 2012, Chambellan 2005), and be associated with increased health care utilization costs (Shorr 2008, Halpern 2006). Red cell transfusion appears to be a reasonable strategy for those with severe anaemia (Schonhofer 1998), though there is no evidence of benefit from RCTs.

O8. Hypoxaemia and pulmonary hypertension

Hypoxaemia

Hypoxaemia in patients with COPD should be identified and corrected with long term oxygen therapy as this has been shown to improve survival and quality of life (Nocturnal Oxygen Therapy Trial Group 1980, Medical Research Council Working Party 1981) (see O8.1). Hypoxaemia is best screened for using pulse oximetry, however, should be confirmed using arterial blood gas (ABG) measurement. Use of ABGs also allows for the detection of hypercapnia which may complicate long term oxygen use. The indications for long term oxygen use are:

- Arterial PaO_2 less than or equal to 55mmHg or
- Arterial PaO_2 less than or equal to 59mmHg in the presence of pulmonary hypertension, right heart failure or polycythaemia

Pulmonary hypertension

The definition of pulmonary hypertension (PHT) was revised in 2009. PHT is now defined as a mean Pulmonary Artery Pressure (PAP) >25mmHg at rest measured by right heart catheterization (Simonneau 2009). PAP assessed during exercise is no longer part of the definition. PHT was seen in approximately 50% of patients with severe emphysema (FEV_1 27% of predicted) studied as part of the National Emphysema Treatment Trial (NETT) (Scharf 2002) but only 5% of these patients had moderate to severe PHT (mean PAP > 35mmHg). In these patients, no correlation was found between PaO_2 and mean PAP although FEV_1, Pulmonary Capillary Wedge Pressure and diffusing capacity of lung for carbon monoxide (D_LCO) test were correlated in a multiple regression model. In those COPD patients with severe PHT, hypoxaemia, reduced D_LCO and PAP are often more impaired than would be expected for their degree of airflow limitation (Chaouat 2005). There are several postulated mechanisms for PHT in COPD (Chaouat 2008). The presence of PHT is associated with a worse prognosis (Chaouat 2008) and increased hospitalisation (Kessler 1999). This has resulted in several small studies of non-selective and selective vasodilators.

No pharmacological therapies have shown to be effective to date. An early study of the non-selective dihydropyridine calcium antagonist vasodilator felodipine in COPD showed improved haemodynamics (Sajkov 1993). However, the low efficacy and high adverse effect profile make such drugs an unattractive option. The first report of a selective pulmonary vasodilator, nitric oxide (NO) in stable COPD (Barbera 1996) was disappointing in that hypoxia was exacerbated, presumably through the mechanism of worsening ventilation/perfusion (V/Q) mismatching. A subsequent 40 patient randomised trial assessed "pulsed" (a burst at the start of inspiration) NO and demonstrated that improved haemodynamics without exacerbation of hypoxia (Vonbank 2003) was possible. No further randomised controlled trials of selective pulmonary vasodilators in COPD patients have yet been published. Although endothelin-1 receptor antagonists and other agents have been used to treat non-COPD-related PHT, a trial of bosentan in COPD (Stolz 2008) once again induced adverse effects on gas exchange and quality of life. Similarly, two randomised controlled trials of the phosphodiesterase-5 inhibitor sildenafil failed to demonstrate improvements in cardiac output, 6-minute walk test (6MWT) or maximal workload on cardiopulmonary exercise testing in COPD patients (Holverda 2008, Rietema 2008). Well-designed trials of agents which selectively dilate the pulmonary vascular bed without worsening V/Q mismatching are urgently needed.

PHT and right heart failure may be complications of exacerbations of COPD. Therapy in these patients has generally been directed at reversing hypoxia and hypercapnia with bronchodilators, corticosteroids, antibiotics as well as supplemental oxygen and ventilatory support. A 16-patient randomised placebo-controlled trial of IV prostacycline showed no benefit, but exacerbated hypoxia in patients receiving conventional therapy including mechanical ventilation for an exacerbation of COPD (Archer 1996).

Thus, there are no data at present that clearly support the use of vasodilators generally in COPD patients with PHT. However severe PHT is uncommon in patients with even advanced emphysema. As such, where appropriate, a careful search for other potential causes of PHT should be undertaken and an alternative diagnosis considered.

Chest x-rays may show enlargement of proximal pulmonary arteries, but right ventricular enlargement is difficult to detect because of hyperinflation. Right axis deviation and P pulmonale on ECG may be difficult to detect because of low voltage traces (also a result of hyperinflation). Multifocal atrial tachycardia and atrial fibrillation are common. A pulmonary artery to aorta ratio of greater than one as measured on CT chest has been used as a marker of possible pulmonary hypertension. Wells et al used this measure in over 1,000 patients and prospectively found its presence led to a significantly increased risk of future exacerbations odds ratio, 3.44; 95% CI 2.78 to 4.25; p<0.001 (Wells 2012) [evidence level III-2].

Retrospective data from 60 patients with severe COPD who had undergone CT chest, transthoracic echocardiography and right heart catheterisation showed that a CT chest pulmonary artery to aorta ratio greater than one was 73% sensitive and 84% specific for pulmonary hypertension with right heart catheter as the gold standard. This was significantly more sensitive and specific than transthoracic echocardiography (Iyer 2014) [evidence level IV].

Echocardiography is the best non-invasive method of assessing pulmonary hypertension, but image quality is reduced by hyperinflation. This can be clarified using the more invasive procedure of trans-oesophageal echocardiography. Patients with COPD may have poor quality images on transthoracic examination and transoesophageal echocardiography may be frequently needed. Echocardiography is indicated in patients with severe disease, or when symptoms seem out of proportion to the severity of airflow limitation. Estimation of pressure relies on at least some tricuspid regurgitation. Other findings include mid-systolic closure of the pulmonic valve and increased right ventricular wall thickness.

O8.1 Treatment of hypoxaemia and pulmonary hypertension

Treat underlying lung disease: The logical first step is to optimise lung function and treat all potential aggravating conditions.

Oxygen therapy: Long term, continuous (>18h/day) oxygen therapy to treat chronic hypoxaemia prolongs survival of patients with COPD, presumably by reducing pulmonary hypertension (Medical Research Council Working Party 1981, Nocturnal Oxygen Therapy Trial Group 1980, Weitzenblum 1985, Gorecka 1997, Zielinski 1998). (For a detailed description of oxygen therapy in COPD, see Section P).

Diuretics: Diuretics may reduce right ventricular filling pressure and oedema, but excessive volume depletion must be avoided. Volume status can be monitored by measuring serum creatinine and urea levels. Diuretics may cause metabolic alkalosis resulting in suppression of ventilatory drive.

Digoxin: Digoxin is not indicated in the treatment of cor pulmonale and may increase the risk of arrhythmia when hypoxaemia is present. It may be used to control the rate of atrial fibrillation.

Vasodilators: Vasodilators (hydralazine, nitrates, nifedipine, verapamil, diltiazem, angiotensin-converting enzyme [ACE] inhibitors) do not produce sustained relief of pulmonary hypertension in patients with COPD (Barbera 1996, Jones 1997). They can worsen oxygenation (by increasing blood flow through poorly ventilated lung) and result in systemic hypotension. However, a cautious trial may be used in patients with severe or persistent pulmonary hypertension not responsive to oxygen therapy. Some vasodilators (e.g., dihydropyridine calcium antagonists) have been shown to reduce right ventricular pressure with minimal adverse effects and increased well-being, at least in the short

term (Sajkov 1993, Sajkov 1997). Nitric oxide worsens V/Q mismatching and is therefore contraindicated in patients with COPD (Barbera 1996, Jones 1997).

O9. Surgery

None of the current surgical approaches in patients with COPD provides a survival advantage (Benditt 1997). In view of the potential for serious morbidity and mortality, all surgical treatments require careful assessment by an experienced thoracic medical and surgical team.

O9.1 Bullectomy

This operation involves resection of large bullae (larger than 5cm). The procedure is most successful where there are very large cysts compressing adjacent apparently normal lung (Mehran 1995). Giant bullae can be defined as occupying more than 50% of the hemithorax with definite displacement of adjacent lung tissue (Laros 1986).

O9.2 Lung volume reduction surgery and bronchoscopic interventions

van Geffen et al performed a meta-analysis of data from randomised controlled trials across all modalities of lung volume reduction (surgical and endobronchial) (van Geffen 2019). The mean differences compared with the control were an increase in FEV_1 of 15·87% (95% CI 12.27-19.47), improvement in 6-minute walk test (6MWT) of 43·28m (31·36 to 55·21), and reduction in the St George's Respiratory Questionnaire (SGRQ) of 9·39 points (−10·92 to −7·86) [evidence level I]. The authors noted a high risk of bias due to lack of blinding. The odds ratio for a severe adverse event, which included mortality, was 6·21 (95% CI 4·02-9·58) following intervention.

Surgical Lung Volume Reduction

The National Emphysema Treatment Trial (NETT) was a large randomised multicentre study which investigated the effectiveness and cost-benefit of this procedure (NETT 1999). A total of 1,218 patients with severe emphysema underwent pulmonary rehabilitation and were then randomised to lung volume reduction surgery (LVRS) or continued medical therapy. Pulmonary rehabilitation plays an important role in preparing patients for interventions such as lung volume reduction (Ries 2005). There was no overall survival advantage of surgery, but after 24 months there was significant improvement in exercise capacity in the surgical group. Patients allocated to LVRS took significantly longer (median 2 vs. 1 year) than those who continued medical therapy to reach a composite endpoint of death or meaningful deterioration in disease related quality of life (Benzo 2009). Among patients with predominantly upper lobe emphysema and impaired exercise capacity, mortality was significantly lower in the surgical than the medical group. However, high risk patients with diffuse emphysema and well-preserved exercise capacity are poor candidates for surgery because of increased mortality and negligible functional gain (Fishman 2003) [evidence level II].

A 2016 Cochrane Review on lung volume reduction surgery was very heavily influenced by data from the NETT study (van Agteren 2016) [evidence level I]. The authors concluded that short-term mortality was higher for LVRS (odds ratio (OR) 6.16, 95% CI 3.22-11.7) than for control, but long-term mortality favoured LVRS (OR 0.76, 95% CI 0.61-0.95) 96% of the patients contributing to the long-term mortality data was from patients enrolled in the NETT study. The authors made note of high post-operative complications, especially persistent air leak and pneumonia. A retrospective analysis of 2,815 LVRS cases performed in America demonstrated an in-hospital mortality rate of 5.5% (Attaway 2019). Pulmonary hypertension was associated with an increased risk in mortality (adjusted OR 4.4, 95% CI 1.7-1.5).

Buttery et al (Buttery 2023) performed the first RCT comparing endobronchial valves to surgical lung volume reduction in a highly selected group of 88 people with COPD who were suitable for both procedures. The trial was performed at 5 expert centres in the UK. At 12 months there was no

significant difference in the primary end point, the 'i-BODE' score [evidence level II]. This composite disease severity measure includes BMI, airflow obstruction, dyspnoea and exercise capacity (incremental shuttle walk test). The CAT score was a secondary end point and the surgical lung volume reduction group experienced a larger reduction in CAT score (treatment effect −6, 95% CI −9– −2; p=0.005). The group undergoing lung volume reduction surgery had a longer median length of hospital stay (9 vs 3 days p = 0.006), however the group undergoing valve placement had a 30% pneumothorax rate and 15% required further procedures. There were no deaths within 30 days of treatment in either group. There was a death at day 44 in an individual that received valves due to complications of the procedure. This trial does not demonstrate that either approach is superior. A larger trial is currently underway.

Endobronchial lung volume reduction

A variety of nonsurgical techniques have been investigated. These include endobronchial one-way valves, self-activating coils, targeted destruction of emphysematous tissue, bypass tract airway stenting and transpleural ventilation. Of these techniques, only valves are in regular clinical use in Australia.

van Geffen performed a meta-analysis of endobronchial lung volume reduction surgery (van Geffen 2019). Six trials were included in the analysis of endobronchial valves (620 participants) and 3 trials were included in the analysis of endobronchial coils (458 participants). The authors reported improvements in lung function, 6-minute walk distance and symptom scores with both modalities. The odds ratio for an adverse event for trials examining endobronchial valves was (9.58, 95% CI 5.56–16.50). The most frequent adverse events with endobronchial valve treatment were pneumothorax (1.4 - 25%) and COPD exacerbations (4 - 20%). A large multi-centre randomised controlled trial reported a 27% pneumothorax rate and a 3% 45-day mortality rate (Criner 2018). The odds ratio (OR) for an adverse event for trials examining coils was 8.73, 95% CI 2.69-28.32). The most common adverse events were pneumonia (5 - 20%), COPD exacerbations (7 - 28%) and pneumothorax (5 - 10%). There was no difference in early mortality between valves/coils and control in this meta-analysis. However, a 2021 randomised controlled study of coils in patients with severe COPD (FEV_1 15-45% predicted) was terminated early with only 120 of the > 200 planned participants recruited. There were 6 month follow up results available for 57 coil and 34 control participants, demonstrating clinically significant improvements in SGRQ of -10.6 (95% CI -15.9 to -5.4) and improvement in FEV_1 +10.3% predicted (95% CI 4.7-16.0) in the coil arm. There were no deaths in the control arm, whilst there were 5 deaths in the coil arm. Also, the incidence of serious adverse events was higher in the coil arm (n=30 of the coil participants, n=3 of the control participants) (Klooster 2021) [Evidence level II]. Overall, these results indicate mixed results for coils.

There was concern regarding the lack of sham bronchoscopy and/or unclear status of blinding in some studies that may cause a risk of bias (van Agteren 2017).

Endobronchial valves may be appropriate in highly selected patients with severe COPD and hyperinflation if collateral ventilation can be excluded (intact fissure on imaging and Chartis negative during bronchoscopy). Based on the data above the role of coils is unclear.

LVRS therapy should only be considered in high volume specialised centres (Herth 2017). All patients being considered for lung volume reduction surgery and bronchoscopic interventions should be referred for pulmonary rehabilitation and discussed by an expert panel that includes a radiologist, respiratory physician, interventional pulmonologist, and thoracic surgeon (Herth 2017).

O9.3 Lung Transplantation

Lung transplantation is a complex therapy for selected patients with severe COPD and it is indicated to improve quality-of-life and most likely improve survival. International guidelines (Weill 2015) and

national consensus guidelines from the Australian Organ and Tissue Donation and Transplantation Authority http://www.tsanz.com.au/organallocationprotocols and NHRMC Ethical Guidelines for Organ Donation from Deceased Donors https://www.nhmrc.gov.au/guidelines-publications/e76 recommend COPD patients be referred to one of Australia's four lung transplant centres for consideration of lung transplantation where the majority of the following are present:

- Progressive symptoms, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy
- Patient is not a candidate for endoscopic or surgical lung volume reduction surgery (LVRS). Simultaneous referral of COPD patients for both lung transplant and LVRS evaluation is appropriate
- BODE index of 5-6
- $PaCO_2$ > 50 and/or PaO_2 < 60 mmHg
- FEV_1 < 25% predicted

The absolute contraindications include recent malignancy, untreatable advanced dysfunction of another major organ system, psychological/psychiatric conditions associated with poor compliance, substance abuse or dependence (including ANY tobacco/marijuana) in the prior six months, absence of social support and poor rehabilitation potential. According to Weill, the Australian Organ and Tissue Donation and Transplantation Authority and the NHMRC, relative contraindications include age older than 65 years, obesity, malnutrition, severe symptomatic osteoporosis, and colonisation with resistant/virulent organisms/viruses.

If successful transplantation is possible, a detailed multi-disciplinary medical assessment and eventual wait-listing for transplant may follow. Not all potential patients will be suitable or appropriate. Based on specific patient and donor variables, waiting times vary from one month to years. The 2017 Australian and New Zealand Cardiothoracic Organ Transplant Registry Report states that the expected one, five and ten-year survival rates post bilateral lung transplant are 91%, 67% and 52%. Complex medications, regular investigations (e.g.: blood work, spirometry etc.) and Transplant Centre follow-up are required indefinitely post-operatively.

O9.4 Pre-operative work-up for surgery

Patients with COPD are at increased risk of post-operative pulmonary complications after any thoracic or non-thoracic surgery. A US database analysis has shown that COPD is associated with increased post-operative mortality and morbidity with major surgical procedures (Gupta 2013), including abdominal operations (Fields 2016). Careful pre-operative work-up of patients with COPD minimises post-operative complications. As no specific thresholds of lung function are mandated for non-thoracic surgery, the risk/benefit ratio for individual patients needs to be estimated for elective and urgent surgery. For lung resection to treat lung cancer, spirometry and diffusing capacity should be measured to estimate predicted post-operative lung function, and if required, exercise tests should be performed (Brunelli 2013).

COPD management should be optimised in the pre-operative period, including smoking cessation, inhaled bronchodilators, and pulmonary rehabilitation. Specific peri- and post-operative management strategies have been suggested for patients with severe COPD. These strategies include early mobilisation and, where appropriate, minimising medications leading to respiratory depression, regional anaesthesia, and controlled oxygen delivery in the post-operative period (Diaz-Fuentes 2016, Lakshminarasimhachar 2016).

O10. Palliative and supportive care

Palliative care - ideally from a multidisciplinary team which includes the primary care team - should be considered early, and should include symptom control and addressing psychosocial issues *[evidence level II, weak recommendation]*

Palliative care

Palliative care aims to improve the quality of life of patients and their families when facing life-threatening illness, through the prevention and relief of suffering by controlling symptoms and addressing physical, psychosocial and spiritual issues (WHO 2002). Palliative care encompasses early, supportive care in addition to offering the traditional model of high-quality, end-of-life care for patients close to death.

The provision of early palliative care can improve survival (Higginson 2014, Temel 2010). Early access to palliative care is now recommended for patients with COPD and persisting symptoms.

General palliative care practices such as symptom management and aligning treatment with patients' goals should be routine aspects of care. For patients with complex symptoms, referral to specialist palliative care may be required (Quill 2013). Specialist palliative care services often work as interdisciplinary teams and may include a wide range of health professionals offering support in hospitals, community, or hospices.

Patients with COPD experience many distressing symptoms including breathlessness, fatigue, depression, anxiety, and insomnia. However, these symptoms are often poorly controlled and undertreated in advanced disease (Ahmadi 2016, Johnson 2012, Mullerova 2014, Walke 2007). In Australia only 17.9% of COPD patients access any palliative care in their last year of life and only 2.6% of palliative care admissions are for COPD (Rosenwax 2016). A review of COPD patient deaths occurring in the ICU in 15 hospitals in the USA identified that patients with COPD were less likely to receive specialist palliative care input or have opportunities to discuss end of life care preferences related to resuscitation in the ICU, compared with cancer patients. This occurred despite patients with COPD having longer hospital and ICU stays than patients with cancer. Therefore, there is a need to improve patient and carer access to palliative care approaches both generally and more specifically also within ICU (Brown 2016). Furthermore, a Belgian population cohort study (Faes 2018) identified that during the last six months of life, patients with COPD used resources which focused on preservation of life, with less use of resources or medications to alleviate symptoms or address end-of-life care needs.

Well-described barriers to patients with COPD accessing palliative care include:

- Difficulty prognosticating in COPD
- Patients' fears of abandonment by their usual physician (Knauft 2005)
- Perceptions that palliative care is only for end-of-life care or patients with cancer
- Clinicians' lacking time to discuss palliative care, being reluctant to take away hope, and having insufficient knowledge (Hardin 2008, Knauft 2005)
- Current palliative care services are already over-stretched (Quill 2013).

New models of well organised, integrated respiratory and palliative care may overcome these barriers (Crawford 2013, Higginson 2014). In the randomised controlled trial by Higginson et al, patients with advanced lung disease (including COPD) who received integrated palliative care together with care from a respiratory medicine team had improved disease mastery and survival, but no change in quality of life, when compared with patients who received standard care alone (Higginson 2014). Further research is needed to evaluate new models of integrated care.

Retrospective data from a study including two Victorian hospitals (Smallwood 2018) demonstrated that in the last two years of life, only 18% of patients with severe COPD accessed specialist palliative care, with 6% prescribed opioids as outpatients, despite most having severe chronic breathlessness. Similarly, only 5% wrote an advance directive. In a substudy of the same population, Ross et al reported that investigation burden was still significant at end of life for patients dying in hospital with COPD, with many patients still undergoing diagnostic investigation even in the last 2 days of life (Ross 2021) [evidence level III-3].

Given the difficulty in determining prognosis in an individual with COPD, including palliative care principles and practices into COPD management should not be dependent on making an accurate prognosis. Instead, symptom palliation and palliative care approaches should be considered earlier as patients become more symptomatic, occurring concurrently with disease directed, active treatment.

A retrospective cohort study from Belgium demonstrated that receiving one or more home specialist palliative care (PHC) visits more than 30 days before death was associated with increased appropriate patient-centred medical resource use and lower inpatient and total costs in the last 30 days before death for COPD compared to no PHC (Scheerens 2020). Notably, very few patients with COPD accessed any PHC.

Supportive care - symptom control

Breathlessness is almost universal in severe COPD; however, this symptom remains under-recognised and undertreated (Ahmadi 2016, Blinderman 2009, Gysels 2008). Therefore, it is important to specifically ask about breathlessness and consider using a simple scoring tool (such as the modified Medical Research Council Breathlessness scale – see **Box 3** in **C2.1 History** above) to quantify breathlessness. Patients with a score of 3 or higher have severe breathlessness.

When breathlessness persists at rest or on minimal exertion, despite optimal treatment of all underlying causes, it is deemed refractory (Abernethy 2003). Refractory breathlessness requires a comprehensive approach, including pharmacological and non-pharmacological strategies.

Non-pharmacological management of breathlessness

Evidence-based, non-pharmacological strategies include smoking cessation, self-management education, physical activity and pulmonary rehabilitation, breathing exercises and the use of a handheld fan to move cool air on the face (**Box 8**) (Galbraith 2010, Johnson 2016, Marchetti 2015, Marciniuk 2011). Additionally, other management strategies such as chest wall vibration (Marciniuk 2011), neuromuscular electrical stimulation (Vieira 2014), activity pacing and energy conservation may be helpful.

There is little evidence to support the use of "palliative" oxygen therapy in patients with breathlessness and mild hypoxaemia (Abernethy 2010), however, the prescription of oxygen in these clinical situations should be made on an individual basis.

Pharmacological management of breathlessness – opioids and benzodiazepines

In COPD, there is growing evidence that regular low dose oral morphine (<30mg/day) may safely and effectively be used to treat refractory breathlessness in patients with advanced COPD (Abernethy 2003, Barnes 2016, Currow 2011, Ekstrom 2015a, Ekstrom 2014).

A 2015 systematic review and meta-analysis comparing opioids with placebo in 16 studies (271 participants, of whom 95% had COPD) found small short-term benefits in dyspnoea with minimal adverse effects and unclear effects on quality of life (Ekstrom 2015a). A review in 2016, which included 26 RCTs with 526 participants, identified a small but beneficial effect from oral and parenteral (but not nebulised) opioids on breathlessness (Barnes 2016). Abdallah et al (Abdallah 2017) have

demonstrated improvements in exertional dyspnoea and exercise endurance, as measured by cardiopulmonary exercise testing with single dose immediate release morphine syrup (0.1mg/kg) up to a maximum of 10mg. Adverse effects from opioids include predictable gastrointestinal effects (constipation, nausea and vomiting), drowsiness and light-headedness. However, in the reviewed studies there were no cases of hypoventilation, respiratory depression, treatment-related hospitalisations or death. Nevertheless, opioids should be used with care in COPD (Barnes 2016, Ekstrom 2015b). Low dose morphine SR, 10mg twice day, with up-titration after 1 week if required, in a double blind RCT with 111 patients, over 4 weeks, significantly improved health status as measured by the CAT score (-2.18 95% CI -4.14 to -0.22). Overall, there was no effect on breathlessness measures; however, in the subgroup of people with MMRC 3-4, there was a significant difference in change of worst breathlessness in the previous 24 hours between the treatment groups (-1.33, 95% CI -2.5 to 0.16; p=0.03). The only adverse effect demonstrated was constipation (Verberkt 2020) [evidence level-II].

While there is good quality evidence to support a once daily, extended-release morphine dosing schedule (Abernethy 2003), some patients may prefer to use immediate-release morphine as required for breathlessness. Morphine dosing should therefore be individualised, taking into consideration comorbidities, starting at a low dose and up titrating weekly until efficacy is achieved, or to a maximum of 30mg/day. Laxatives should be prescribed to prevent constipation and patients should be warned of side effects. Both patients and carers require both verbal and written education regarding how to use morphine for breathlessness. Additionally, early medical review within 1-2 weeks is recommended on initiating morphine or increasing the dose. Morphine sulfate pentahydrate (modified release) capsules are approved for use in people with severe chronic breathlessness, despite optimal treatment of all the underlying causes contributing to dyspnoea. Please refer to PBS criteria for further detail: http://www.pbs.gov.au/medicine/item/11760Y-8349K.

There is no evidence to support a beneficial effect from benzodiazepines for the relief of breathlessness in patients with COPD, however, they may be considered as a second- or third-line treatment when non-pharmacological strategies and opioids have failed (Simon 2016).

As breathlessness management is complex, requiring multiple approaches, in addition to significant self-management education of patients and their carers, individualised written breathlessness management plans may be useful.

A retrospective single-centre study (Taverner 2019) found overuse of antibiotics occurred commonly at the end of life in patients with COPD dying in hospital.

Goals of care

Discussing goals of care and future treatment wishes should occur early, in a non-acute setting and should involve their General Practitioner. The option of including carers or family members should be raised.

Topics to consider:

- Disease severity, symptoms, quality of life and possible prognosis
- Patients' and carers' values and beliefs
- Treatment options including non-invasive ventilation, admission to an intensive care unit, and intubation for mechanical ventilation (specialist input may be required)
- What death might be like
- End-of-life care wishes, including place of death preferences

These conversations occur as several discussions over multiple appointments. This has the advantage of gently adding each new topic gradually, thereby reducing the chance of causing distress.

As a result of discussing goals of care, some patients may wish to appoint a medical power of attorney or write an advance treatment directive (which must also be signed by a medical practitioner). It is vital that other health professionals involved in the patient's care and family members, or carers are fully aware of the person's future care wishes and of the existence of any advance treatment directive.

All patients should routinely and regularly be asked if they wish to discuss or update their goals of care. More than a third of patients with severe medical problems were observed to change their preferences regarding life supporting measures at least once over a period of twelve months (Janssen 2012).

End-of-life care

Patients with distressing symptoms or other challenging situations may benefit from referral to a specialist palliative care team for:

- Management of persisting refractory symptoms
- Psychosocial, spiritual or existential care
- Co-ordination of care
- Active management of the terminal phase (at home or in a hospice)
- Emotional care and bereavement support of relatives and carers

Key points

1. Palliative care should be considered early and should include symptom control and addressing psychosocial and spiritual issues.
2. Active treatment of persisting symptoms or challenging issues may require a multidisciplinary team (which includes primary care, respiratory medicine, and palliative care)
3. The introduction of palliative and supportive care principles and discussion of goals of care should be routine in patients with persisting symptoms despite optimal disease-directed treatment.

Box 8: Breathlessness management strategies

Non-pharmacological strategies
Smoking cessation Physical activity Pulmonary rehabilitation Exercise training Self-management education Breathing exercises e.g. pursed lip breathing, breathing control, timed breathing techniques Use of walking aids Activity pacing Use of breathlessness recovery positions e.g. sitting upright, forward lean Handheld fans to move cool air on the face Energy conservation including using equipment to perform tasks
Pharmacological options
Low dose morphine

P: Prevent deterioration

Preventing exacerbations has a key role in preventing deterioration [evidence level III-2, strong recommendation]

REDUCING RISK FACTORS FOR COPD is a priority, and smoking is the most important of these. A systematic review of 47 studies with an average follow-up of 11 years found a significantly higher decline in FEV_1 in people who continued to smoke compared to those who ceased (Lee 2010) [evidence level I]. The annual decline in FEV_1 for those who stopped at the beginning of follow-up was 12.4 ml/year (95% CI 10.1-14.7) and for those who stopped during the period of follow-up 8.5 ml/year (95% CI 5.6-11.4), both less than people who continued to smoke. While there were limitations to the data, the review clearly found that in people who continue to smoke the annual decline in FEV_1 is >10 ml/year greater than in people who have never smoked or stopped smoking. Reduction of exposure to occupational dust, fumes and gases and to indoor and outdoor air pollutants is also recommended. Influenza immunisation reduces the risk of exacerbations and death [evidence level I], while long term oxygen therapy reduces mortality [evidence level I].

Avoidance of passive smoking is also recommended to prevent deterioration. In a cohort study exposure to second-hand smoke (SHS) was found to be associated with worse clinical outcomes for people with COPD. Living with a smoker was associated with poorer health-related quality of life (HRQoL) (on both St George's Respiratory Questionnaire (SGRQ) and COPD Assessment Test (CAT) scores) and increased risk of severe exacerbations (OR 1.51, 95% CI 1.04-2.17), while SHS exposure in the last week was associated with worse SGRQ and more symptoms (Putcha 2016) [evidence level III-2].

P1. Risk factor reduction

P1.1 Smoking cessation

Smoking cessation is the most important intervention to prevent the worsening of COPD [evidence level II, strong recommendation]

Australia has made substantial progress in reducing the prevalence of tobacco smoking. In 2017-18 the prevalence of daily smoking in adults (people aged 18 and over) was 13.8% compared to 16.1% in 2011-12 and 23.8% in 1995. The proportion of First Nations people aged 15 years and over was 37% in 2018-19, a decrease from 41% in 2012-13. Despite the decrease in prevalence in 2018 tobacco use remained the leading risk factor contributing to disease burden and death (8.6% of total disease burden). In 2018 tobacco use was estimated to be the cause of death for almost 20,500 Australians.

The Australian National Tobacco Strategy 2023-2030 (Commonwealth of Australia 2023) aims to achieve a national daily smoking prevalence of less than 10% by 2025 and 5% or less by 2030. For First Nations people the goal is to reduce daily smoking to 27% or less by 2030. One of the priorities of the strategy is to provide greater access to evidence-based cessation services to help people quit tobacco. Actions related to this priority include improving and extending Quitline services, providing policy guidelines and accredited training in smoking cessation and reviewing restrictions on and the access to smoking cessation pharmacotherapies on the PBS.

Comprehensive treatment of tobacco dependence involves providing both behavioural support and pharmacotherapy (Zwar 2014). International data show that smoking cessation strategies are cost effective but with a 10-fold range in cost per life-year gained depending on the intensity of the program and the use of pharmacological therapies (Ekpu 2015). A range of health professionals can help smokers quit (Rice 2013, Stead 2013a, Carr 2012, Sinclair 2004) but relapse is common [evidence

level I].

Currently accepted best practice is summarised in the 5-A strategy: (Zwar 2014).

- Ask and identify smokers. Document smoking status in the medical record.
- Assess the degree of nicotine dependence and motivation or readiness to quit
- Advise smokers about the risks of smoking and benefits of quitting and discuss options
- Assist cessation — this may include specific advice about pharmacological interventions or referral to a formal cessation program such as the Quitline
- Arrange follow-up to reinforce messages.

Brief interventions for smoking cessation involve opportunistic advice, encouragement and referral. Quit Victoria has summarised this as Ask, Advise, Help.
The brief advice model has three steps:

- **Ask** all patients about smoking status and document this in their medical record.
- **Advise** all patients who smoke to quit in a clear, non-confrontational and personalised way, focusing on the benefits of quitting and advising of the best way to quit.
- **Help** by offering referral to behavioural intervention through Quitline (13 7848) and prescribe (or help patients to access) pharmacotherapy, such as nicotine replacement therapy.

Cessation rates increase with the amount of support and intervention, including practical counselling and social support arranged outside of treatment.

People with COPD often have barriers to smoking cessation. There is evidence that smokers with COPD report lower self-efficacy and lower self-esteem, impairing their ability to quit. Co-existing depression is common with depression reported in 44% of hospitalised patients with COPD (Jimenez-Ruiz 2015). Despite this there is evidence that smoking cessation interventions can be effective. The 2016 update of the Cochrane Review (van Eerd 2016) on smoking cessation for people with COPD includes 16 studies involving 13,123 participants. Only two studies were rated as high quality. The review found high-quality evidence from a meta-analysis of four (1,540 participants) of the 16 studies that a combination of behavioural treatment and pharmacotherapy is effective in helping smokers with COPD to quit smoking.

A systematic review of behaviour change techniques to support smoking cessation in patients with COPD found that four techniques were associated with higher rates of cessation. The behaviour change techniques found to be effective (usually in comparison to usual care) were; facilitate action planning/develop treatment plan, prompt self-recording, advise on methods of weight control, and advise on/facilitate use of social support. In addition, linking COPD and smoking was found to result in significantly larger effect sizes (Bartlett 2014) [evidence level I]. Personalising smoking cessation advice based on lung function results increase cessation rates (Parkes 2008) [evidence level II].

Smoking tobacco can alter the metabolism of a number of medicines. This is primarily due to substances in tobacco smoke, such as hydrocarbons or tar-like products that cause induction of some liver enzymes (CYP 1A2, in particular). When a person stops smoking, the enzyme activity returns to normal, which may result in increased levels of these medicines in the blood. Monitoring and dosage reduction may often be required. For information on medicines affected by smoking see **Appendix 3** of the RACGP smoking cessation guidelines (http://www.racgp.org.au/your-practice/guidelines/smoking-cessation/). Heavy marijuana smoking (> 20 joint-years of exposure) increases the risk of COPD and accelerates FEV_1 decline in concomitant tobacco smokers beyond that observed with tobacco alone (Tan 2019).

P1.2 Treatment of nicotine dependence

Pharmacotherapies for nicotine dependence are effective and should be offered to all nicotine dependent smokers who express an interest in quitting, except when contraindicated (Tobacco Use and Dependence Guideline Panel 2008, Cahill 2013) [evidence level I]. Caution is recommended in

people with medical contraindications, pregnant women and adolescent smokers. Nicotine patches, varenicline and bupropion sustained release are all PBS listed for smoking cessation. Details of PBS listing are available are available in the RACGP smoking cessation guidelines (http://www.racgp.org.au/your-practice/guidelines/smoking-cessation/) and the Australian Medicines Handbook (https://shop.amh.net.au/).

A Cochrane network analysis concluded that combination NRT (nicotine patch combined with a quick-acting oral form) and varenicline (used as monotherapy) are the most effective forms of drug treatment and work equally well. It has been shown that varenicline is more effective than bupropion in a number of studies. Head-to-head comparisons between bupropion and NRT monotherapy have shown these medicines are equivalent to each other in efficacy (Cahill 2013).

In a study of 690 current smokers identified from Melbourne general practices (Liang 2018), 52.2% self-reported attempts to quit at least once during the previous 12 months. The pharmacological treatments most frequently tried were nicotine replacement therapy (205, 57.4%) and varenicline (110, 30.8%). However, non-evidence-based treatments such as hypnotherapy (62, 17%) and electronic cigarettes (38, 11%), were also frequently tried. Under-utilisation of evidence-based smoking cessation pharmacotherapies during admission and at the time of discharge was observed in a Tasmanian study of smokers admitted for an acute exacerbation of COPD (Pham 2019). Limited access to formal smoking cessation training for doctors and poor uptake of nurse-led smoking cessation services were also reported.

P1.2.1 Nicotine replacement therapy

All forms of nicotine replacement therapy (NRT) appear to be useful in aiding smoking cessation and increase the rate of quitting by 50 to 70% (Stead 2012) [evidence level I]. NRT is most suitable for nicotine dependent smokers who are motivated to quit. All forms of NRT (at equivalent doses) are similarly effective in aiding long-term cessation. Evidence for efficacy of NRT is strongest in in those who smoke more than 15 cigarettes daily but there is also evidence of benefit in lighter smokers who choose to use pharmacotherapy (Shiffman 2005) [evidence level II). There are a range of forms available in Australia (transdermal patch, gum, inhalator, lozenge, and mouth spray). The choice of type of NRT depends on patient preference, needs and tolerance. NRT is more effective when combined with counselling and behavioural therapy (Schwartz 1987). All forms of NRT should be used for at least eight weeks. Information on the forms of NRT available, PBS listing and initial dosing guidelines are available in the RACGP smoking cessation guidelines (http://www.racgp.org.au/your-practice/guidelines/smoking-cessation/) and the Australian Medicines Handbook (https://shop.amh.net.au/).

NRT is safe in patients with stable cardiac disease such as angina pectoris (Joseph 1996, Mahmarian 1997, Nitenberg 1999) [evidence level II]. NRT should be used with caution in people with recent myocardial infarction, unstable angina, severe arrhythmias and recent cerebrovascular events (Meine 2005) [evidence level III-2]. NRT produces lower peak levels of nicotine than active smoking, so theoretically, should be safer than smoking, even in patients with unstable disease.

Combination NRT. Combining two forms of NRT (patch plus oral form, such as gum or lozenge) has been shown to be more efficacious than a single form of nicotine replacement. The patch provides a steady background nicotine level, and the oral forms provide relief for breakthrough cravings as needed. There is evidence from nine trials that this type of combination NRT is more effective than a single type (Stead 2012) [evidence level I]. Combination NRT can be recommended:
as first-line treatment for those who smoke and are nicotine dependent
for those unable to quit using NRT monotherapy alone
for those who experience cravings using NRT monotherapy alone.

Pre-cessation nicotine patch. There is evidence to support use of the nicotine patch prior to smoking cessation. A meta-analysis found that the nicotine patch used prior to quit day increased success rates compared to standard therapy (Shiffman 2008) [evidence level I].

Reduce to quit. There is also evidence for use of NRT to help smokers who are not willing to quit immediately to reduce their tobacco and then progress to quitting. A meta-analysis found that reducing cigarettes smoked before quit day versus quitting abruptly, with no prior reduction, produced comparable quit rates (Lindson 2010).

P1.2.2 Nicotine receptor partial agonists

The addictive properties of nicotine are considered to be mediated through its action as an agonist at alpha4beta$_2$ nAnti-Cholinergic Receptors (α4β2 nAChR), which stimulate the release of dopamine (Coe 2005). Varenicline was developed to counteract the effects of nicotine on the nAChRs, and its efficacy in smoking cessation has been assessed in a Cochrane systematic review (Cahill 2008). In five trials of varenicline compared to placebo for smoking cessation, it was found to be significantly more effective for continuous abstinence at 12 months than placebo (n= 2023, OR 3.22, 95% CI 2.43-4.27, NNT= 8, 95% CI 6-11). A 12-week course of treatment is recommended, starting 1–2 weeks before the quit date and titrating the dose as follows: days 1–3: 0.5 mg daily; days 4–7: increase to 0.5 mg twice daily; and continue with 1 mg twice daily from day 8 to the end of a 12-week treatment course. Efficacy has also been demonstrated in people with COPD in a double-blind, multinational study of 504 patients with mild to moderate COPD (Tashkin 2011a). The primary end point of carbon monoxide-confirmed continuous abstinence rate (CAR) for weeks 9 to 12 was significantly higher for patients in the varenicline group (42.3%) than for those in the placebo group (8.8%) (OR 8.40, 95% CI 5-14, p<.0001) [evidence level II]. Although adverse effects could not be pooled for analysis in the systematic review, multiple trials reported an increased incidence of minor effects, particularly nausea, which was mostly at mild to moderate levels and usually subsided over time, but also insomnia and abnormal dreams. People planning to use the drug should set a date to stop smoking and be warned that varenicline frequently causes nausea which may settle over time and taking it with food and a full glass of water may help reduce nausea. Varenicline has no known clinically meaningful interactions with other drugs. Two trials have tested the use of varenicline beyond the 12-week standard regimen and found the drug to be well-tolerated and effective during long-term use. Three studies comparing varenicline with bupropion found it to be significantly more effective in achieving continuous abstinence at one year (n= 1,622, NNT= 14, 95% CI 9-32). An open-label study comparing varenicline with NRT did not find any difference in one-year cessation rates, despite higher abstinence at the end of treatment (Aubin 2008). There have been questions about the safety of varenicline in people with mental health conditions. Psychiatric comorbidity is common in those who smoke, and in a large randomised trial varenicline was found to be safe in those with stable mental illness or a past history of mental illness (Anthenelli 2013). There is also evidence that varenicline is safe and effective to assist cessation in people with schizophrenia (Pachas 2012, Williams 2012). Varenicline can be used in those who smoke with mental health problems, but these patients should be monitored during quit attempts. These patients should be advised to report unusual mood changes, depression, behaviour disturbance and suicidal thoughts, and stop using the medicine if these occur.

Cytisine, a naturally occurring substance chemically related to varenicline, has been used for smoking cessation for decades in parts of Eastern Europe. In the Cochrane meta-analysis of trials comparing cytisine with placebo, the risk ratio for cessation was 3.98 (95% CI 2.01-7.87). A non inferiority trial conducted in Australia compared standard cytisine treatment (25 days) with standard varenicline treatment (84 days). The verified 6-month continuous abstinence rates were similar (11.7% for the cytisine group vs 13.3% for the varenicline group) but the difference did not meet the noninferiority margin of 5% (Courtney 2021). Cytisine is not currently registered for use in Australia or New Zealand but importation is possible.

P1.2.3 Antidepressants

Antidepressants for smoking cessation have been shown to be effective in a number of trials which have been pooled in a Cochrane systematic review (Hughes 2014). This review included a total of 90 trials, 44 of which assessed the effect of bupropion and 10 nortriptyline. Pooling six available trials using nortriptyline as the only pharmacotherapy showed evidence of a significant benefit for over placebo in achieving cessation in the longer (6-12 months) term (NNT= 10, 95% CI 6-21). Nortriptyline has the potential for serious adverse effects, but it was not possible to pool adverse effects from the few small trials for smoking cessation. While none of the included trial reported major adverse effects, individual studies did report an increased incidence of antimuscarinic adverse effects such as dry mouth and constipation.

Bupropion, when used as the sole pharmacotherapy, doubled the odds of smoking cessation compared to placebo at ≥ 6 months (44 trials, NNT= 16, 95% CI 13-20). There were few serious adverse effects reported, although it is known there is a risk of about 1 in 1000 of seizures associated with bupropion use. As a result, it is contraindicated in patients with past seizures, known CNS tumours, bulimia, alcohol abuse or a history of head trauma. Bupropion may interact with other antidepressants, especially monoamine oxidase inhibitors, which require a 14-day washout. While minor adverse effects could not be pooled, individual trials frequently reported insomnia, dizziness and headache to be more common with bupropion than placebo. Initial concerns that bupropion may increase suicide risk are currently unproven. It is recommended as first-line pharmacotherapy for smoking cessation alongside NRT (Hughes 2014) [evidence level I] and is of similar efficacy as NRT monotherapy (Cahill 2013). The recommended dose is 150 mg orally once daily for three days, then 150 mg twice daily (at least eight hours apart) for between seven and nine weeks, in combination with counselling. A quit date should be set (e.g. Day 5–10). The drug works equally well in smokers with and without a past history of depression. It is also effective in people who have relapsed and are motivated to quit again. There is insufficient evidence that adding bupropion or nortriptyline to nicotine replacement therapy provides an additional long-term benefit. Pooled results from four trials comparing bupropion to varenicline showed significantly lower quitting with bupropion than with varenicline (RR 0.68, 95% CI 0.56-0.83). Three trials of extended therapy with bupropion to prevent relapse after initial cessation did not find evidence of a significant long-term benefit.

The Cochrane systematic review included four trials of selective serotonin reuptake inhibitors or their own (two of fluoxetine, one of sertraline and one of paroxetine) and two trials of fluoxetine as an adjunct to NRT. None of these detected significant long-term effects, and there was no evidence of a significant benefit when results were pooled. There was one trial of the monoamine oxidase inhibitor moclobemide, and one of the atypical antidepressant venlafaxine, neither of which detected a significant long-term benefit. Two trials of the herbal therapy St John's Wort also showed no benefit.

Based on a Cochrane meta-analysis of six trials, the tricyclic antidepressant nortriptyline doubles cessation rates compared with placebo treatment at six months when used as sole pharmacotherapy (RR 2.03, 95% CI 1.48-2.78) (Hughes 2014). All studies included in the Cochrane Review were placebo-controlled and used doses of 75 to 100 mg/day or titrated doses to serum levels recommended for depression during the week prior to the quit date. Side effects include dry mouth, constipation, nausea, sedation, and headaches. Nortriptyline is not licensed for smoking cessation. It is dangerous in overdose and can increase the risk of arrhythmia in patients with cardiovascular disease.

P1.2.4 Other agents

A number of other agents have been shown to be effective in smoking cessation but are not commonly used in clinical practice. Clonidine, an antihypertensive agent, increased smoking cessation 12 weeks following the end of treatment compared to placebo, although abstinence was not objectively confirmed in all studies (NNT= 12, 95% CI 6-32). There was a high incidence of dose-dependent adverse effects, particularly dry mouth and sedation (Gourlay 2004). Anxiolytics have not been shown to be effective in smoking cessation. A Cochrane systematic review including one trial each of diazepam, meprobamate, metoprolol and oxprenolol and two trials of buspirone concluded there was

no strong evidence of an effect for any of these drugs, but confidence intervals were wide, and an effect of anxiolytics cannot be ruled out on current evidence (Hughes 2000).

P1.2.5 Electronic cigarettes (e-cigarettes)

E-cigarettes are battery-powered devices that may deliver nicotine in a vapour without tobacco or smoke. Nicotine e-cigarettes can relieve cravings and symptoms of nicotine withdrawal as well as simulating the behavioural and sensory aspects of smoking.

Concerns about e-cigarettes include limited evidence for short-term efficacy and short-and long-term safety, particularly in patients with current chronic disease. Rather than cessation, concurrent use with smoking may continue. A 2022 NHMRC CEO Statement on electronic cigarettes was informed by a systematic review of global evidence by Banks et al (Banks 2022) [evidence level I]. The statement was based on evidence reviews commissioned by the NHMRC on the topics of e-cigarette use and smoking behaviour (uptake and cessation), the effects of e-cigarette advertising, promotion and sponsorship, and e-cigarette use and health outcomes. Relevant evidence statements from the publication are:

- E-cigarettes can be harmful. All e-cigarette users are exposed to chemicals and toxins that have the potential to cause adverse health effects.
- E-cigarette-related poisonings have substantially increased over the past 5 years. E-cigarette related calls to Australian Poisons Information Centres have more than doubled between 2020 and 2021.
- There are no health benefits of using e-cigarettes if you do not currently smoke tobacco cigarettes.
- Short-term e-cigarette use may benefit smokers if they are able to quit smoking and have been previously unsuccessful with other smoking cessation aids.
- There are other proven safe and effective options available to help smokers quit.

In November 2022 the Cochrane Library published an update of its review on electronic cigarettes for smoking cessation (Hartmann-Boyce 2022). The review included 78 studies of which 17 were new to the update. The comparison of nicotine e-cigarettes versus NRT was of studies comparing smoking cessation at six months or more and measures of harm at one week or longer of e-cigarette use. There were six studies in the analysis including one study in a pregnant population. The total number of participants was 2378. The risk ratio was 1.63 (95% CI: 1.30 to 2.04) favouring nicotine e-cigarettes over NRT. Using the Grade criteria, the authors rated the certainty of evidence as high meaning that further studies would be unlikely to change the effect estimate in a way that would alter its clinical interpretation. A key factor in the rating of the evidence was the rating of risk of bias in the included studies. The review authors rated the risk of bias as low in five of the six studies, including the largest study (Hayek et al 2019) which exerted the greatest influence on the risk estimate.

There are limited studies of nicotine e-cigarettes in populations of people with COPD. An observational study of more than 4,500 current or former smokers aged 45 to 80 years (at least 10 pack years) has found that starting around 2010, there has been a rapid rise in the prevalence of e-cigarette use among older adults with or at risk for COPD (Bowler 2017). Patients with mild, moderate, and severe COPD were just as likely to try and continue to use e-cigarettes as those without COPD. E-cigarette users had a heavier conventional cigarette smoking history and worse respiratory health, were less likely to reduce or quit conventional cigarette smoking, had higher nicotine dependence, and were more likely to report chronic bronchitis and exacerbations. As stated in the e-cigarettes position paper from the Forum of Respiratory Societies, since electronic cigarettes generate less tar and carcinogens than combustible cigarettes, use of electronic cigarettes may cause less disease related to these components. However, the health risks of electronic cigarettes have not been adequately studied and evidence on the safety and efficacy of e-cigarettes is still emerging (Hartmann-Boyce 2016). Until long-term safety and efficacy is established, e-cigarettes cannot be recommended as a harm minimisation strategy among smokers with, or at risk of COPD.

In some cases, doctors may choose to prescribe nicotine e-cigarettes as a means of supporting smoking cessation. TGA approved pharmacotherapy combined with behavioural support should be offered as first line therapy. Nicotine e-cigarettes are an unapproved product, meaning that unlike other forms of nicotine replacement therapy, they have not been assessed by the TGA for safety, quality and efficacy. From 1 October 2021, the Australian government introduced restrictions aimed at reducing access to the use of nicotine e-cigarettes among adolescents and young adults while making them available for supporting smoking cessation. The arrangements include requiring a valid prescription in order to get access to nicotine vaping products whether dispensed in Australia or imported from overseas. A focussed update of the RACGP Smoking Cessation guidelines was undertaken to provide guidance about the rescheduling of nicotine e-liquids. Therapeutic Goods (Standard for Nicotine Vaping Products) (TGO 110) Order 2021 (TGO 110) came into effect on 1 October 2021. TGO110 sets minimum standards for nicotine vaping products supplied in Australia.

Refer to the following to access these guidelines: https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/supporting-smoking-cessation/pharmacotherapy-for-smoking-cessation

Therapeutic Goods Administration provides information: https://www.tga.gov.au/resource/nicotine-vaping-products-and-vaping-devices

Lung Foundation Australia has a position statement about electronic cigarettes: https://lungfoundation.com.au/lung-health/protecting-your-lungs/e-cigarettes-and-vaping/e-cigarettes-for-smoking-cessation/

https://lungfoundation.com.au/health-professionals/clinical-information/smoking-cessation/

The rapid uptake of nicotine vaping in young people, including people who have never smoked, has prompted the federal health minister to propose further restrictions on access to nicotine vaping products. If passed, the legislation will:

- ban the importation of vaping products (including devices, e-liquids and pods, whether they contain nicotine or not), except by pharmacies who will be permitted to dispense them under a prescription
- introduce minimum quality standards for vaping products, including restricting flavours, colours and other ingredients
- require all vaping products to have pharmaceutical-like packaging
- reduce permissible nicotine concentrations and volumes
- ban all single-use disposable vaping devices
- allow all GPs to write prescriptions for vaping products without applying to become an "authorised prescriber" of NVPs.

P1.3 Prevent smoking relapse

Family, friends and workmates should be advised of the intention to quit and asked to provide understanding and support. The relapse rate is increased if there are other smokers in the household. Success is more likely if all the smokers agree to quit together. Suggest the patient ring the Quit Line or other local services (Australia 137 848 www.quitnow.gov.au/; NZ, 0800 778 778).

Former smokers who attend for follow-up are more likely to be successful in the long term. Support is most needed in the first few weeks, so regular follow-up visits then and over the first three months should be encouraged.

P2. Immunisations

Vaccination reduces the risks associated with influenza and pneumococcal

infection [evidence level I, strong recommendation]

P2.1 Influenza immunisation

In people aged 65 years and older, annual influenza immunisation may lower the risk of influenza and probably lowers the risk of influenza-like illness (Demicheli 2018). A Cochrane systematic review has shown that in people with COPD, inactivated influenza vaccine reduced the total number of exacerbations per vaccinated person, compared to placebo (mean difference -0.37, 95% CI -0.64 to -0.11, n=180 patients; rated as low-quality evidence due to only 2 RCTs) (Kopsaftis 2018a) [evidence level I]. There was no change in rates of hospital admission or mortality. Adverse effects are mild, local, transient and self-limiting and include sore arm, mild fever and arthralgia. Please see the link to The Australian Immunisation Handbook on the NHMRC's website for the latest details about available vaccines and timing of influenza vaccination: https://immunisationhandbook.health.gov.au.

P2.2 Pneumococcal immunisation

Pneumococcal immunisation is recommended for all patients with COPD. Pneumococcal immunisation with conjugated vaccines covering 13 virulent serotypes (13vPCV) is highly effective in preventing community-acquired pneumococcal pneumonia in older adults (Bonten 2015). In contrast, the pneumococcal polysaccharide vaccine covering 23 virulent serotypes (23vPPV) is less effective in elderly or immunosuppressed patients (Simberkoff 1986). People with COPD vaccinated with injectable polyvalent pneumococcal vaccines are less likely to experience an episode of community-acquired pneumonia (OR 0.62, 95% CI 0.43-0.89) with a NNTB of 21 to prevent one episode of pneumonia (95% CI 15-74) and vaccination also reduces the likelihood of an exacerbation of COPD (OR 0.6, 95% CI 0.39-0.93), NNT of 8 to prevent one exacerbation (95% CI 5-58) (Walters 2017) [evidence level I]. Evidence was insufficient in this meta-analysis by Walters et al for comparison of different pneumococcal vaccine types.

For those with newly diagnosed COPD who have never received pneumococcal immunisation: a first dose of 13vPCV (conjugated vaccine) is recommended at diagnosis followed by up to two additional doses of 23vPPV regardless of age. The number of lifetime doses of 23vPPV is now limited to 2 doses for all people who are recommended to receive 23vPPV. The doses of 23vPPV received in the past are also counted when deciding how many more are required. If a person has already received at least two doses based on previous recommendations, no further doses of 23vPPV are to be given.

In the current national immunization program (NIP) patients under the age of 70 years with COPD and chronic emphysema are not included in the risk conditions for National Immunisation Program (NIP) funded pneumococcal vaccination. Consequently, they are not eligible for reimbursement. The NIP provides funding for 13vPCV followed by 23vPCV vaccine for Aboriginal and Torres Strait Islander adults 50 years and over.

Please see The Australian Immunisation Handbook for further details.

The additive effect of pneumococcal immunisation to annual influenza immunisation has been studied in one small randomised, controlled trial over two years in Japanese patients with chronic lung disease (Furumoto 2008). They found a significant additive effect of receiving both vaccines on exacerbations in patients with COPD (influenza vaccine alone = 26% versus both vaccines =10.3%, p=0.037), supporting current recommendations for dual immunisation.

P2.3 Haemophilus influenzae immunisation

A Cochrane Review/meta-analysis of six placebo-controlled RCTs evaluating 557 patients, conducted to test the efficacy of enteric-coated, killed preparations of *H. influenzae* in populations prone to recurrent exacerbations of chronic bronchitis or COPD, concluded that there was no significant reduction in exacerbations in the vaccinated group when compared to the placebo group (Teo 2017)

[evidence level I].

P3. Immunomodulatory agents

A Cochrane review of 36 studies published between 1981 and 2015 and involved 6192 participants with chronic bronchitis or COPD treated with either immunostimulants or placebo over a mean treatment period of 6 months (Fraser 2022) [evidence level I]. Participants treated with immunostimulants were slightly more likely to be free of exacerbations during the treatment period (OR 1.48, 95% CI 1.15 to 1.90; 15 RCTs, n=2961; I2 = 53%). Based on a mean estimate of baseline risk of 52%, 11 (95% CI 7 to 29) participants required treatment with an immunostimulant agent for one to be exacerbation-free. Compared to placebo, fewer participants receiving immunostimulants required antibiotics during treatment (OR 0.34, 95% CI 0.18 to 0.63; 542 participants). The odds of experiencing an adverse event were similar between immunostimulant and placebo groups (OR 1.01, 95% CI 0.84 to 1.21; 20 RCTs, 3780 participants). Because there were so few events, the effect of immunostimulants on all-cause and respiratory-related mortality was unclear. The evidence assessed in this Cochrane review has several limitations. The agents used across studies were diverse, and detail about their purity and composition was limited, though the majority are designed to stimulate an immune response from bacterial products. The external validity of the study findings are uncertain, as only two of the 15 included trials were published in the last 10 years, and they will not reflect the current standards of practice. Furthermore, the reviewed population may not represent people with COPD according to our current definition, as included participants with chronic bronchitis who did not necessarily have airflow limitation, making it less generalisable to COPD. In conclusion, it is uncertain whether immunostimulants improve quality of life, and whether they are associated with reduced exacerbation risk and duration of respiratory-related hospitalisations in people with COPD. Further trials are needed to determine efficacy along with current recommended treatments.

The available evidence suggests that the putative immunomodulatory agent OM-85 BV is well tolerated (Sprenkle 2004) [evidence level I]. However, consistent results across important clinical outcomes, such as exacerbation and hospitalisation rates, are lacking to determine whether it is effective. Further randomised, controlled trials enrolling large numbers of persons with well-defined COPD are necessary to confirm the effectiveness of this agent.

P4. Macrolides

For patients with moderate-severe COPD and recurrent exacerbations, trials have found that long-term low-dose oral macrolides reduce the number of patients experiencing an exacerbation and the frequency of exacerbations. The number needed to treat to prevent one exacerbation (NNT) was 8 (95% CI 5-18) (Herath 2018).

A systematic review of prophylactic macrolide treatment in severe COPD, which included 6 RCTs involving 1,485 COPD patients, showed that regular treatment of at least 6 months in duration results in a significant decrease in COPD exacerbations (RR 0.65, 95% CI 0.43-0.89, p=0.01). Participants treated with macrolides were more likely to experience non-fatal adverse (gastrointestinal reactions, ototoxicity, rash, and liver injury) events compared to the placebo treated group (Yao 2013) [evidence level I]. However, prudence would suggest this treatment should be reserved for patients who have severe disease with recurrent exacerbations, in whom other treatments (for example: smoking cessation, pulmonary rehabilitation, vaccination and optimal use of other preventive pharmacotherapy known to reduce exacerbations) have been optimised. Retrospective analysis of the trial by Albert et al found no evidence of treatment benefit among current smokers, with the greatest benefit seen in milder COPD and older patients (Han 2014). Prospective data in predefined groups is required before any sub-group treatment recommendations can be made.

A Cochrane network meta-analysis of various prophylactic antibiotics for patients with COPD (12 studies, n=3,405 patients) found beneficial effects of macrolides for reducing exacerbations (hazard ratio 0.67, 95% credible interval 0.60 –0.75) compared to placebo and improving quality of life (mean difference in SGRQ of -2.30, 95% credible interval -3.61 to -0.99, although this difference did not

reach the MCID) (Janjua 2021) [evidence level I]. No significant benefits were associated with use of long-term quinolones or tetracyclines, compared to placebo.

Since the publication of the above two systematic reviews, a further 12-month double-blind RCT comparing doxycycline 100mg daily to placebo has also demonstrated a lack of benefit of long-term doxycycline. The UK-based study recruited 222 patients with COPD and a history of exacerbations. Doxycycline did not reduce the exacerbation rate. Those receiving doxycycline experienced a deterioration in health status on the SGRQ by 5.2 points (95% CI 1.44 to 9, p=0.007) compared to the placebo group (Allinson 2023) [evidence level II].

Given the potential significant adverse effects of macrolides (including cardiac toxicity, ototoxicity, diarrhoea, and the development of antibiotic resistance which affects both the individual and the community), expert advice is recommended before starting long-term macrolide therapy. It should be noted that azithromycin is not available on the PBS for long term use.

P5. Long-acting bronchodilators

P5.1 Antimuscarinics

A Cochrane Review of nine RCTs (6,584 patients) found that tiotropium reduced the odds of a COPD exacerbation (OR 0.74, 95% CI 0.66-0.83) and related hospitalisations (OR 0.64, 95% CI 0.51-0.82) compared to placebo or ipratropium. The number of patients who would need to be treated with tiotropium for one year was 14 (95% CI 11-22) to prevent one exacerbation and 30 (95% CI 22-61) to prevent one hospitalisation (Barr 2005) [evidence level I]. Another systematic review of 22 trials with 15,276 participants found that anticholinergic (antimuscarinic) use also significantly reduced respiratory deaths (RR 0.27, 95% CI 0.09-0.81) compared with placebo. It would be necessary to treat 278 patients with antimuscarinic agents to prevent one death (Salpeter 2006) [evidence level I].

A randomised double-blind placebo-controlled trial of four years duration found that tiotropium was associated with a reduced risk of death at end of treatment (hazard ratio 0.84, 95% CI 0.73-0.97) (Celli 2009). It would be necessary to treat at least 53 patients to prevent one death. The precise statistical significance varied with the period of analysis. The hazard ratio for tiotropium compared to placebo varied from 0.87 (95% CI 0.76-0.99, p=0.034) for the full 4 years to 0.89 (0.79-1.02, p=0.086) for 4 years+ 30 days [evidence level II]. A pre-specified subgroup analysis of this four-year trial (Decramer 2009) found that tiotropium reduced the rate of decline of post-bronchodilator FEV_1 in patients with GOLD II COPD (43 ml/year versus 49 ml/year, p=0.024). However, the of pre-bronchodilator FEV_1 decline was not different between the groups.

P5.2 Comparison of inhaled medications

A systematic review examined the relative effectiveness of inhaled medications to reduce the risk of exacerbations of COPD (Puhan 2009a). The authors identified 35 randomised controlled trials of at least 4 weeks duration that enrolled 26,786 patients with COPD of whom 27% had one or more exacerbations. All regimes significantly reduced the odds of exacerbation compared with placebo - no single inhaled medication was more effective than another. If FEV_1 was ≤ 40% predicted, long acting antimuscarinics, inhaled corticosteroids and combination treatment reduced exacerbations significantly compared with long-acting beta agonists alone. However the authors did not have FEV_1 data for individual patients.

In 2012, Chong et al (Chong 2012) performed a meta-analysis that compared tiotropium to a range a long-acting beta-agonists, data from over 11,000 patients were included and trials were at least 3 months long. Chong reported that tiotropium was more effective in preventing COPD exacerbations leading to hospitalisation (OR 0.86, 95% CI 0.79-0.93). There was no difference in mortality, all-cause hospitalisations, quality of life and lung function. There were fewer serious adverse events with tiotropium (OR 0.88; 95% CI 0.78-0.99).

P6. Corticosteroids

The effect of inhaled corticosteroids on the disease progression in COPD has been the subject of a series of controlled trials and systematic reviews and the effect remains unclear. A Cochrane systematic review found benefits of inhaled corticosteroids in reducing exacerbations and reducing decline in quality of life, but no consistent benefit on rate of decline in lung function or mortality (Yang 2012) [evidence level I]; see Section **O3.2 Inhaled corticosteroids** for details). While these data do not support the use of inhaled corticosteroids in all people with COPD, they are indicated for those with more severe disease (FEV_1 <50% predicted) and a history of frequent exacerbations.

P7. Mucolytic agents

Mucolytics may benefit certain patients with COPD [evidence level I, strong recommendation]

Mucolytics, including N-acetylcysteine (NAC), ambroxol (3), sobrerol, carbocysteine, sobrerol, letosteine, cithiolone, iodinated glycerol, N-isobutyrylcysteine (NIC), myrtol and erdosteine have multiple possible actions in COPD including decreasing sputum viscosity, and antioxidant, anti-inflammatory or antibacterial activity.

A 2019 Cochrane Review (Poole 2019) [evidence level I] included 38 trials involving 10,377 participants with COPD or chronic bronchitis, who were randomised to receive at least daily oral N-acetylcysteine, carbocysteine, erdosteine, ambroxol, or placebo. The authors found treatment with mucolytics was associated with an increased likelihood of being exacerbation free during the period of study (OR 1.73, 95% CI 1.56-1.91) and calculated the number needed to treat with mucolytics for an average of nine months to keep an additional participant exacerbation free was eight (NNTB 8, 95% CI 7-10). For this outcome there was high heterogeneity ($I^2 = 62\%$), and the authors recommend caution with the interpretation of the results. Overall, the effect size of the more recent trials was smaller. Further the number of people with one or more hospitalisation was reduced, but study results were not consistent (Peto OR 0.68, 95% CI 0.52-0.89; $I^2 = 58\%$). Mucolytic use resulted in a reduction of 0.43 days of disability per participant per month compared to placebo (95% CI -0.56 to -0.30; $I^2 = 61\%$). The authors concluded that the use of mucolytics in patients with chronic bronchitis or COPD may produce a small reduction in the likelihood of an exacerbation, in days of disability per month, and possibly hospitalisation. There was no clinically or statistically significant effect on quality of life.

In another meta-analysis of 10 RCTs involving 1,278 patients, Cazzola reported that compared to placebo, erdosteine improved the clinical condition of COPD, as measured by global overall clinical scores comprising a number of measures (SMD -0.56, 95% CI -0.94 to 0.17; p=0.001) (Cazzola 2018a). Erdosteine treatment also reduced the risk of COPD exacerbation and the risk of experiencing at least one exacerbation compared to control.

There is evidence to support the use of high dose oral N-acetylcysteine in the reduction of COPD exacerbations and improvements in lung function. This is supported by the results of a systematic review and meta-analysis by Cazzola et al (Cazzola 2015a). In their meta-analysis of 13 studies involving 4155 COPD patients, both low (<600mg/day) and high doses (>1200mg/day) of N-acetylcysteine significantly reduced the frequency of exacerbations (relative risk 0.75, 95% CI 0.66–0.84; p<0.01). The effectiveness of N-acetylcysteine in reducing exacerbations was also confirmed by seven RCTs performed in patients who were enrolled based on ATS/ERS or GOLD guidelines, spirometry confirmed COPD (relative risk 0.78, 95% CI 0.65–0.93; p<0.01) [evidence level I]. In patients with COPD, high dose (≥ 1200mg/day) N-acetylcysteine should be considered as an effective therapy for reducing exacerbations. In patients with chronic bronchitis but without airflow limitation, a dose of 600mg/day leads to reduced exacerbations.

P8. Humidification and nasal high flow (NHF) therapy

Several trials have shown that nasal high flow (NHF) humidified air in stable COPD patients reduces transcutaneous CO_2 ($PtCO_2$) and respiratory rate (Fraser 2016, Biselli 2017, McKinstry 2018,2019).

A randomised trial by Rea et al (Rea 2010) found that NHF for up to 2 hours daily reduced annual exacerbation days and days to first exacerbation but not hospital admission compared with usual care in a group of 108 patients, with COPD/ bronchiectasis. Quality of life and lung function also improved. No sham treatment was given.

In a small study crossover by Nagata et al (Nagata 2018), use of nocturnal HFNC in addition to LTOT also demonstrated significant benefit in quality of life (St George's Respiratory Questionnaire COPD (SGRQ-C)) score improved by 7.8 points; (95% CI 3.7-11.9; $p<0.01$) and measured PCO_2 (-4.1, 95% CI -6.5 to -1.7), other studies have not demonstrated benefits in patient related outcomes. In a 12-month multi-centre study of just over 100 patients with severe COPD and resting hypercapnia on LTOT in Japan by Nagata (2022), reductions were found in annual moderate to severe exacerbation rates and days to first exacerbation in the group receiving high flow nasal oxygen in addition to long term oxygen therapy, but there were no changes in breathlessness scores, for example, between the groups, over the duration of the study. No sham treatment was given in these studies by Rea and Nagata, and in the 2022 Nagata study, hospitalisation rate was not reported. The arm without the high flow nasal canula intervention had significantly higher combined moderate and severe exacerbations, which was the primary outcome of interest, by an adjusted odds ratio of 2.85 (95% CI 1.48-5.47). Hospital admissions were classed as severe exacerbations but were not significantly reduced (Nagata 2022) [evidence level II].

In a 12-month study by Storgaard et al (Storgaard 2018), 200 Danish patients with stable hypoxaemic COPD who had commenced long term oxygen therapy (LTOT) within the preceding 3 months were randomised to LTOT alone or LTOT plus high flow nasal cannula (HFNC) at 20 litres/minute with oxygen flow unchanged (mean 1.75 (0.8) L) for at least 6 hours per day. 67 patients in the HFNC group completed the trial and 71 in LTOT group. Analysis was by intention to treat. Exacerbation rate was decreased in the HFNC group but not hospitalisations.

The role of long term domiciliary HFNC is as yet still unclear. Prospective randomised controlled trials in the appropriate COPD patient population with meaningful clinical endpoints are required before long term domiciliary NHF can be broadly recommended.

In the acute setting, high flow nasal oxygen has a role in hypoxic respiratory failure where hypercapnia has been excluded (Frat 2015, Stephan 2015). Please see section X3.2.1 for further details.

P9. Regular review

Regular review, with objective measures of lung function, health status (COPD Assessment Test (CAT)), consideration of referral to pulmonary rehabilitation and medication review, is recommended. This may reduce complications and the frequency or the severity (or both) of exacerbations and admissions to hospital. Please see comments in section D.

P10. Oxygen therapy

Long-term oxygen therapy has survival benefits for COPD patients with hypoxaemia [evidence level I, strong recommendation]

Long term oxygen therapy (LTOT) reduces mortality in COPD (Medical Research Council Working Party 1981, American Thoracic Society 1995, Gorecka 1997, Nocturnal Oxygen Therapy Trial Group 1980, Siafakas 1995, Tarpy 1995, Zielinski 1998). It may also have a beneficial impact on haemodynamics, haematological status, exercise capacity, lung mechanics and mental state (Weitzenblum 1985, Zielinski 1998, Tarpy 1995). Although effective, it is a potentially expensive and cumbersome therapy that should only be prescribed for those in whom there is evidence of benefit (see below). Information on prescribing oxygen therapy is given in **Appendix 3**.

Long-term continuous oxygen therapy (ideally at least 18 hours a day) is appropriate for patients who have PaO_2 consistently < 55 mmHg (7.3 kPa; SpO_2 less than 88%) (Medical Research Council Working Party 1981, Nocturnal Oxygen Therapy Trial Group 1980) when breathing air, at rest and awake [evidence level I]. If oxygen is prescribed when the patient's condition is unstable (e.g., during an exacerbation), then the requirement for it should be reviewed four to eight weeks after initiation as it has been demonstrated in several studies that patients frequently do not fulfil the criteria for LTOT at subsequent follow up (Eaton 2004, Levin 2018, Khor 2019). The studies by Khor and Levin demonstrated that approximately 50% of patients no longer required LTOT at review 1-2 months after discharge. At assessment for ongoing therapy, the patient's condition must be stable, all potentially reversible factors must have been treated and the patient must have stopped smoking at least one month previously.

Polycythaemia (haemoglobin level > 170 g/L), clinical or electrocardiographic evidence of pulmonary hypertension, as well as episodes of right heart failure, are consistent with the systemic effects of chronic hypoxaemia, and continuous oxygen should be supplied if the stable $PaO_2$is 55– 59 mmHg (7.3–7.9 kPa; SpO_2 < 90%) (Siafakas 1995, American Thoracic Society 1995). Continuous oxygen therapy is of most benefit for patients with increased arterial $PaCO_2$ (> 45 mmHg, or 6 kPa) (Nocturnal Oxygen Therapy Trial Group 1980).

Government funding is available on the basis that the prescribing doctor is an approved prescriber (usually a respiratory physician). Oxygen is usually supplied to patients meeting specific criteria and means testing by state or regional health departments in Australia and New Zealand (Serginson 2009).

Oxygen in patients with moderate hypoxaemia

A large study of patients with moderate hypoxaemia (SpO_2 89 to 93%) was powered originally to determine whether continuous oxygen therapy improved mortality (Long-Term Oxygen Treatment Trial Research Group 2016). Subsequently, inclusion criteria were altered to include those who desaturated with exertion but were minimally hypoxaemic at rest (SpO_2 ≥ 94% resting but desaturating to <90% for >10 seconds and with SpO_2 ≥ 80% for ≥ 5 mins). The study demonstrated no difference between groups in the composite outcome of mortality or time to first hospitalisation, nor in any other outcome including quality of life.

738 participants were randomised to receive oxygen at 2 litres per minute or no oxygen. 57% had resting hypoxaemia and were prescribed continuous oxygen at 2 litres per minute and 43% were prescribed oxygen at 2 litres per minute during exercise and sleep. Over a median follow-up of 18.4 months, the median use of oxygen was 15.1 ± 6.2 hours per day in the continuous group and 11.3 ± 5 hours per day in the exercise and nocturnal group. 51 adverse events were noted, with three patients requiring hospitalisation on account of these. The majority of adverse effects were slips and falls, but fire and burns also occurred.

Limitations to this study included an absence of blinding, no placebo arm, and lack of clarity as to whether the study was adequately powered for the modified composite primary outcome.

The findings from this study and its accompanying editorial are consistent with clinical practice guidelines on adult domiciliary oxygen provided by the Thoracic Society of Australia and New Zealand which recommend provision of long-term continuous oxygen therapy only in those who are significantly hypoxaemic (see P10 above) and recommend use of ambulatory oxygen only in the few patients who demonstrate benefit in a blinded test (McDonald 2016a).

In a systematic review and meta-analysis of the effects of home oxygen (delivered either as LTOT or nocturnally) in patients with moderate hypoxaemia, six high quality studies were included. The results demonstrated the effect of home oxygen in reducing 3 year mortality was small or absent and the authors concluded the data did not support the widespread use of home oxygen in this population of patients with moderate hypoxaemia (Lacasse 2022) [evidence level I].

Ambulatory oxygen therapy

In patients who qualify for long-term oxygen therapy (LTOT), ambulatory oxygen therapy can be used in order to maximize usage achieve an average usage of 18 hours day (Nocturnal Oxygen Therapy Trial Group 1980).

In patients who do NOT qualify for LTOT, available evidence does not allow any firm conclusions to be made about the use of long-term intermittent ambulatory domiciliary oxygen therapy in patients with COPD who do not meet the criteria for LTOT. This conclusion is based on a Cochrane Review comprising four studies (total of 331 patients) (Ameer 2014) who received oxygen or air (blinded) for between two and 12 weeks in the home setting. This review found no significant difference in exercise tolerance or mortality in those receiving supplemental oxygen compared to breathing air supplied by a cylinder. Although statistically significant benefits favouring oxygen were found in health-related quality of life (HRQoL) (dyspnoea and fatigue domains of the Chronic Respiratory Disease Questionnaire (CRQ)), the improvements did not reach the threshold for clinical significance. A clinically significant reduction in end exercise dyspnoea favouring oxygen was found in two studies [evidence level I].

Ambulatory oxygen should not be routinely offered to patients who are not eligible for LTOT. However, the use of short-term intermittent oxygen therapy may be considered for:

People who experience oxygen desaturation on exertion

A Cochrane Review of 31 studies found that ambulatory oxygen was efficacious in single assessment studies (in the hospital or laboratory setting) when comparing an exercise test performed breathing oxygen or air in patients with moderate to severe COPD (Bradley 2005) [evidence level I]. Benefits were shown in endurance exercise capacity, dyspnoea at isotime and oxygen saturation. However, the minimum clinically important difference in these variables with oxygen therapy is unknown. Due to the heterogeneity of the studies, subgroup analyses were not possible to determine which patients were more likely to benefit. Acute benefit may be established by comparing exercise tolerance, oxygen saturation and dyspnoea on a field walk test or treadmill test when breathing oxygen and when breathing air (blinded). A cycle ergometry test should not generally be used for this purpose as oxygen desaturation is significantly greater in COPD patients when walking as compared to cycling (Turner 2004, Poulain 2003). It is important to consider that most patients will walk further on a repeat walk test and hence a practice test is usually necessary (Singh 2014c). The endurance shuttle walk test (ESWT) has been shown to be more responsive than the 6-minute walk test when assessing the benefits of ambulatory oxygen (Revill 2010) and it would appear that a practice ESWT may not be necessary when two ESWTs are performed on the same day (Singh 2014c). However, the ESWT requires patients to first perform the incremental shuttle walk test in order to determine the walking speed for the ESWT. Ideally, the oxygen system used in the assessment should be the same as the system the patient would use if oxygen were prescribed at home (e.g. trolley or shoulder bag to

transport the cylinder). It is to be noted that short-burst oxygen i.e. oxygen inhaled immediately prior and/or following exertion with the aim of relieving breathlessness or improving exercise tolerance is not effective (O'Neill 2006) [evidence level I], (O'Driscoll 2008) [evidence level II].

The prescription of supplemental oxygen should not be based solely on an improvement in the distance achieved on a walk test. Factors such as a reduction in dyspnoea and agreement to use oxygen within the home and outdoors during activity should also be considered. As the relationship between single assessments and long-term benefits is unclear, the acute assessment should form only part of the determination and benefit of ongoing ambulatory oxygen therapy. Long-term review and determination of oxygen usage are also important (Bradley 2007).

Ambulatory oxygen therapy during pulmonary rehabilitation

In the absence of need for LTOT there is no direct evidence that the treatment of exercise-induced hypoxaemia retards long-term pulmonary hypertension or prolongs life. Nevertheless, in patients who desaturate during exercise training, supplemental oxygen has been proposed with the aim of delaying the onset of dynamic hyperinflation and the associated dyspnoea (O'Donnell 1997, O'Donnell 2001), and to improve the benefit from training (Emtner 2003). However, neither a 2019 RCT (Alison 2019), nor a systematic review of earlier studies (Nonoyama 2007) [evidence level I] support this approach. In the Australian RCT (Alison 2019), 111 subjects with moderate to severe COPD who had oxygen desaturation to <90% during 6-minute walk tests were randomised to either air or oxygen via nasal prongs at 5L/minute for 8 weeks of 3X/week treadmill and cycle exercise sessions. Both groups improved with respect to outcomes of Chronic Respiratory Disease Questionnaire and endurance shuttle walk test, however there was no additional benefit with supplementary oxygen. This RCT provides strong evidence that the provision of supplementary oxygen does not improve these important outcomes in such exercise programs even when subjects are known to desaturate to <90%.

Other indications for intermittent oxygen therapy

Patients living in isolated areas or prone to sudden life- threatening episodes while they are awaiting medical attention or evacuation by ambulance.

Patients travelling by air: Flying is generally safe for patients with chronic respiratory failure who are on long- term oxygen therapy, but the flow rate should be increased by 1-2 L/minute during the flight (see also below).

Nocturnal oxygen therapy

A large multicentre randomised controlled trial of nocturnal oxygen therapy versus air delivered via concentrator or sham concentrator (the so-called INOX trial) was performed in patients with COPD who did not fulfil criteria for LTOT (Lacasse 2020). Exclusion criteria included smoking cessation less than 6 months previously, significant obstructive sleep apnoea (AHI>15), BMI>40, known left heart failure and bronchiectasis. Inclusion criteria included desaturating to SPO2<90% for at least 30% of the recording time on nocturnal oximetry. Recruitment to this trial was stopped early because of recruitment and retention difficulties after n=243 patients, of a planned n=600, had undergone randomisation. At three years of follow up there was no difference between the groups in the composite endpoint of death from any cause or a requirement for long-term oxygen therapy as defined by the Nocturnal Oxygen Therapy Trial (NOTT) criteria in the intention-to-treat population Although this trial was underpowered, based on these results and those of two previous studies by Fletcher et al (Fletcher 1992) and Chaouat et al (Chaouat 1999) current evidence does not support the prescription of nocturnal oxygen therapy to improve survival or slow disease progression in patients with COPD. However, the confidence intervals around the pooled treatment effects from a meta-analysis of these three studies performed by the authors of this recent INOX trial and presented as supplementary to this study concluded that the confidence limits around these outcomes are wide, and clinically

significant effects are plausible [evidence level I]. More research is needed. In the meantime, some patients with hypoxaemia during sleep may benefit from nocturnal oxygen therapy. Nocturnal hypoxaemia should be considered in patients whose arterial gas tensions are satisfactory when awake, but who have daytime somnolence, polycythaemia or right heart failure. Oxygen may be indicated for patients whose nocturnal arterial oxygen saturation repeatedly falls below 88%. Sleep apnoea should be excluded and treated independently.

P10.1 Fitness to fly

Commercial aircraft operate at altitudes of up to 12 500 metres, with the plane's interior pressurised to 2100–2400 metres. At this "altitude" the alveolar PaO_2 for healthy individuals decreases from 103 mmHg (13.7 kPa) to 64 mmHg (8.5 kPa) and oxygen saturation declines from 97% to 93%.

As a general rule, supplemental oxygen is unlikely to be required if the resting oxygen saturation is 95% or higher, and likely to be required if oxygen saturation is 88% or lower. Patients with oxygen saturation values between these levels might require specialist assessment.

Before flying, patients should ideally be clinically stable. Patients recovering from an exacerbation are particularly at risk. Those already on long-term oxygen therapy need an increase in flow rate of 1–2 L per minute during flight. Careful consideration should be given to any comorbidity that may impair delivery of oxygen to the tissues (e.g., cardiac impairment, anaemia). Exertion during flight will exacerbate hypoxaemia.

The American Thoracic Society currently recommends that PaO_2 during air travel should be maintained at more than 50 mmHg (6.7 kPa). At altitude, PaO_2can be estimated from PaO_2at sea level by means of published nomograms. If the PaO_2at sea level is less than 70 mmHg (9.3 kPa), PaO_2 at 2300 metres is less than 50 mmHg (6.7 kPa). The natural conclusion is that all patients with a PaO_2 less than 70 mmHg (9.3 kPa) at rest at ground level should receive supplemental oxygen (American Thoracic Society 1995, Ahmedzai 2011).

Many lung function laboratories perform high altitude simulation tests (HAST) to assess fitness to fly. These measure arterial blood gas levels or transcutaneous oxygen saturation while breathing a mixture of 15% oxygen and 85% nitrogen, mimicking conditions at 2800 metres.

P11 Long-term home non-invasive ventilation

Raveling et al (2021) performed a meta-analysis of chronic non-invasive ventilation use in patients with COPD and hypercapnia compared to usual care. The analysis was separated into studies where NIV was commenced in a stable phase and studies where NIV was commenced after an exacerbation. Data was included from 13 stable COPD studies (n= 778) and 3 post exacerbation studies (n =364). There is a high risk of bias due to lack of blinding. Note is made of significant differences in trial design and NIV pressures delivered. Smoking status was not reported. Most studies excluded people with obstructive sleep apnoea. For the outcomes of quality of life and mortality sub-group analyses based on NIV pressures and baseline PaCO2 were not performed.

In the stable COPD group, quality of life scores improved with NIV, after three months (SMD 0.39, 95% CI 0.15-0.62, 5 studies, 259 participants); however, the improvement in quality of life was not sustained to 12 months. There was no effect of NIV on exercise capacity. The risk for all-cause mortality is reduced by NIV (adjusted hazard ratio 0.75, 95% CI 0.58-0.97; 3 studies, 405 participants; moderate-certainty evidence).

In the group where NIV was commenced after an exacerbation there was no improvement in quality of life or mortality however, NIV did lead to an improvement in admission-free survival (adjusted hazard ratio 95% CI 0.54-0.94; 2 studies, 317 participants) (Raveling 2021) [Evidence level I].

There was no effect of NIV on lung function in either group. There was no improvement in lung function in either group.

Long term NIV can be considered in patients with severe stable COPD and hypercapnia. Such patients should be referred to a centre with expertise in home NIV.

P12 Alpha1-antitrypsin deficiency

Alpha1-antitrypsin deficiency (AATD) is an inherited condition that increases the risk of developing pulmonary emphysema. Evidence for the diagnosis and treatment of patients with AATD-related lung disease has been comprehensively reviewed in a position statement endorsed by the Thoracic Society of Australia and New Zealand (TSANZ) (Dummer 2020).

D: Develop a plan of care

Good chronic disease care anticipates the wide range of needs in patients with COPD [evidence level I, strong recommendation]

IN THE EARLY STAGES OF DISEASE, patients with COPD will often not recognize and perhaps may ignore mild symptoms, and this contributes to delay in diagnosis. As the disease progresses, impairment and disability increase. As a health state, severe COPD has the third-highest perceived "severity" rating, on a par with paraplegia and first-stage AIDS (Mathers 1999). Depression, anxiety, panic disorder, and social isolation add to the burden of disease as complications and comorbidities accumulate. Patients with severe COPD often have neuropsychological deficits suggestive of cerebral dysfunction. The deficits are with verbal (Incalzi 1997) and visual short-term memory (Crews 2001), simple motor skills (Roehrs 1995), visuomotor speed and abstract thought processing (Grant 1982). Severe COPD is also associated with lower cognitive performance over time (Hung 2009) [evidence level III-2]. One of the most effective means of improving the patient's functional and psychological state is pulmonary rehabilitation.

People with chronic conditions are often cared for by partners or family members. There is evidence that family carers of people with COPD experience significant psychological and physical burdens (Strang 2018).

Health systems around the world are reorienting health care delivery in ways that continue to provide services for people with acute and episodic care needs while at the same time meeting the proactive and anticipatory care needs of people with chronic diseases and multiple morbidities. Wagner and colleagues have articulated domains for system reform in their Chronic Care Model (Wagner 1996). These include Delivery System Design (e.g. multi-professional teams, clear division of labour, acute versus planned care); Self-Management Support (e.g. systematic support for patients / families to acquire skills and confidence to manage their condition); Decision Support (e.g. evidence-based guidelines, continuing professional development programs) and Clinical Information Systems (e.g. recall reminder systems and registries for planning care) (Adams 2007). Many of these domains are addressed in the following sections.

D1. Support team

Clinical support teams working with the primary healthcare team can enhance quality of life and reduce disability for patients with COPD [evidence level III-2, weak recommendation]

Patients and their family and friends should be actively involved in a therapeutic partnership with a range of health professionals (Celli 1995, Spruit 2013, Ries 1995, Lorig 1999). In advanced disease, the many comorbidities, social isolation and disability mean that a multidisciplinary approach to coordinated care may be appropriate. Studies have demonstrated the potential benefits of an interdisciplinary approach on patient quality of life, symptom control, exercise tolerance and hospital episodes (Chavannes 2009, Kruis 2014). Many different healthcare professionals are involved in the crucial components of COPD management, including case finding, smoking cessation support, pharmacotherapy, exercise training and self-management and education and exercise training. A program with an emphasis on co-operation and collaboration between these providers should be established for more effective patient care.

Multidisciplinary collaboration can improve the diagnosis and management of COPD in primary care. Structuring collaboration and communication between primary care professionals involved in the management of COPD (i.e. general practitioners (GP), nurses, physiotherapists, pharmacists and

dieticians) is elementary to achieve this. Links should also be built between primary and secondary care in order to accomplish optimal multidisciplinary care for COPD patients (Schermer 2008).

The general practitioner plays a key role in the delivery and coordination of care for people with chronic disease including COPD and can access a range of Medicare items to support the delivery of multi-disciplinary care. The multidisciplinary team, depending on local resources, may include the members listed below. The role of respiratory specialists is outlined in Section C.

D1.1 General Practitioner

As the primary healthcare provider, the general practitioner (GP) is uniquely placed to identify smokers and help them quit, diagnose COPD in its early stages and coordinate care as the disease progresses (Johnston 2011). Improving GP uptake of spirometry for COPD diagnosis and recommendation of evidence-based behavioural treatments, including smoking cessation and pulmonary rehabilitation, are key to better management of COPD in Australian primary care.

Smoking cessation: A doctor's advice is an important motivator for smoking cessation, especially if the doctor is the family physician. The GP can help initiate the cycle of change by repeated brief interventions. Since relapse to smoking is common, GPs should make enquiries about smoking status routinely at each visit. There are several smoking cessation programs that have been developed for use in general practice. The GP is also the appropriate health professional to recommend or prescribe nicotine replacement therapy and pharmacological and/or non-pharmacological treatment of nicotine addiction (for a detailed discussion of smoking cessation interventions, see Section P).

Early diagnosis: Simple questions relating to smoking history, daily cough and degree of breathlessness should lead to lung function testing. A study in 31 general practice clinics in Melbourne found that although GPs recognised the value of spirometry in differentiating between asthma and COPD, most general practices only used spirometry in diagnostically difficult cases leading to more accurate diagnosis of asthma (69%), but substantial underdiagnosis of COPD (14%) (Abramson 2012). Spirometry needs to be more widely used to improve the accuracy of respiratory diagnoses in general practice.

A national survey of Australian GPs in 2014 identified reactive, relatively passive and delayed approach to diagnosis of COPD, potentially delayed smoking cessation advice and under-utilisation of pulmonary rehabilitation. Less than half of the GP respondents reported using COPD management guidelines (Bereznicki 2017).

In a cluster-randomised controlled trial of general practices in the UK, routine practice identified fewer new cases of COPD, while an active targeted approach to case finding including mailed screening questionnaires before spirometry was found to be a cost-effective way to identify undiagnosed patients and had the potential to improve their health (Jordan 2016).

Coordinate investigation and management: GPs will manage patients with mild to moderate COPD. Referral to a respiratory physician may be indicated to confirm the diagnosis, exclude complications and aggravating factors, and to help develop a self-management plan (**Section C**, **Box 6**).

Coordinate care in advanced disease: GPs play a crucial role coordinating services provided by a range of healthcare professionals and care agencies (the "multidisciplinary team").

A cluster randomised controlled trial of an interdisciplinary COPD intervention in 43 Australian primary care clinics coordinated by general practitioners (GPs) and involving smoking cessation support, home medicines review (HMR) by a consultant pharmacist and home-based pulmonary rehabilitation delivered by a specially trained physiotherapist did not improve health-related quality of life (HRQoL), symptom severity or lung function in a cohort of patients with predominantly mild COPD

(Liang 2019) [evidence level II]. Uptake of the intended intervention components by both GPs and patients was suboptimal (31% completed the full intervention, 26% partially completed the intervention). Exploratory analyses of the 31% who received the intended full intervention showed statistically and clinically significant differences in HRQoL over usual care at 6 months (adjusted mean difference 5.22, 95% CI 0.19–10.25, p=0.042).

D1.2 Other specialist physicians

COPD is an important morbidity in older people which impacts on comprehensive medical management and quality of life. It is important to note that the support team involved in the management of COPD patients may include a geriatrician, cardiologist, endocrinologist and psychiatrist amongst others.

D1.3 GP practice nurse/ nurse practitioner/ respiratory educator/ respiratory nurse

Nurses play an integral role in the assessment and delivery of education and management for people living with COPD. The training, expert knowledge and skills of respiratory nurses allow them to undertake multidimensional assessments and to work with patients to tailor specific therapeutic interventions and to co-ordinate the delivery of person-centred care (McDonald 2018).

Specific aspects of COPD care provided by nurses may include:

- respiratory assessment, including spirometry and pulse oximetry;
- assessment of comorbidity and delivery of interventions for comorbid disease, for example cognitive behavioural therapy for anxiety, and education for diabetes and heart failure;
- evaluation of risk factors and the provision of evidence-based interventions, such as smoking cessation techniques and education to promote physical activity, good nutrition and appropriate vaccination;
- symptom assessment and management in the context of the community, primary and tertiary care settings and pulmonary rehabilitation;
- implementation of, or referral for interventions such as exercise training, pulmonary rehabilitation, airway clearance techniques and oxygen therapy;
- skills training with inhalation devices;
- assessment of adherence and implementation of interventions to improve adherence;
- patient education and skill development regarding the importance of exacerbation avoidance, recognition and treatment;
- education to promote better self-management;
- organisation of multidisciplinary case conferences and participation in care-plan development;
- assessment of the home environment;
- end of life planning;
- *respiratory* nurses also deliver specialised assessments and treatments such as, oxygen assessment and the provision of NIV.

Nurse led self-management programs have led to improved outcomes for people with COPD. Patients discharged from a Hong Kong hospital after a COPD exacerbation were randomised to an intervention group (IG) or usual care group (UG). The IG received a comprehensive, individualised care plan which included education from a respiratory nurse, physiotherapist support for pulmonary rehabilitation, three-monthly telephone calls by a respiratory nurse over one year, and follow-up at a respiratory clinic with a respiratory specialist once every three months for one year. The UG was managed according to standard practice. At 12 months, the adjusted relative risk of readmission was 0.668 (95% CI 0.449–0.995, p=0.047) for the IG compared with the UG. At 12 months, the IG had a shorter length of stay (4.59±7.16 versus 8.86±10.24 days, p≤0.001), greater improvement in mean Modified Medical Research Council Dyspnoea Scale (-0.1±0.6 versus. 0.2±0.6, p=0.003) and St George's Respiratory Questionnaire (SGRQ) score (-6.9±15.3 versus. -0.1±13.8, p=0.003) compared with the UG (Ko 2017). Another nurse led RCT of an intensive self-management intervention resulted in a

reduction in hospitalizations (at 12 months) and in emergency department visits at 6 and 12 months. Additionally, exercise capacity improved as measured by the 6MWD, as did health related quality of life (Wang 2019). See self-management section.

D1.4 Physiotherapist

Physiotherapists are involved in a broad range of areas, including exercise testing and training, assessment for oxygen therapy, patient education, airway clearance techniques, breathing retraining, mobility, non-invasive ventilation (NIV), postoperative respiratory care and assessment and treatment of musculoskeletal disorders commonly associated with COPD. Please refer to O6 for more detailed information.

D1.5 Occupational therapist

Occupational therapists provide specific skills in task optimisation and prescription for those with severe disease of adaptive equipment and home modifications. Some therapists also teach energy conservation for activities of daily living and can help in the set-up of home and portable oxygen.

The effect of individualised occupational therapy in patients with moderate to severe COPD was evaluated in an RCT (Martinsen 2017). 52 patients were randomly assigned to the intervention group (occupational therapy) or control group (treatment as usual). Participants were recruited from the outpatient and inpatient pulmonary department at a hospital in Norway and through advertisements in local newspapers and distribution of leaflets to GPs' offices. The primary outcome was assessed using the Canadian Occupational Performance Measure (COPM), and participants were assessed at baseline and after four and 12 months. The results indicate that compared with the usual care, occupational therapy did not improve occupational performance or satisfaction with performance. Small but significant changes in activity performance in favour of the intervention group were found in some of the secondary outcomes.

In a randomised controlled trial, activity training by occupational therapists combined with exercise improved functional status more than exercise alone or together with education, especially in elderly people with moderate to severe COPD (Norweg 2005).

D1.6 Social worker

Social workers can provide counselling for patients and their carers, organisation of support services, respite and long- term care.

D1.7 Clinical psychologist/psychiatrist

Anxiety and depression are common disorders in patients with COPD (Di Marco 2006, Gudmundsson 2006, Kunik 2005, Laurin 2007, Schane 2008), which worsen quality of life and add to disability (Gudmundsson 2005, Ng 2007, Xu 2008, Laurin 2009, Giardino 2010, Eisner 2010b) [evidence level III]. The prevalence of panic attacks and panic disorder in COPD are particularly high (Yellowlees 1987, Pollack 1996, Kunik 2005, Laurin 2007) [evidence level III]. There is promising evidence that anxiety and depression can be treated by clinical psychologists and psychiatrists using approaches such as cognitive behaviour therapy (Kunik 2001, de Godoy 2003, Hynninen 2010, Yohannes 2017) [evidence level II]. Psychiatrists can also advise whether pharmacological treatment may be appropriate.

A systematic review of various psychological interventions in patients with COPD showed some improvements in psychological outcomes, especially with cognitive behavioural therapy (CBT). In contrast, for physical outcomes, only mind-body interventions (e.g. mindfulness-based therapy, yoga, and relaxation) revealed a statistically significant effect. These findings favour psychosocial intervention as a tool in the management of COPD (Farver-Vestergaard 2015).

A directed psychological intervention consisting of six sessions of group-based CBT delivered by a psychologist added to an eight-week pulmonary rehabilitation program, showed significant improvements in the CBT group in the 6-minute walk test (6MWT), fatigue, depression and stress measures (Luk 2017).

Telephone-administered CBT can reduce depression symptoms in people with COPD. People with COPD who have mood disorders would prefer to have CBT than befriending (Doyle 2017).

D1.8 Speech pathologist/therapist

Speech pathologists are involved in the assessment and management of dysphagia (difficulty swallowing) in individuals with COPD and can be accessed in the community or in a hospital setting (inpatient or outpatient). Early identification of dysphagia in those with COPD and adequate management can minimise COPD exacerbations and hospital admissions (Kobayashi 2007, Schermer 2006) [evidence level III-2].

Speech Pathologists use case history from patients and their partners or carers, clinical swallow examinations, patient self-report scales and instrumental swallowing assessments - videofluoroscopy and fibreoptic endoscopic evaluation of swallowing (FEES) to assess and diagnose dysphagia (Ghannouchi 2016, Regan 2017). Strategies for the management of dysphagia are listed in **O7.6 Aspiration.**

Management of dysphagia in individuals with COPD is dependent on the individual's swallowing difficulties and is prescribed by the Speech Pathologist (McKinstry 2010).

D1.9 Pharmacist

Community pharmacists are medicines experts in the primary care setting and are well placed to engage in early detection/case finding of COPD, and COPD care programs due to their frequent interactions with patients during prescription refill. Monitoring and optimising COPD maintenance therapy in a community pharmacy has the potential to improve COPD management. Evidence from overseas suggests that such interventions significantly improved both inhalation technique and medication adherence, and significantly decreased the estimated annual severe exacerbation rate (Tommelein 2014). Structured education about COPD provided by a clinical pharmacist and a comprehensive pharmaceutical care program significantly improved medication adherence, improved quality of life, decreased severe exacerbation and hospitalisation rate, and higher quit rates (Xin 2016). Such interventions have not been evaluated in Australian community pharmacies in large trials. A pharmacist-led medication adherence management intervention in 53 Spanish community pharmacies comprising motivational interviewing principles to assess adherence, identification of barriers for medication adherence and tailored strategies to address identified barriers, and monthly follow-ups was effective at improving medication adherence (self-reported data) compared to usual care in patients with COPD at 6 months (92.9% (87.0%-96.2%) vs 72.5% (62.3%-80.7%); 4.93 (2.20 - 11.1) p=0.0001). Patients in the intervention group also had lower Clinical COPD Questionnaire (CCQ) scores (MD −0.50, 95% CI −0.82 to −0.18, p<0.05) when compared with the control group (Torres-Robles 2022) [evidence level II].

Community pharmacists are ideally positioned to play a vital role in all key stages of an integrated COPD patient care pathway, smoking cessation support, support/monitoring of management plans to the provision of advice and counselling regarding medications, inhaler technique and treatment adherence (van der Molen 2017). The skill sets, frequency of contact with patients, expertise regarding available treatments, and convenience to patients, in terms of the location, opening times and 'open door' consultation opportunities are the strengths of community pharmacists (Fathima 2013). Australian community pharmacists, with adequate training could play a bigger role in optimising medicine use by patients with chronic respiratory conditions.

Pharmacists are involved in education about medications and supply of medications. They can help smokers quit by advising about nicotine replacement and can counsel patients requesting over-the-counter salbutamol. They are well placed to monitor for medication problems and complications and suggest solutions (e.g., individual dosing dispensers) (Beney 2000). This is particularly important where multiple comorbid conditions require treatment with multiple medications that have potential interactions, or when confusion exists about timing of medication administration.

D1.10 Dietitian/Nutritionist

Excessive weight-loss is a common problem in patients with end-stage COPD. Conversely, obesity in patients with COPD is associated with sleep apnoea, CO_2 retention and cor pulmonale. Dietitians play a central role in managing these problems.

A Cochrane Review of 17 studies (632 participants) that provided nutritional supplementation for patients with COPD for more than two weeks found growing evidence that nutritional supplementation improved body weight, respiratory muscle strength, walking and quality of life, especially if malnourished (Ferreira 2012).

In obese (body mass index ≥ 30 kg/m2) COPD patients a 12 week weight reduction program involving meal replacements and dietary counselling by a dietitian and resistance exercise training prescribed and supervised by a physiotherapist, with face to face review by the dietitian and physiotherapist every two weeks for counselling, achieved modest weight loss of 6.2%, and improved clinical outcomes including health status, symptoms, exercise and functional capacity, whilst preserving skeletal muscle mass (McDonald 2016b).

D1.11 Exercise physiologist

Exercise physiologists are predominantly involved in exercise testing, exercise prescription and supervision of exercise rehabilitative programs. They also provide patient education on the importance of regular exercise and on activity/behavioural modification. They may also play a role in the assessment of exertional oxygen and the exercise rehabilitation of associated co morbidities.

D1.12 Non-medical care agencies

Many patients with COPD have difficulties with activities of daily living and may require a range of non-medical support services, including governmental and non-governmental organisations. Availability of services varies between states and between areas within states (e.g., urban, rural, remote). Some examples include:

- financial support and organisation of oxygen, CPAP machines, nebulisers, etc.;
- Homecare;
- Government-supported assistance with activities of daily living (showering, cleaning, shopping, etc.);
- home maintenance;
- Meals on Wheels;
- exercise programs; and
- support groups.

D2. Multidisciplinary care plans

A multidisciplinary care plan involves documentation of the various medical, paramedical and non-medical services required to keep a patient functioning in the community. Various generic and disease-specific proformas are available. The care plan may be initiated in the context of a multidisciplinary case conference involving the GP and at least two other health professionals (one of whom is not a

doctor).

GPs are remunerated for their involvement in case conferences. This is supported by Extended Primary Care (EPC) item numbers, which vary according to the level of involvement of the GP and the location of the patient. The GP may participate by telephone. A consultant physician is also entitled to claim rebates for organising or participating in case conferences. Further information about item numbers is available at http://www.health.gov.au/mbsprimarycareitems.

The multidisciplinary care plan may include a component of self-management with appropriate support.

D3. Chronic Disease Self-management

Patients may benefit from self-management support [evidence level I, strong recommendation]

Chronic disease management can broadly be defined as a comprehensive strategy for improving overall health status and reducing health care costs (Hunter and Fairfield 1997). It is well suited to chronic conditions as it takes a holistic approach, treating patients as individuals throughout the clinical course of a disease rather than viewing their care as a series of discrete episodes (Hunter 2000). The essence of disease management includes a system of patient education and self-management, implementation of practice guidelines, appropriate consultation, and supplies of medications and services (Hunter 2000). Self-management support is the systematic provision of education and supportive interventions by health care staff to support patients increase their skills and confidence in managing their health problems (Institute of Medicine Committee on the Crossing the Quality Chasm: Next Steps Toward a New Health Care, 2004).

Disease management approaches in COPD include a number of the Chronic Care Model domains. A systematic review by Peytremann-Bridevaux (2008) assessed the impact of COPD management programs attended by patients, which they defined as interventions with two or more different components (e.g. physical exercise, self-management, structured follow-up), at least one of which continued for 12 months, were delivered by two or more health care professionals and incorporated patient education. It found such programs improved exercise capacity and health-related quality of life (HRQoL), and reduced hospitalisation [evidence level I]. However, it is unclear from this review which specific components of the disease management programs contribute the most benefit to patients. A Cochrane Review (Kruis 2013) examined 26 trials of integrated disease management programs defined as "a group of coherent interventions designed to prevent or manage one or more chronic conditions using a systematic, multidisciplinary approach and potentially employing multiple treatment modalities." The review found positive effects on disease-specific QoL measured by the Chronic Respiratory Questionnaire (all domains) and on the impact domain of the St George's Respiratory Questionnaire (SGRQ). There were also positive effects on exercise tolerance, hospital admissions and hospital days per person [evidence level I].

An updated Cochrane Review of RCTs and clusters RCTs of self-management support interventions published since 1995 included 27 studies and 6008 participants. Follow-up time ranged from 2.5 to 24 months. The review found improvement in HRQoL measures by the SGRQ with a mean difference from usual care of -2.86 points (95% CI -4.87 to -0.85). This is less than the minimal clinically importance difference of 4 points. There was also a lower risk of at least one respiratory-related hospital admission (OR 0.75, 95% CI 0.57-0.98). The NNT to prevent one respiratory hospital admission over a mean of 9.75 months follow-up was 15 (95% CI 8-399). No excess respiratory-related and all-cause mortality risks were observed. The review had stricter inclusion criteria than previous reviews (Schrijver 2022).

A cluster RCT conducted in Canadian primary care of an integrated disease management intervention aimed at patients with frequent and/or severe exacerbations and comprising on-site spirometry, case management, education, and skills training including self-management education by a certified respiratory educator resulted in improved disease-related quality of life, improved disease knowledge and FEV_1 and fewer exacerbations and unplanned service use compared to usual care (Ferrone 2019) [evidence level II]. In another large multicentre randomised controlled trial (Rice 2010) involving veterans who received a single education session, an action plan for self-treatment of exacerbations and monthly follow-up calls from a case manager, found that, when compared to usual care, the intervention group had a significant reduction in hospitalisation and ED visits for COPD, mortality and quality of life, measured with the Chronic Respiratory Questionnaire [evidence level II].

An alternative approach of home care outreach nursing was studied in a systematic review by Wong (Wong 2012), in which the intervention included home visits to provide education and social support,

identify exacerbations and reinforce correct inhaler technique. They also found a significant benefit in quality of life, measured by the St George's Respiratory Questionnaire (SGRQ), but no significant effect on mortality or hospitalisations [evidence level I]. In all these studies, it remains unclear which specific components contribute the most benefit to patients, are the most cost effective or should be combined to provide optimal benefit on the many different outcomes.

Box 9: Comparison of outcomes for COPD management programs

Study/Outcome	Mortality	Hospitalisation	QOL	Exercise
Peytremann-Bridevaux	OR = 0.85 (0.54 to 1.36)	Benefit in 7/10 studies	Not reported	WMD = 32.2 (4.1 to 60.3)
Rice	#MD = 3.7 (-1.4 to 8.8)	*MD = 0.34 (0.15 to 0.52)	MD = 5.1 (2.5 to 7.6)	Not reported
Wong	OR = 0.72 (0.45 to 1.15)	OR = 1.01 (0.71 to 1.44)	WMD = -2.60 (-4.81 to -0.39)	WMD = 5.05 (-15.08 to 25.18)
McLean	OR = 1.05 (0.63 to 1.75)	OR = 0.46 (0.33 to 0.65)	WMD = -6.57 (-13.62 to 0.48)	Not reported

Outcome presented as OR = odds ratio or (W)MD = (weighted) mean difference, with 95% confidence intervals in brackets. *Hospitalisation and ED visits. # difference per 100 patient years.

A number of systematic reviews have been undertaken to evaluate the effect of self-management in COPD (See **Figure 6** for abbreviated table and **Appendix 6** for full table). Whilst these have consistently reported improvements to quality of life, there have been conflicting findings in terms of their effect on healthcare utilisation (Jolly 2016, Jonkman 2016a, Jonkman 2016b, Majothi 2015, Schrijver 2022).

A Cochrane review found self-management interventions that included action plans for exacerbations were associated with reduced probability of respiratory-related but not all-cause hospitalisation, all-cause mortality, dyspnoea or exacerbation rate (Lenferink 2017). However, exploratory analysis showed a small but significantly increased respiratory-related mortality. The differences may be related to differences in the study populations, study context and extent of self-management support provided. Other reviews of self-management in COPD have found reductions in both respiratory-related, ED (Schrijver 2022), and all-cause hospitalisations (Jonkman 2016b), a reduction in urgent health care, improved exercise capacity measured by the 6-minute walk distance (6MWD) (Cannon 2016, Schrijver 2022), and improved anxiety and repression (Schrijver 2022). However, reviews have also reported no differences in 6MWD, anxiety and depression, hospital admissions and mortality (Majothi 2015, Cannon 2016, Jolly 2016, Jonkman 2016b). A systematic review and meta-analysis of nurse-led COPD interventions concluded that such interventions were associated with improvements in 6MWD, activities of daily living, and anxiety and depression, but failed to reduce the number of hospital admissions or improve HRQoL measured using the SGRQ. Interventions carried out by hospital and respiratory nurse-led interventions were associated with greater effectiveness compared to community nurses (Aranburu-Imatz 2022) [evidence level I]. These systematic reviews should be interpreted with caution due to the methodological weaknesses of the studies and heterogeneity of the interventions and outcome measures.

In 2019, Aboumatar et al reported an RCT that showed increased rates of exacerbation in the intervention group without any change in health status. They recruited patients admitted to hospital with a COPD exacerbation, or patients who had a previous diagnosis of COPD who were hospitalised and were receiving treatment for an increase in COPD symptoms (Aboumatar 2019). Patients (n=240) were randomised to a three-month intervention that involved: 1. A transition support aimed at preparing patients and caregivers for discharge and ensuring they understood the post discharge plan of care, 2. Individualised COPD self-management support to help patients take medications correctly, recognise exacerbation signs and follow action plans, practice breathing exercises and energy conservation techniques, maintain an active lifestyle, seek help as needed, and stop smoking, and 3.

Facilitated access to community programs and treatment services. The intervention was delivered by COPD nurses. Usual care involved a general transition coach to follow the patient for 30 days after discharge, with a focus on adherence to the discharge plan, and connecting to outpatient care. The intervention resulted in an increased number of COPD-related acute events per participant at 6 months compared to usual care (difference 0.68, 95% CI 0.22-1.15, p=0.004). There were no differences observed in health status measured by the SGRQ at 6 months (difference 5.18, 95% CI 2.15-12.51, p=0.11). The interventions included assessment and management of knowledge and skills, physical activity, pharmacological and nonpharmacological interventions and health behaviours.

A RCT reported in 2022 evaluated the effect of self-management strategies delivered by health care professionals compared to a dual intervention of self-management delivered by health care professionals and peer supporters (defined as patients with COPD and their family- caregivers who were nominated by pulmonary clinic and rehabilitation program staff). Of the 1061 patients identified as eligible, only 292 were randomised. There was no effect on the primary outcome of quality of life measured by the SGRQ at 6 months (unadjusted difference of 1.26 points with 95% CI -5.44 to 7.96, p=0.591), nor at nine months. The intervention did however improve the secondary outcome of COPD-related acute care events during the 6-month intervention (Aboumatar 2022) [evidence level II], signalling the potential role of peers and family carers in the management of COPD.

The high degree of heterogeneity within interventions and study designs limits the ability to analyse which characteristics of self-management programs are associated with the most significant improvements. However, a meta regression review of complex interventions identified that general education, exercise and relaxation therapy components contributed to reduced use of urgent healthcare (Dickens 2014) [evidence level I]. Additionally, Jonkman et al (2016a) demonstrated that intervention duration, regardless of composition, displayed the strongest association with reduction in all cause hospitalisations in COPD patients. Newham et al. identified that interventions targeting mental health were the most effective in improving health-related quality of life (HRQoL) and reducing ED visits (Newham 2017).

Health coaching, when using motivational interviewing methods, and including components of goal setting and education, when delivered in person, has been demonstrated in a meta-analysis of 10 RCTs, to lead to significant improvements in quality of life, as well as COPD–related hospital admissions (54% reduction [OR 0.46, 95% CI 0.31-0.69]). However, the benefit appears not to be sustained beyond 12 months post-intervention (Long 2019).

Overall, COPD self-management programs appear to improve HRQoL. The effect of these interventions on exacerbations remains unclear. Studies have reported positive outcomes, whilst others have reported increased rates of exacerbations associated with self-management interventions (Aboumatar 2019). Due to the heterogeneity of the study designs, setting and outcomes, and conflicting results, we are unable to make recommendations regarding the essential elements of a COPD self-management program.

Written COPD Action Plans

The concept of written action plans for patients with COPD is derived from their success in asthma management indicating doses and medications to take for maintenance therapy and for exacerbations. Instructions for crises are often also included. Lung Foundation Australia has developed a COPD Action Plan which can be downloaded from https://lungfoundation.com.au/resources/copd-action-plan. The Action Plan should be completed in partnership with the clinician and patient and guides patients in recognising when their symptoms change and what action they should take. Written action plans are often included as an integral part of COPD self-management programs described above but have also been tested as independent interventions.

A Cochrane systematic review by Howcroft et al synthesized the findings of seven RCTs conducted in people with COPD in which the intervention included the provision of actions. A single short educational component was included in the interventions in which the clinician personalised the plan according to management needs and symptoms. Ongoing support directed at the use of the action plan was permitted, however studies with a broader self-management approach or exercise intervention were excluded. The comparator was usual care. Action plans reduced ED visits and hospital admissions (Howcroft 2016). The number needed to treat to reduce one hospital admission was 19. A subsequent RCT not included in this review confirmed a reduction in ED visits in patients who utilised an action plan (Zwerink 2016).

A multicentre RCT (Lenferink 2019) (n=201) evaluated the effect of patient-tailored symptom-based written action plans embedded within a multi-disease self-management intervention on COPD exacerbation days compared to usual care in patients with COPD and one or more comorbidity. Patients were given written action plans to prompt management of both COPD exacerbations and comorbidities (congestive heart failure (CHF), ischaemic heart disease (IHD), anxiety, depression and diabetes), together with a self-management education program. No difference in the primary outcome of COPD exacerbation days/patient/year was observed (intervention median 9.6 (interquartile range (IQR) 0.7 to 31.1) versus usual care 15.6 days (3.0 to 40.3); (Incidence Rate Ratio (IRR) 0.87, 95% CI 0.54-1.30 (p=0.546)). There were however observed differences in the secondary outcome of duration of COPD exacerbations, in favour of the intervention (8.1, IQR 4.8 to 10.1 versus 9.5, IQR 7.0 to 15.1 days; p=0.021). There was no difference in overall HRQoL between groups, and the intervention group reported poorer emotional function on the CRQ compared to usual care.

Figure 6: Table of Systematic Reviews Evaluating the Effect of Self-Management in COPD

Authors	Design	Studies included	Participants n=	HRQoL	All-cause hospitalisations	Respiratory-related hospitalisations	Mortality	ED pres	Anxiety & depression	Dyspnoea	6M WD	Respiratory-related mortality	Medication use	Urgent healthcare
Dickens 2014	RCT	32 studies, database inception-2013	3941											☺
Zwerink 2014	RCT, CCT	29 studies, 1995-2014	3688	☺	☺	☺	😐			☺	😐			
Majothi 2015	RCT	9 studies, Moderate-severe COPD, database inception-2012	1466	☺	😐		😐	😐						
Cannon 2016	RCT	25 studies, 1990-2016	4082	☺	😐				😐		☺			
Howcroft 2016	RCT, quasi RCT	7 studies, Database inception -2015	1550	☺			😐	☺	😐				☺	
Jolly 2016	RCT	173 studies, database inception-2012	n/a	☺	😐									
Jonkman 2016	RCT	14 studies, 1985-2013	3282	☺	☺	☺	😐							
Lenferink 2017	RCT	22 studies, 1995-2017	3854	☺	😐	☺	😐	😐		😐		☹		

☺= improved, 😐= no change, ☹= worsened., grey shading indicates outcome was not analysed. HRQoL= health related quality of life, 6MWD= 6-minute walk distance, RCT= randomized controlled trial, CCT= controlled clinical trials, COPD= chronic obstructive pulmonary disease, ED= emergency department, PR = pulmonary rehabilitation.

D3.1 Maintenance therapy

Detailed discussion of the maintenance therapy for COPD appears in Section O. In general, the use of drugs in COPD does not involve back-titration, which is a core principle in asthma management. The exception is when oral corticosteroids have been given for an exacerbation. There is at present no evidence for back titration and further clinical trials are required.

D3.2 Exacerbation prevention

Detailed discussion of the management of exacerbations is found in Section X.

Committee Commentary (see below)

COPD Exacerbation Terminology

In patient education and for effective patient-clinician partnerships, the words we use as clinicians' matter. This is particularly important when discussing COPD exacerbations. COPD exacerbations are common and have deleterious impacts on patients at the time of the event, on their recovery and on their future risk (McDonald 2019). Unfortunately, exacerbations of COPD are frequently under-reported and untreated (Calderazzo 2019, Jones 2014). It has been proposed that patients and clinicians do not recognise the need for urgent treatment of these events or their impact on future outcomes (Holverda 2020, Bafadhel 2020, Jones 2019). For example, COPD mortality risk at one year following a hospitalisation for an acute exacerbation is approximately 25% (García-Sanz 2017, Ho 2014), which is greater than the mortality risk of someone hospitalised for an acute myocardial infarction (McDonald 2019, Halpin 2008).

Patients in part may not understand the impact of exacerbations due to language clinicians use to describe these events (Holverda 2020, Bafadhel 2020). Terms such as 'exacerbations' and 'flare ups' trivialise these events in asthma and may do the same in COPD (Holverda 2020, Bafadhel 2020, Jones 2019, Pavord 2018). Furthermore, most patients do not understand the term exacerbation. In a qualitative study of 125 people with moderate to severe COPD <2% understood what the term 'exacerbation' actually meant (Kessler 2006). This is a similar concern in asthma (Jones 2019).

There are calls for the abandonment of the terms exacerbations and flare ups and to replace these with terms such as attack, lung attack or COPD crisis (Holverda 2020, Bafadhel 2020, Jones 2019, Pavord 2018, Fitzgerald 2011). We recognise that it is important to agree on the most appropriate person-centred language to improve response to COPD exacerbations and suggest that this is an area for future collaborative work among the respiratory community and patients.

For severe exacerbations there is evidence for the use of bronchodilators, antibiotics, systemic corticosteroids and supplemental oxygen (if patients are hypoxaemic). Selected patients may benefit from early intervention with these agents according to a predetermined plan developed by a GP or respiratory specialist, that is a COPD action plan as described above. Some patients can be instructed

to start using a "crisis medication pack" while awaiting medical review. They may also be instructed to contact a particular member of the multidisciplinary care team as part of their overall care plan. For a COPD action plan template see, https://lungfoundation.com.au/resources/copd-action-plan/

Controlled trials are required to document the efficacy of self-management plans in patients with stable COPD, but, drawing on the success of asthma action plans, education of patients with COPD in self-management is recommended. Written plans are usually required to complement such interventions (see examples at https://lungfoundation.com.au/resources/copd-action-plan/)

D4. Telehealth

Telemonitoring interventions ranging from simple telephone follow-up to daily telemonitoring of physiological or symptom scores, to more complex telemonitoring interventions with greatly enhanced clinical support; have been evaluated in patients with COPD. A Cochrane Review found that telehealth may have an impact on quality of life and emergency attendances in COPD, however, further research is needed to clarify its precise roles, as to date trials have included telecare as part of more complex packages (McLean 2011) [evidence level I]. The positive effect of telemonitoring seen in some trials could thus be due to enhancement of the underpinning clinical service rather than to the telemonitoring communication.

Pinnock et al separated the effects of telemonitoring from the effects of existing services by adding telemonitoring alone to background self-management and clinical support in the usual care group. Adults registered with general practices in Scotland who had been admitted to hospital with an exacerbation of COPD in the previous year and who were thus at risk of future admissions were randomised to telemonitoring or usual care. All participants received self-management advice - education on self-management of exacerbations reinforced with a booklet, a written management plan, and an emergency supply of antibiotics and steroids, integrated within the standard clinical care service for the region. The telemonitoring package consisted of touch screen operated daily questionnaires about symptoms and drug use, with an instrument to measure oxygen saturation. Data were transmitted daily by an internet connection to the clinical monitoring team, which contacted patients whose score reached a validated threshold. Algorithms, based on the symptom score, alerted the clinical monitoring team if daily readings had not been submitted or if a high symptom score had been recorded. Clinicians responded by advising rescue drugs, a home visit, admission to hospital, or further review. Intervention fidelity was high. After 12 months, no difference was seen in hospital admissions for COPD between the two groups (hazard ratio 0.98, 95% CI 0.66-1.44). Furthermore, no differences were seen in health-related quality of life (HRQoL), anxiety or depression, self-efficacy, knowledge, or adherence to drugs. This trial suggested that the addition of telemonitoring to the management of high-risk patients, over and above the backdrop of self-management education and a good clinical service, is costly and ineffective (Pinnock 2013) [evidence level II]. These findings are in agreement with a 2011 systematic review of telemonitoring, which suggested that in the absence of other care packages the benefit of telemonitoring is not yet proven and that further work is required before its wide-scale implementation (Bolton 2011). A systematic review (Gregersen 2016) examined the effects of telehealth on quality of life in COPD. Of 18 suitable studies found, only three demonstrated significant improvements in quality of life as a consequence of a telehealth intervention. A further study of telehealth with multiple components (COMET) also failed to demonstrate reduction in hospitalisation based on intention to treat analysis (Kessler 2018). It is noted there was reduced mortality as a safety/secondary outcome in the per-protocol analysis.

A number of RCTs have been published since the McLean et al (2011) systematic review. An RCT of 577 patients with mild COPD, obtained from UK primary care COPD registers of 71 general practices evaluated a telephone health coaching program which included the provision of a pedometer, written educational documents, diary, inhaler use education and encouragement of medication adherence

(Jolly 2018). Most potential participants did not respond to the study invitation. While there was no benefit on the primary outcome of quality of life as measured by the St George's Respiratory Questionnaire (SGRQ), nor the secondary outcomes of anxiety and depression, other secondary outcomes of self-reported physical activity and inhaler usage did improve [evidence level II]. In contrast, in an RCT of 375 people with COPD, a 12-week remote patient monitoring system focusing on daily step count and exercise practice along with weekly health coaching telephone calls utilising motivational interviewing, improved health-related quality of life measured by the Chronic Respiratory Disease Questionnaire which was maintained to 24 weeks (Benzo 2022) [evidence level II].

PROMETE II was a randomised control trial of a telehealth package offered to 229 patients, recruited from across 5 centres, over 12 months, with a comprehensive range of outcomes (Soriano 2018) [evidence level II]. The intervention included an educational home visit, and provision of home oximeter, blood pressure gauge, spirometer, and oxygen therapy compliance monitor. It was rated as highly satisfactory with most patients as well as clinicians, and followed on from the earlier single site, 7-month, n=30 participants 'PROMETE' study, which had demonstrated a reduction in acute exacerbations. Despite the earlier study's promising positive finding, the larger PROMETE II study failed to demonstrate any such benefit in any of the diverse range of outcomes, including costs. This calls into question the generalisability of a single site positive finding (Segrelles Calvo 2014), where a very small number of highly motivated staff may be able to achieve extraordinary positive results, but which may prove difficult to replicate elsewhere.

An RCT that evaluated a simple nurse-initiated telephone follow-up of COPD patients following admission to hospital with an acute exacerbation of COPD or pneumonia (n=224), did not demonstrate any reduction in readmission or mortality at 30- or 84-days post discharge. The intervention group received a nurse-initiated phone call at two days post discharge and further calls if deemed necessary. At 30 and 84 days the proportion of those readmitted in the intervention and control groups was 33 and 34% (p=0.84), and 32 and 27% (p=0.66), respectively. The intervention group did however report more confidence in disease management (Lavesen 2016).

In another RCT, 470 people with COPD with at least 2 comorbidities were recruited from a metropolitan and a rural centre. The intervention comprised a combination of telephone consults, action plans, and other components and was found to have no effect on the number of emergency department visits and hospital admissions; however, mortality was reduced (Rose 2018) [evidence level II]. A further RCT including telemonitoring to detect deteriorations over 9 months reported no benefit on outcomes including time to first hospitalisation or quality of life (Walker 2018) [evidence level II].

Baroi et al reviewed feasibility and comparative studies, which used a heterogeneous range of measurement devices (including spirometers, respiratory rate sensors, impedance oscillometers, auscultation microphones, pedometers, capnometers, and oximeters), which aimed to identify COPD, and/or to detect early exacerbations of COPD. Information communication methods between subjects and clinicians included videoconferencing and questionnaires. The studies that did report positive results were more likely to be those that were more integrated into existing respiratory outpatient services, and in people with high risk of readmission due to a COPD exacerbation. The combination of online consultations with availability of home-based nebuliser and medical therapies could provide an effective "virtual hospital" (Baroi 2018).

An intensive, comprehensive health coaching intervention that included motivational interviewing-based intervention delivered via telephone, a written action plan for exacerbations including the use of antibiotics and oral steroids, and an exercise prescription decreased COPD-related hospitalisations at 1, 3, and 6 months after hospital discharge, but not at one year after discharge. The absolute risk reductions of COPD-related rehospitalisation in the health coaching group were 7.5% (p=0.01), 11.0%

(p=0.02), 11.6% (p=0.03), 11.4% (p=0.05), and 5.4% (p=0.24) at 1, 3, 6, 9, and 12 months, respectively, compared with the control group. Disease-specific quality of life improved significantly in the health coaching group compared with the control group at 6 and 12 months, based on the Chronic Respiratory Disease Questionnaire (CRQ) emotional score (emotion and mastery domains) and physical score (dyspnoea and fatigue domains) (p<0.05). There were no differences between groups in measured physical activity at any time point (Benzo 2016). It should be noted that several of these individual components have been shown to be effective in isolation.

Similar to the studies of self-management support, the COPD telehealth studies are heterogeneous in design and outcome, and the results are also conflicting, again making it difficult to make recommendations regarding the essential elements of telehealth program in COPD. Telehealth has become an increasingly important aspect of COPD care, particularly during periods of pan/epidemics, as such an important area for further research.

D5. Assessment and management of anxiety and depression

Symptoms of anxiety and depression and associated disorders are common in people with COPD (Ng 2007, Xu 2008, (Weiss 2022) and have a range of negative impacts [evidence level III-2].

A retrospective cohort study of 80,088 U.S. Medicare recipients found a 34% higher 30-day readmission rate in COPD patients with depression, and 43% higher in those with anxiety (Singh 2016). These and other co-existing psychological disorders were also associated with being less likely to have follow up appointments (23.8% versus 16.25%). Although the study design had the potential for confounding by severity of disease, the relationships of psychological disorders with readmissions were much higher than index admission ICU length of stay or need for mechanical ventilation. The results therefore support the case that depression and anxiety are important independent predictors of readmission.

Anxiety symptoms in COPD are associated with worse quality of life (Blakemore 2014), self-management (Dowson 2004) and exercise performance (Eisner 2010) [evidence level III], and with increased medical symptom reporting (Katon 2007), exacerbations (Laurin 2012), hospitalisations (Gudmundsson 2005), length of hospitalisations (Xu 2008), medical costs (Katon 2007), and mortality (Celli 2008) [evidence level III]. The prevalence of one anxiety disorder in particular, panic disorder, is approximately 10 times greater in COPD than the population prevalence of 1.5 to 3.5%, and panic attacks are commonly experienced (American Psychiatric Association 2004, Smoller 1996).

Cognitive behaviour therapy has been shown to be an effective treatment for panic disorder in the physically healthy (Mitte 2005) [evidence level I]. There is consistent evidence from randomised controlled trials supporting the positive effect of cognitive behaviour therapy on anxiety and/or depressive symptoms in people with COPD (Williams 2020), in preventing the development of panic attacks and panic disorder (Livermore 2010), and reducing ratings of dyspnoea (Livermore 2015, Yohannes 2017). A nurse-delivered minimalist version of cognitive behaviour therapy (1-2 home visits of 20-60 minutes duration) provided clinically and statistically significant improvements on the Hospital Anxiety Depression Scale (HADS) and also the Chronic Respiratory Disease Questionnaire (CRQ) Mastery scale at 3 month follow up in the intervention arm (n=22) compared to the control arm (n=22) (Bove 2016). In a larger RCT, self-help leaflets for anxiety management were compared to a brief nurse led CBT intervention with self-help leaflets in 279 patients with COPD. At 3 months the CBT groups had greater improvements in the HADS Anxiety subscale [3.4 (95% CI 2.62–4.17, p<0.001)] compared to the active control (leaflets) [1.88 (95% CI 1.19–2.55, p<0.001)]. The effect was maintained at 12 months. The CBT intervention was also cost effective (Heslop-Marshall 2018). In a trial of 28 patients undergoing pulmonary rehabilitation, cognitive behaviour therapy was associated

with an improvement in fatigue, stress, depression and anxiety scores over the 3 month follow up period (Luk 2017).

A record linkage study in Canada found that elderly COPD patients prescribed benzodiazepines for anxiety were at increased risk of an outpatient exacerbation (NNH 66, 95% CI 57–79) or an emergency department visit for COPD or pneumonia (NNH 147, 95% CI 123–181). There was also a slightly elevated albeit not significant risk of hospital admission (Vozoris 2014) [evidence level III-2]. Caution is warranted in using these medications, due to their potential depressive effects on respiratory drive (Shanmugam 2007), and their inherent risks in the elderly of dependence, cognitive impairment, and falls (Uchida 2009).

People with COPD are not only at high risk of symptoms of depression and mood disorders but are at higher risk than people with other chronic conditions (Ng 2007 [evidence level III], Siraj 2020 [evidence level III-2]). When depressive symptoms are comorbid with COPD they are associated with worse health-related quality of life (HRQoL) (Ng 2007, Hanania 2011) and difficulty with smoking cessation (Ng 2007) [evidence level III], and with increased exacerbations (Laurin 2012), hospitalisations (Bula 2001, Xu 2008, Hanania 2011), length of hospitalisations (Ng 2007) [evidence level III], medical costs (Bula 2001), and mortality (Bula 2001, Ng 2007) [evidence level III]. Depressive symptoms have been more strongly associated over four years with patient reported outcomes, including symptom control and physical activity related dyspnoea, than with change in FEV_1 (O'Toole 2022) [evidence level II]. Depression may also influence decisions about end-of-life issues (Stapleton 2005). In summary, these findings support the benefit of screening for symptoms of depression and anxiety in people with COPD and of providing mental health care as a component of comprehensive multidisciplinary care.

A systematic review of randomised controlled trials has shown that symptoms of depression and anxiety can be decreased by cognitive behaviour therapy (Williams 2020) [evidence level I]. Mindfulness-based cognitive therapy in conjunction to pulmonary rehabilitation also improved depressive symptoms compared to pulmonary rehabilitation alone (Farver-Vestergaard 2018). A 2019 Cochrane review concluded that, while cognitive behaviour therapy may be an effective treatment for depression in COPD, the quality of the evidence is currently limited (Pollok 2019).

In a 2018 Cochrane systematic review conducted to assess the effectiveness and safety of pharmacological interventions for depression in patients with COPD, there was not enough evidence relating to efficacy and safety to make recommendations on use of SSRIs (Pollok 2018) [evidence level I]. In a meta-analysis involving two RCTs of 148 participants there was no difference in the primary outcome of change in depressive symptoms post-intervention (SMD 0.75, 95% CI -1.14 to 2.64; I^2 = 95%). Due to the risk of bias and high level of heterogeneity in depression levels, as well as in the types of medication and doses used, these results should be interpreted with caution (Pollok 2018). Case management to support adherence to antidepressant medication in conjunction with attending pulmonary rehabilitation has been associated with improvements in both depression and dyspnoea-related disability (Alexopoulos 2016). As for anxiety symptoms, psychiatrists can advise on the most appropriate medications for particular patients (Shanmugam 2007).

Multiple systematic reviews have demonstrated that pulmonary rehabilitation is associated with short-term reductions in anxious and depressive symptoms (Coventry 2013, Yohannes 2017, Gordon 2019). The existing evidence warrants the referral of anxious and depressed people with COPD to clinical psychologists and psychiatrists for assessment and treatment. Depressed COPD patients referred to mental health specialists have lower odds of two-year mortality than those treated in primary care settings (Jordan 2009). Screening for clinically significant anxiety and depression, given their serious impacts, should therefore be part of routine care (including during admissions for exacerbations) (Lecheler 2017). The Hospital Anxiety Depression Scale (HADS) is an example of an easily

administered, widely used screening questionnaire, developed for use with medical patients (Zigmond 1983), and used in numerous studies of people with COPD (Ng 2007, Xu 2008, Bock 2017) [evidence level III]. Another screening option is the Patient Health Questionnaire (PHQ), which screens for symptoms of the most seen mental disorders in medical patients – depression, generalised anxiety, panic attacks, somatoform and eating disorders. The full scale, or the depression and anxiety subscales, may be administered (Spitzer 1994). The PHQ has the advantages of high statistical reliability and validity, while being an easily administered measure that is available on the internet at no cost (Kroenke 2010).

D6. Referral to a support group

Patients may benefit from support groups and other community services [evidence level III-2, weak recommendation]

Greater improvements in exercise performance and self-efficacy for exercise have been shown for people with COPD who received education and psychosocial support than for those who received education without support (Ries 1995). Patient support groups aim to empower participants to take a more active role in the management of their healthcare, and thus reduce the psychosocial impact of their disease. Benefits of support groups on quality of life and psychological outcomes in people with COPD have not yet been demonstrated, although studies of other chronically ill patient groups indicate that positive effects can be expected (Kennedy 2007). One pathway to initiate attendance of support groups is through pulmonary rehabilitation programs. The likely benefits of support groups for people with COPD are summarised in **Box 10**.

Box 10: Patient Support Groups

Typical support group activities

- Regular meetings
- Guest speakers providing information on a range of topics
- Receiving and distributing lung health education information
- Education and information days
- Exercise programs
- Social or recreational activities
- Group newsletters
- Member to member support (through telephone calls, hospital, and home visits)

Benefits of support groups

- Reinforce and clarify information learnt from health professionals
- Provide access to new information on lung health
- Share experiences in a caring environment
- Empower patients to be more actively involved in their healthcare through self-management techniques
- Participate in social activities and exercise programs
- Encourage patients to think more positively about their lung disease
- Help carers understand lung disease

A list of Patient Support Group names and locations can be accessed via Lung Foundation Australia's website at https://lungfoundation.com.au/patient-support/support-for-you/patient-support-groups/. Contact details can be obtained from Lung Foundation Australia's Information and Support Centre (free-call 1800 654 301).

In New Zealand, Asthma and Respiratory Foundation NZ list Pulmonary Rehabilitation and Support Groups on their website: https://www.asthmafoundation.org.nz/about-us/support-groups, free-call 0800 100 506. Asthma New Zealand list COPD Support Groups and the 'Find your local group' directory: https://www.asthma.org.nz/pages/copd-support-groups, free-call 0800 227 328.

X: Manage eXacerbations

A COPD exacerbation is characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication or hospital admission [evidence level III-2, strong recommendation]

EXACERBATIONS of COPD which are more frequent in the winter months in temperate climates (Jenkins 2012) [evidence level II] often require hospital admission for treatment of respiratory failure. A record linkage study in WA (Geelhoed 2007) demonstrated that the rate of hospital admission for COPD has been declining. The risk of readmission was highest within three months of discharge, and more than half of all patients were readmitted within 12 months. About 10% of patients with a primary diagnosis of COPD died either during admission or within the same year. Median survival from first admission was five years in men and eight years in women. The poorest survival was among older patients with recognised emphysema. In one study of more than 1,000 patients admitted to several hospitals with an exacerbation of severe COPD, about 50% were admitted with a respiratory infection, 25% with congestive cardiac failure, and 30% with no known cause for the exacerbation (Connors 1996). A study of 173 patients with COPD reported an average of 1.3 (range 0 to 9.6) exacerbations annually. An ecological study of hospital admissions for COPD in Victoria found higher rates of admission in rural and remote areas with greater socioeconomic disadvantage and higher rates of smoking (Ansari 2007).

Exacerbations become more frequent as severity of COPD worsens (Hoogendoorn 2010a). In the study by the ECLIPSE investigators, exacerbation rate increased with increasing GOLD stage, such that 22% of patients with GOLD stage 2 disease had two or more exacerbations during one year of follow-up, whereas 47% of patients with GOLD stage 4 disease had frequent exacerbations over the same period. The single best predictor of exacerbations across all GOLD stages was prior exacerbations. Other predictors included a history of heartburn, poorer quality of life and elevated white cell count (Hurst 2010). ECLIPSE data also showed that a history of prior hospitalisation for COPD is the strongest predictor of subsequent hospitalisation. Han et al prospectively examined exacerbation rates in 1,105 patients with COPD over a three-year period from the SPIROMICS cohort (Han 2017). Contrary to the ECLIPSE study, Han reported that individual exacerbation rates vary significantly from year to year, and very few patients experience two or more exacerbations over successive years. In addition to a history of past exacerbations, Han reported that interleukin-15 (IL-15) and interleukin-8 (IL-8) levels in blood as well as small airway abnormalities on CT chest predicted frequent exacerbations (Han 2017).

The ECLIPSE data also confirmed 12-month mortality rates were significantly higher in patients hospitalised for COPD (15%) compared to those without hospitalisation (5%) ($p<0.001$) (Mullerova 2015). In a Spanish cohort of (predominantly male) patients prospectively followed, Guerrero et al demonstrated that re-admission to hospital within 30 days following discharge for an exacerbation of COPD increased 12-month mortality rates (37% in readmitted versus. 17% in non-readmitted patients, $p=0.001$) and was an independent risk factor for mortality at one year (HR 2.48, 95% CI 1.1-5.59) (Guerrero 2016).

Studies have confirmed that although the prognosis of exacerbations is poor, the prognosis post-exacerbation is improving. Hoogendoorn et al (Hoogendoorn 2010b) identified six cohort studies that followed the survival of COPD patients for at least 1.5 years after a severe exacerbation resulting in hospitalisation. A meta-analysis resulted in a weighted average case-fatality rate of 15.6% (95% CI 10.9-20.3). The excess risk of mortality continued after discharge from hospital. Almagro et al (Almagro 2010) prospectively examined three-year mortality after a severe exacerbation resulting in hospitalisation in two well matched cohorts seven years apart (1996/97 and 2003/04). The 1996/97 three-year survival rate was 53% and the 2003/4 three-year survival rate was significantly improved at 61% (log rank $p = 0.017$). The 2003/4 cohort had increased usage of tiotropium, long acting $beta_2$ agonists, angiotensin receptor blockers, statins and anti-platelet therapy. The authors speculated that

the increased survival may be due to improved treatment options for COPD and co-morbidities including cardiac disease [evidence level III-2].

Soltani et al (Soltani 2015) prospectively evaluated a cohort of 150 severe COPD patients admitted with an exacerbation of COPD at an Australian tertiary hospital and reported a 28% readmission rate at three months and a 12-month mortality rate of 24.5%. It should be noted that patients requiring invasive or non-invasive ventilation were excluded from this study. A retrospective database study of over 2 million COPD admissions among American Medicare recipients above the age of 65 reported a 12-month mortality rate of 26.2% (Lindenauer 2018). The 12-month mortality rate for those requiring invasive and non-invasive ventilation was 45.7% and 41.8% respectively. This study showed a 12-month readmission rate of 64% (Lindenauer 2018). Analysis of over 1 million COPD admissions from a US national database that included patients of all age groups and all healthcare providers demonstrated a 19.2% 30-day readmission rate (Jacobs 2018). A systematic review of over 40 studies reported a 30-day COPD related readmission rate of 11% and a 12-month readmission rate of 37% (Ruan 2023) [evidence level III-2].

DECAF (see **Figure 7**) is a 30-day mortality prediction score for COPD admissions (Steer 2012). DECAF was derived with data from 920 consecutive patients admitted with a COPD exacerbation from two neighbouring hospitals in the UK. COPD had been confirmed on spirometry. The five strongest predictors of mortality that comprise the score are extended MRC Dyspnoea Score, eosinopenia, consolidation, acidaemia, and atrial fibrillation. The score showed high discrimination for mortality with an area under the receiver operator characteristic curve =0.86, 95% CI 0.82-0.89. A DECAF score of 3 predicts confers a 27.2% 30-day mortality risk. Echevarria et al examined the performance of the DECAF score in 2,645 patients with an admission of COPD across 6 hospitals in the UK and reported a similarly high performance for mortality prediction (Echevarria 2019).

Figure 7: The DECAF Score

The DECAF Score

Variable	**Score**
Dyspnoea	
eMRCD 5a*	1
eMRCD 5b**	2
Eosinopenia (<0.05 $X10^9$/l)	1
Consolidation	1
Acidaemia (pH <7.3)	1
Atrial fibrillation	1
Total DECAF Score	6

DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; eMRCD: extended MRC dyspnoea

* eMRCD 5a - too breathless to leave the house unaided but independently able to manage washing and/or dressing

**eMRCD 5b - too breathless to leave the house and requiring assistance with both washing and dressing

Table (see **Figure 6**) reproduced from Steer J et al. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax 2012; 67: 970-976 (Steer 2012) with permission from the BMJ publishing Group Ltd.

In patients with COPD the normally sterile lower airway is frequently colonised by *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis*. While the number of organisms may increase during exacerbations of COPD, the role of bacterial infection is controversial (Macfarlane 1993, Smith 1980, Soler 1998, Wilson 1998, Stockley 2000, Walsh 1999, Mogulkoc 1999, Murphy 1999, Miravitlles 1999).

Exacerbations can also be caused by viral infection (Seemungal 2001). Retrospective data from an Australian tertiary hospital demonstrated that influenza virus and rhinovirus were the most common viral pathogens found in patients admitted to hospital with an exacerbation of COPD (Biancardi 2016). Given the current COVID-19 pandemic, it is recommended that patients with COPD take adequate precautions to stay well (https://lungfoundation.com.au/lung-health/protecting-your-lungs/coronavirus-disease-covid-19/what-you-need-to-know/). Guidance for diagnosis and management of COVID-19 infection is highly relevant to patients with COPD. Living guidelines from the National COVID-19 Clinical Evidence Taskforce are available at https://covid19evidence.net.au/#living-guidelines.

Other causes of exacerbations of COPD include left ventricular failure and pulmonary embolus (PE). A systematic review comprising seven studies with a total of 880 patients who were hospitalised with an exacerbation of COPD and underwent a CT pulmonary angiogram (CTPA) found that 16% had a PE (Aleva 2017). There was large variation in the prevalence of PE between studies (3% to 29%). One third of patients had only small, isolated, sub-segmental PE. A prospective study of 740 patients with COPD with an acute worsening of respiratory symptoms presenting to 7 French hospitals found a prevalence of 5.9% of PE on CTPA, based on a predefined diagnostic algorithm including clinical probability based on the Geneva score and D-dimer testing (Couturaud 2021). A diagnosis of PE should be considered in patients presenting with an exacerbation of COPD when signs of respiratory infection are absent, and chest pain or cardiac failure are present.

A panel study of patients with moderate to severe COPD demonstrated that exacerbations could also be triggered by urban air pollutants such as PM10, black smoke and NO_2 (Peacock 2011) [evidence level II]. Chest trauma and inappropriate use of sedatives can lead to sputum retention and hypoventilation.

Early diagnosis and treatment of exacerbations may prevent hospital admission and delay COPD progression (Wilkinson 2004) [evidence level III-2, strong recommendation].

Prolonged COPD exacerbations are associated with worse health status and the exacerbation that follows occurs sooner. Exacerbations of COPD are associated with accelerated loss of lung function, particularly in patients with mild disease. In patients with mild COPD each severe exacerbation was associated with an additional FEV_1 loss of 87 ml/year (95% CI 23-151) (Dransfield 2017). Retrospective analysis of data from the UPLIFT study also demonstrated an accelerated loss of lung function after a single COPD exacerbation (Halpin 2017).

Early diagnosis and prompt management of exacerbations of COPD may prevent progressive functional deterioration and reduce hospital admissions (Lorig 1999, Shepperd 1998). Education of the patient, carers, other support people and family may aid in the early detection of exacerbations. A self-management plan developed in conjunction with the patient's GP and specialist to indicate how to step-up treatment may be useful (see examples at https://lungfoundation.com.au/resources/copd-action-plan-for-hps/). This plan might indicate which medications to take, including antibiotics and oral corticosteroids. The plan should also require patients to contact their GPs or community nurses to allow rapid assessment (see section D).

Statins have been shown to reduce rates of hospitalisation (for COPD or any other reason), lung-function decline, the need for mechanical ventilation, and all-cause mortality in observational studies of COPD patients. The Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations (STATCOPE) examined the effect of daily treatment with simvastatin in patients with moderate-to-severe COPD who were at high risk for exacerbations and had no other

indications for statin treatment. Simvastatin at a daily dose of 40 mg for at least 12 months did not affect exacerbation rates or the time to a first exacerbation (Criner 2014) [evidence level II].

Hospital admissions are indicators or failed prevention and are highly expensive to health care systems. Hospitalisations are being included increasingly as an outcome measure in randomised controlled trials of a range of interventions. **Box 11** below summarises the interventions that have been demonstrated, in such randomised control trials to statistically significantly reduce hospitalisation.

Box 11: Reducing hospital utilisation: current level I and II evidence from COPD-X

Intervention	Demonstrated impact	Effect estimate	Where to find it
Level I			
LAMAs	"…LAMAs had reduced exacerbation rates…and **exacerbation-related hospitalisations**…compared to LABAs" NB: most participants in this analysis had *Tiotropium* as their LAMA	**22% improvement** (RR 0.78, 95% CI 0.69 to 0.87)	O1.2.1 *Maia 2017*
Tiotropium	"… tiotropium **reduced the odds of a COPD exacerbation … and related hospitalisations** compared to placebo or ipratropium." "… tiotropium was more **effective in preventing COPD exacerbations leading to hospitalisation** [compared to a range of other LABAs]"	**36% improvement** (OR 0.64, 95% CI 0.51 to 0.82 NNT 30, 95% CI 22 to 61) **14% improvement** (OR 0.86, 95% CI 0.79 to 0.93)	P5.1 *Barr 2005* P5.2 *Chong 2012*
Aclidinium	"…Aclidinium resulted in marginal improvements in quality of life and FEV_1, and **reduced the number of patients with exacerbations requiring hospitalisation**"	**NNT 77**, 95% CI 51 to 233	O1.2.1 *Ni 2014*
Systemic corticosteroids	"… systemic corticosteroids **reduce treatment failure (defined as additional treatment, hospital admission/re-admission for index episode, return to emergency department, unscheduled physician visit for the index episode)**, improve lung function, shorten recovery and reduce the severity of exacerbations of COPD … **reduced the risk of treatment failure by over half** compared with placebo in … median treatment duration 14 days"	**52% improvement** (OR 0.48, 95% CI 0.35 to 0.67 NNT 9)	X2.2.2 *Walters 2014*
Non-invasive ventilation	"The use of NIV **reduces hospital length of stay**."	**MD -3.39 days**, 95% CI -5.93 to -0.85	X3.2 *Osadnik 2017*
Hospital at home	"… compared to standard care, participants allocated to hospital in the home were significantly less likely to be readmitted to hospital within the next 1 to 6 months."	**24% improvement** (RR 0.76, 95% CI 0.59 to 0.99)	X1 *Jeppesen 2012*
Multi-faceted care plans	"… integrated disease management programs defined as 'a group of coherent interventions designed to prevent or manage one or more chronic conditions using a systematic, multidisciplinary approach and potentially employing multiple treatment modalities.' … found **positive effects** on disease-specific QoL … exercise tolerance, **hospital admissions and hospital days per person**…"	Admissions: **32% improvement** (OR 0.68, 95% CI 0.47 to 0.99 NNT 15) Length of stay: **MD -3.78 days**, 95% CI -5.90 to -1.67	D *Kruis 2013*

Pulmonary rehabilitation	"Pulmonary rehabilitation following hospitalisation for an exacerbation also **reduced hospital readmissions**."	**56% improvement** OR 0.44, 95% CI 0.21 to 0.91	X3.6 *Puhan 2016*
Intervention	**Demonstrated impact**	**Effect estimate**	**Where to find it**
Level II			
LAMA/LABA/ICS (umeclidinium/ vilanterol/ fluticasone furoate)	"In selected COPD patients with a history of **exacerbations there was a 34% reduction in admissions with triple therapy** using a single inhaler (fluticasone [ICS], vilanterol, umeclidinium – IMPACT study), as well as other benefits, regardless of baseline bronchodilator responsiveness, compared to dual therapy (no ICS), and with even greater benefits in some outcomes demonstrated in those with high eosinophil counts (>150 cells/ microlitre)."	**34% improvement** (RR 0.66, 95% CI 0.56 to 0.78)	O4.2 *Lipson 2018*
Airway clearance techniques	"The use of ACTs was associated with a **significant short-term reduction** in the need for increased ventilatory assistance … duration of ventilatory assistance …and **hospital length of stay**."	**MD - 0.75 days**, 95% CI -1.38 to -0.11	X3.4 Osadnik 2012
Discharge bundles	"… the use of **COPD discharge bundles reduced hospital readmissions** …"	**20% improvement** (RR 0.80, 95% CI 0.65 to 0.99)	X3.7 *Ospina 2017*
Supported discharge programs & medication adherence	"…has been shown to **reduce re-admissions for COPD exacerbations** compared to usual care …" "Adherence to inhaled medication regimes is associated with **reduced risk of death and admissions to hospital** due to exacerbations in COPD..."	**45% improvement** (HR 0.55, 95% CI 0.35 to 0.88) **44% improvement** (RR 0.56, 95% CI 0.48 to 0.65)	X3.8 *Casas 2006* O *Vestbo 2009*

X1. Home management

Multidisciplinary care may assist home management of some patients with an exacerbation [evidence level I, weak recommendation].

The shortage of hospital beds, especially in winter, has prompted interest in home care for management of COPD exacerbations, with involvement of multidisciplinary teams assisting GPs. Such "Hospital in the Home" schemes were studied in a systematic review by Jeppesen (Jeppesen 2012) that included eight randomised controlled trials which entered patients into a hospital in the home scheme within 72 hours of presenting to hospital. The review found that compared to standard care, participants allocated to hospital in the home were significantly less likely to be readmitted to hospital within the next 1 to 6 months (risk ratio =0.76, 95% CI 0.59-0.99) [evidence level I]. There was no significant difference in mortality (risk ratio = 0.65, 95% CI 0.40-1.04), and while there was no difference in satisfaction levels for patients or carers, these comparisons were based on small numbers. Economic studies of such programs have shown mixed results.

X2. COPD exacerbation management

X2.1 Confirm exacerbation and categorise severity

Assessment of severity of the exacerbation includes a medical history, examination, spirometry and, in severe cases (FEV_1 < 40% predicted), blood gas measurements, chest x- rays and electrocardiography.

Patients should be provided with and bring a summary of their medical problems and treatment (e.g., a personal health record). If available, results of previous stable lung function tests and arterial blood gas measurements are invaluable for comparison.

Spirometry: Because COPD is defined by demonstration of airflow limitation, which is not fully reversible, spirometry is essential for its diagnosis, and this may be performed prior to discharge from hospital to confirm the diagnosis (Rea 2011).

Assess Oxygenation

Pulse oximetry should be recorded routinely, in conjunction with other vital signs

Arterial blood gases: Measurement of pulse oximetry and venous blood gases has significant limitations, particularly when assessing ventilation, Arterial blood gasesshould be considered if the FEV_1 is less than 1.0 L or less than 40% predicted, if percutaneous oxygen saturation is less than 92% in the presence of adequate peripheral perfusion, in patients where SpO_2 is falling and increased fraction of inspired oxygen (FiO_2) is required and in patients at risk of hypercapnia. . Values obtained while breathing room air are the most useful for assessing ventilation–perfusion inequality. A PaO_2 less than 60 mmHg (8 kPa) indicates hypoxaemic respiratory failure, while a $PaCO_2$ greater than 45 mmHg indicates ventilatory failure. Respiratory acidosis indicates acute respiratory failure warranting consideration for assisted ventilation.

All prospective RCTs that have demonstrated a mortality advantage with the use of NIV in exacerbations of COPD have used ABG (arterial blood gas), not VBG (venous blood gas) samples to determine need for NIV. McKeever et al examined paired ABG-VBG (venous blood gas) samples in 234 patients admitted to hospital with a doctor diagnosed exacerbation of COPD (McKeever 2016). A VBG pH ≤7.34 gave a sensitivity of 88.9% and specificity of 95.6% for an ABG pH ≤7.35. The authors argued that all patients presenting with an exacerbation of COPD should initially be assessed with a

VBG and only go on to an ABG if the VBG pH ≤7.34. The primary reasons for preferring VBG samples cited by the authors were less pain and lower risk of bruising. The general applicability of these findings is limited by the fact that this cohort had relatively few patients with pH below 7.30. The authors did not propose that VBGs should replace ABGs to assess severity of respiratory failure or be used to monitor patient response to treatment/ NIV. Caution is required due to the lesser precision with VBGs compared to ABGs.

Chest x-ray and electrocardiogram: These help to identify alternative diagnoses and complications, such as pulmonary oedema, pneumothorax, pneumonia, empyema, arrhythmias, myocardial ischaemia and others.

Studies have identified a simple clinical prediction score, the BAP-65, based on age, basal urea nitrogen, acute mental status change and pulse, which predict in-hospital mortality (Tabak 2009, Shorr 2011). In-hospital mortality in both studies increased as patient classification escalated from 1 (no risk factors, age <65 years) to 5 (3 risk factors present), the highest class being associated with an in-hospital mortality between 14.1% and >25%.

A 2012 prospective single centre study of 920 patients admitted with an exacerbation of COPD found that those with CXR confirmed pneumonia had a far higher mortality (20.1% versus. 5.8%, p<0.001). Severity of dyspnoea in the stable state was strongly associated with both in-hospital mortality and early re-admission (Steer 2012) [evidence level III-2].

X2.2 Optimise treatment

An exacerbation of COPD may involve an increase in airflow limitation, excess sputum production, airway inflammation, infection, hypoxia, hypercarbia and acidosis. Treatment is directed at each of these problems.

- ***Bronchodilators:*** Inhaled beta-agonist (e.g., salbutamol, 400–800mcg; terbutaline, 500–100mcg) and antimuscarinic agent (ipratropium, 80mcg) can be given by pressurised metered dose inhaler and spacer, or by jet nebulisation (salbutamol, 2.5–5 mg; terbutaline, 5 mg; ipratropium, 500mcg). The dose interval is titrated to the response and can range from hourly to six-hourly. There is a lack of evidence in favour of one mode of delivery over another for bronchodilators during exacerbations of COPD. In a Cochrane Review by van Geffen (van Geffen 2016) there were no differences between nebulisers and pressured metered dose inhalers plus spacer regarding the primary outcomes of FEV_1 at one hour (MD 36 ml, 95% CI −38 to 110, n=40) and serious adverse events (OR 1.00, 95% 0.18-5.53, n=70) [evidence level I].

- ***Corticosteroids:*** Oral corticosteroids hasten resolution and reduce the likelihood of relapse. Up to two weeks' therapy with prednisolone (40–50 mg daily) is adequate. Longer courses add no further benefit and have a higher risk of adverse effects.

- ***Antibiotics:*** Antibiotics are given for purulent sputum to cover for typical and atypical organisms.

- ***Controlled oxygen therapy:*** This is indicated in patients with hypoxia, with the aim of improving oxygen saturation to 88 to 92%. Use nasal prongs at 0.5–2.0 L/minute or a Venturi mask at 24% or 28%. Minimise excessive oxygen administration, which can worsen hypercapnia.

- ***Ventilatory assistance:*** This is indicated for increasing hypercapnia and acidosis. Non-invasive ventilation by means of a mask is the preferred method.

Although the adherence to pharmacological, rehabilitation and vaccination management as recommended in GOLD have each been shown to reduce health care costs, uptake of GOLD recommendations has had little evaluation. A study in a Victorian hospital setting demonstrated significant overuse of antibiotics and oxygen therapy, as well as a greater evidence practice gap in general medical units than respiratory medical units (Tang 2014) [evidence level III-2].

X2.2.1 Inhaled bronchodilators for treatment of exacerbations

Inhaled bronchodilators are effective for initial treatment of exacerbations [evidence level I, strong recommendation]

In exacerbations of COPD, the immediate bronchodilator effect is small, but may result in significant improvement in clinical symptoms in patients with severe obstruction.

Studies of acute airflow limitation in asthma indicate that beta-agonists are as effectively delivered by metered dose inhaler and spacer as by nebuliser (Cates 2006) [evidence level I]. The applicability of this evidence to patients with COPD is unknown. There is evidence in patients with a COPD exacerbation that a dry powder inhaler delivering formoterol is as effective in improving lung function as a metered dose inhaler delivering salbutamol, with or without a spacer device (Selroos 2009) [evidence level II]. An adequate dose should be used. The dose equivalent to 5 mg of salbutamol delivered by nebuliser is 8–10 puffs of 100mcg salbutamol by metered dose inhaler and spacer. Limited evidence indicates dry powder inhalers are as effective as other delivery devices for the administration of short-acting *bronchodilators* in the setting of exacerbations of COPD (Selroos 2009) [evidence level II]. Airflow in the nebuliser should be 6 L per minute or higher to achieve an appropriate aerosol, but using high- flow oxygen should be avoided as this may worsen carbon dioxide retention (Bardsley 2018).

People with COPD often have cardiac co-morbidities, although these may be undiagnosed at the time of presentation with a COPD exacerbation. Such patients may be susceptible to adverse events from high dose, frequent short acting beta agonists. A review by Kopsaftis (Kopsaftis 2018b) identified 10 relevant randomised or controlled trials and demonstrated that higher (5mg versus 2.5mg) doses of salbutamol were associated with increased risk of tremors, elevated heart rate, palpitations and lower blood pressure, but without evidence of any additional benefit. Given that elevated cardiac stress markers during COPD exacerbations are predictive of 30-day mortality (Chang 2011), the review authors recommend caution in prescribing frequent high doses of short-acting beta agonists, such as doses of salbutamol exceeding 2.5mg, when treating exacerbations of COPD [evidence level I].

A small (n=30) single centre pilot randomised controlled trial performed in New Zealand (Mukerji 2015) [evidence level II] showed that 2g IV magnesium when added to standard bronchodilator therapy in an exacerbation of COPD significantly improved FEV_1 at 120 mins (mean percentage change in FEV_1 was 27.07% with magnesium versus 11.39% in the placebo group, 95% CI 3.7-27.7,oxygen titration p=0.01). Asthma was excluded on clinical grounds on review of past spirometry. Larger trials with meaningful clinical endpoints are required before this can be recommended as standard therapy.

X2.2.2 Systemic corticosteroids for treatment of exacerbations

Systemic corticosteroids reduce the severity of and shorten recovery from mild to severe exacerbations (Walters 2014) [evidence level I, strong recommendation]

Walters et al report that there is high-quality evidence that systemic corticosteroids reduce treatment failure (defined as additional treatment, hospital admission/re-admission for index episode, return to emergency department, unscheduled physician visit for the index episode), improve lung function, shorten recovery and reduce the severity of exacerbations of COPD (Walters 2014) [evidence level I]. Systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n=917) with median treatment duration 14 days, odds ratio (OR) 0.48 (95% CI 0.35-0.67. The number needed to treat to avoid one treatment failure is 9. There is no evidence that treatment with corticosteroids alters mortality.

Unlike earlier reviews this review included four papers that compared intravenous corticosteroids with oral corticosteroids and two papers with ventilated patients in ICU. In patients requiring ventilation in ICU, pooled data did not show a reduction in length of stay, duration of ventilation or mortality in those receiving corticosteroids compared with placebo (Walters 2014). Walters et al concluded that there is no evidence of benefit for intravenous treatment compared with oral treatment with corticosteroids on treatment failure, relapse or mortality. Hyperglycaemia rates were higher with intravenous corticosteroids.

With regards to duration of treatment, a meta-analysis by Walters et al (Walters 2018) concluded that five days of oral corticosteroids is likely to be sufficient [evidence level I].

In summary, a 5-day course of oral prednisolone of 30mg to 50mg is adequate. In patients who have been on oral corticosteroids for longer than 14 days, tapering may be necessary. Patients on long-term oral corticosteroid therapy (> 7.5 mg prednisolone daily for more than 6 months) are at risk of developing osteoporosis. Prevention and treatment of corticosteroid-induced osteoporosis should be considered. Longer courses of prednisolone may increase mortality and pneumonia (Sivapalan 2019).

There is emerging evidence that blood eosinophil levels can be used as a biomarker to determine which patients require oral corticosteroids for exacerbations of COPD. A small, single centre, double blind randomised controlled trial used blood eosinophils as a biomarker to determine if prednisolone would be given for an exacerbation of COPD. In the intervention arm, only patients with blood eosinophils above 2% received prednisolone. In the standard arm all patients received prednisolone. The prednisolone dose was 30mg for 14 days and both groups received oral antibiotics. There was no difference in treatment failure or health status between the biomarker and standard groups (Bafadhel 2012). Bafadhel re-analysed data from 3 additional randomised controlled trials that examined the use of oral corticosteroids in COPD exacerbations (n=243) (Bafadhel 2014). Patients had blood eosinophil levels measured at the time of COPD exacerbation. Blood eosinophils $\geq$2% were a useful biomarker to determine which patients benefit from systemic corticosteroids. The trial designs had considerable heterogeneity. Further, larger studies with long term follow up are required before any firm recommendations can be made.

X2.2.3 Antibiotics for treatment of exacerbations

Independent of the severity and practice setting, exacerbations with clinical features of infection (increased volume and change in colour of sputum and/or fever) benefit from antibiotic therapy [evidence level I, strong recommendation].

Bacterial infection may have either a primary or secondary role in about 50% of exacerbations of COPD (Macfarlane 1993, Wilson 1998, Miravitlles 1999, Patel 2002). *Haemophilus influenzae, Streptococcous pneumoniae* and *Moraxella catarrhalis* are most commonly involved (Macfarlane 1993, Soler 1998, Murphy 1999). *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have also been reported (Macfarlane 1993, Mogulkoc 1999). As lung function deteriorates (FEV_1 < 35%), *Pseudomonas aeruginosa* and *Staphylococcus aureus* are often encountered (Macfarlane 1993, Soler 1998, Miravitlles 1999). Multi drug resistant Ps. aeruginosa is associated with 6-fold increased risk of death (Montero 2009) [evidence level III-2].

Nonetheless, sputum colour was shown to have limited value as a stand-alone test in diagnosing bacterial infection in a systematic review and meta-analysis of 13 studies by Spies et al (Spies 2023) [evidence level I).

A re-examination of data from the placebo arm of a Spanish antibiotic trial that recruited patients with mild to moderate COPD from primary care confirmed that sputum purulence increased the likelihood of treatment failure 6-fold. A CRP elevated greater than 40 mg/L was also independently associated with a 13-fold increase in the risk of treatment failure (Miravitlles 2013) [evidence level III-2].

A study of 220 patients hospitalised with exacerbations of COPD with clinical features of infection, randomised to CRP-guided antibiotic therapy (antibiotics if CRP ≥ 50mg/L) or GOLD criteria based antibiotic treatment found a significant reduction in antibiotic use in the CRP guided group, with an absolute reduction in antibiotic use of 14.5% (Prins 2019) [evidence level II]. An open label RCT (n=653) of patients in the UK showed that in patients with COPD exacerbations treated in primary care, use of point-of-care CRP testing to guide prescribing of antibiotics lowered patient-reported antibiotic use (OR 0.31, 95% CI 0.20-0.47) (Butler 2019) [evidence level II]. The judicious use of CRP testing in primary or tertiary care may assist in determining the need for antibiotics for exacerbation management.

El Moussaoui et al (El Moussaoui 2008) conducted a systematic review of 21 randomised controlled trials of antibiotics in exacerbations of chronic bronchitis and COPD. There were similar rates of clinical or bacteriological cure with short courses (≤ 5 days) and longer courses of antibiotics [evidence level I]. A related systematic review (Falagas 2008) found that patients receiving short courses experienced fewer adverse effects than those receiving longer courses. It would be necessary to treat 26 (95% CI 15-134) patients with short course antibiotics to prevent one adverse effect. However, the antibiotics evaluated were late generation cephalosporins, macrolides and fluoroquinolones, which are not those recommended in Australia.

Procalcitonin is an acute phase reactant. Procalcitonin levels increase in bacterial infections but do not increase in viral infections or auto-immune inflammation (Gilbert 2011). Procalcitonin has been proposed as a measure to determine if patients with an exacerbation of COPD require oral antibiotics. In most clinical trials, use of antibiotics was discouraged if procalcitonin was 0.1ng/ml or lower and encouraged if procalcitonin was above 0.25ng/ml.

A meta-analysis of eight randomised or quasi-randomised trials, evaluating 1,062 patients, compared procalcitonin-based protocols to initiate or discontinue antibiotics, versus standard care in COPD exacerbation (Mathioudakis 2017). Procalcitonin-based protocols decreased antibiotic prescription

(relative risk (RR) 0.56, 95% CI 0.43–0.73) without affecting clinical outcomes such as rate of treatment failure, length of hospitalisation, exacerbation recurrence rate or mortality (low to moderate quality evidence). Since the publication of this meta-analysis, a further trial has also reported that procalcitonin-based protocols reduce antibiotic use without increasing complications (Wang 2016).

A meta-analysis of RCTs and observational studies investigating the impact of a procalcitonin-based protocol on antibiotic prescription and clinical outcomes in patients with COPD exacerbations, found that the use of procalcitonin-based protocols significantly reduced the length of antibiotic treatment in COPD exacerbation (MD = -2.01 days, 95% CI -3.89 to -0.14 days, p=0.04, moderate quality, and MD = -1.64 days, 95% CI -2.91 to -0.36 days, p=0.01, very low quality for RCTs and observational study, respectively), while no apparent effects were found on length of hospital stay, treatment failure and all-cause mortality. The effect of procalcitonin on antibiotic duration was no longer significant (MD = -1.88 days, 95% CI -3.95 to 0.19 days, p=0.08, and MD = -1.72 days, 95% CI -4.28 to 0.83 days, p=0.19, respectively), when studies with high risk of bias were excluded. Procalcitonin has limited value in guiding antibiotic use in COPD exacerbation (Chen 2020) [evidence level I].

It is important to note that patients with pneumonia were excluded from these trials. Based on the evidence from these trials, it may be possible to withhold antibiotic therapy in patients presenting to the emergency department with an exacerbation of COPD, who are afebrile, have no pneumonia on chest imaging, and have a serum procalcitonin level of <0.1ng/ml. This test is not currently funded by Medicare in Australia and is only available in some centres. Despite promising data from multiple clinical trials, cross-sectional and longitudinal analysis of over 200,000 COPD admissions from 505 US hospitals did not show a change in antibiotic prescribing rates or duration of use in hospitals that had begun using procalcitonin testing (Lindenauer 2017). The authors conclude that further implementation research is required.

Therapeutic guidelines: Antibiotic (Therapeutic Guidelines Limited 2019) recommend the use of oral agents such as amoxycillin or doxycycline.

A retrospective cohort study from the Danish registry of COPD by Bagge et al (2021) examined outcomes following patients redeeming prescriptions for amoxycillin (AMX) or amoxycillin clavulanic acid (AMC) for presumed community exacerbations of COPD. They found pneumonia hospitalisation or death by all cause after 30 days was decreased with AMX compared to AMC (adjusted HR 0.6, 95% CI 0.5-0.7, p<.0001). This was also observed for all cause hospitalisation or death (aHR 0.8, 95% CI 0.8-0.9, p<0.0001). Although confounding by severity is not excluded, the findings of this study support the recommendation broad -spectrum antibiotics such as AMC should not be the drug of first choice for outpatient exacerbations of COPD (Bagge 2021) [evidence level III-2].

If pneumonia, Pseudomonas or staphylococci or resistant organisms are suspected, appropriate antibiotics should be used.

Typically, a course of antibiotics should be five days. A systematic review and meta-analysis by Llor et al (2022) including *only patients with spirometrically-proven COPD* (n=eight trials) concluded that there were no significant differences in clinical cure rates or bacterial eradication rates of short courses of antibiotics (≤5 days) compared with longer courses (≥6 days). Nonetheless, the majority of studies included fluroquinolones as first line therapy, which is not common practice in Australia, raising questions about the face validity of this study [evidence level I] (Llor 2022). A historical population-based cohort study found that co-treatment of an exacerbation with oral corticosteroids and oral antibiotics significantly increased the time to subsequent exacerbations (median 312 versus 418 days, p<0.001 to next compared to oral corticosteroids alone) (Roede 2008) [evidence level III-2].

Two Australian retrospective case series of hospitalised COPD patients have found that antibiotic treatment was guideline concordant in less than 15% of cases (Brownridge 2017, Fanning 2014). This

was due to over-use of intravenous antibiotics and prescription of dual antibiotics. Further efforts are needed to increase adherence to the use of oral antibiotics in patients hospitalised with exacerbations of COPD, where appropriate.

Radiologically proven pneumonia in patients with COPD, especially in those who have been frequently hospitalised, may not be restricted to the above organisms. Gram-negative organisms, *Legionella* spp. and even anaerobic organisms may be responsible. Initial empiric antibiotic therapy should be tailored according to clinical and radiographic criteria.

X2.2.4 Combined systemic corticosteroids and antibiotics for treatment of exacerbation

A randomised placebo-controlled trial (Daniels 2010) has provided evidence to support the traditional practice of treating exacerbations with a combination of systemic corticosteroids and antibiotics. In this study, hospitalised patients were commenced on a tapering dose of prednisolone and randomised to receive doxycycline 200mg daily or placebo for 7 days. Clinical cure, defined as complete resolution of signs and symptoms, at day 10 was significantly higher in the antibiotic treated group compared to placebo (OR 1.9, 95% CI 1.2-3.2, NNT=7, 95% CI 4-523). By day 30, the primary end point, there was no significant difference in clinical cure. Serious adverse effects occurred in 9% of the doxycycline group (7 deaths) and 5% of the placebo group (3 deaths). Medication adverse events were similar between groups, 3% in the doxycycline group and 4% in the placebo.

X3. Refer appropriately to prevent further deterioration ('P')

The risk of death from exacerbations of COPD increases with acute carbon dioxide retention (respiratory acidosis), the presence of significant comorbid conditions (e.g., ischaemic heart disease) and complications (e.g., pneumonia and empyema). Depending on the nature and severity of the exacerbation, the patient may require urgent specialist review, hospital assessment or admission to a high-dependency or intensive care facility for ventilatory support and appropriate monitoring (see **Boxes 12 and 13**).

Box 12: Indications for hospitalisation of patients with chronic obstructive pulmonary disease

Marked increase in intensity of symptoms

Patient has acute exacerbation characterised by increased dyspnoea, cough or sputum production, plus one or more of the following:

- Inadequate response to ambulatory management
- Inability to walk between rooms when previously mobile
- Inability to eat or sleep because of dyspnoea
- Cannot manage at home even with home-care resources
- High risk comorbidity condition — pulmonary (e.g., pneumonia) or non-pulmonary
- Altered mental status suggestive of hypercapnia
- Worsening hypoxaemia or cor pulmonale
- Newly occurring arrhythmia

Box 13: Indications for non-invasive or invasive ventilation

- Severe dyspnoea that responds inadequately to initial emergency therapy
- Confusion, lethargy or evidence of hypoventilation
- Persistent or worsening hypoxaemia despite supplemental oxygen, worsening hypercapnia ($PaCO_2$ > 70 mmHg), or severe or worsening respiratory acidosis (blood pH < 7.3)
- Assisted mechanical ventilation is required.

X3.1 Controlled oxygen delivery

Controlled oxygen delivery (0.5–2.0 L/min) is indicated for hypoxaemia in patients with exacerbations (Beasley 2015) [evidence level II, strong recommendation]

In the emergency setting, supplemental oxygen may be required to relieve hypoxaemia. Oxygen flow should be carefully titrated to achieve a target SpO_2 range of 88 to 92%. Nasal cannulae deliver a variable concentration of oxygen, but a flow of 0.5–2.0 L per minute is usually sufficient. The TSANZ position paper on acute oxygen use in adults highlights the importance of assessment of hypoxia, prescription of oxygen and always implementing SpO2 targets to prevent over-oxygenation (Barnett 2022).

High flow oxygen via a Hudson mask or non-rebreather mask should be avoided, as it is rarely necessary and may lead to hypoventilation and worsening respiratory acidosis and increased mortality. A randomised study has demonstrated that in the pre-hospital emergency setting titrated oxygen via nasal cannula compared with high flow oxygen reduced mortality by 78% in COPD patients (NNH=14) (Austin 2010) [evidence level II]. In an observational study from the UK of 1027 patients admitted across 6 hospitals with an exacerbation of COPD and receiving supplemental oxygen, Echevarria et al reported that in-hospital mortality was lowest in those with admission oxygen saturations between 88 and 92%. This mortality effect was dose-responsive with mortality rates highest in the sub-group with oxygen saturations 97-100%. The effect was also present in patients with normocapnia. The authors recommend that all patients with COPD receiving supplemental oxygen should have an oxygen saturation target of 88-92% independent of the presence of hypercapnia (Echevarria 2020). In a Victorian retrospective case file emergency department audit of patients admitted to hospital with an exacerbation of COPD between Jan 2012 and March 2013, 84.4% had a final ambulance oxygen saturation reading of ≥ 93% (95% CI 79.5-88.3%) (Chow 2016). A retrospective Australian study examined oxygen use in 111 patients admitted with hypercapnia due to an exacerbation of COPD. Over-oxygenation was common and was significantly more likely to occur on non-respiratory ward admissions (76% vs 57%, p=0.03) (Anderson 2020). In Wellington, New Zealand, an audit of patients with an exacerbation of COPD transferred by ambulance to hospital before and after an education program to reduce high concentration oxygen delivery was undertaken (Pilcher 2015). Significantly fewer patients received high concentrations of oxygen in 2010; however, concern was voiced by the authors about the continued use of high concentration oxygen to drive nebulisers. Education may be the key to changing practice.

Where there is evidence of acute respiratory acidosis (or a rise in $PaCO_2$) on ABG, together with signs of increasing respiratory fatigue and/or obtunded conscious state, assisted ventilation should be considered. Early non-invasive positive pressure ventilation (NIV) may reduce the need for endotracheal intubation (see below for more detail).

X3.2 Non-invasive ventilation

Non-invasive ventilation (NIV) is effective for patients with rising paCO2 levels [evidence level I, strong recommendation].

Non-invasive ventilation (NIV) should be strongly considered in patients with an exacerbation of COPD who present with hypercapnic respiratory failure as defined on an arterial blood gas with a PaCO2 above 45mmHg and a pH less than 7.35 *(Osadnik 2017)* [evidence level I].

NIV is an effective and safe means of treatment of ventilatory failure. Its use allows preservation of cough, physiological air warming and humidification, and normal swallowing, feeding and speech. Applying NIV in addition to conventional therapy reduces the risk of mortality by 46% (risk ratio (RR)

0.54, 95% CI 0.38-0.76); NNT 12 and decreases the risk of needing endotracheal intubation by 65% (RR 0.36, 95% CI 0.28-0.46; NNT 5) (Osadnik 2017). This benefit is similar for patients with mild acidosis (pH 7.30 to 7.35) versus. a more severe nature (pH < 7.30), and when NIV is applied in a ward or intensive care unit (Osadnik 2017). The use of NIV reduces hospital length of stay mean difference -3.39 days (95% CI -5.93 to -0.85) (Osadnik 2017).

A local prospective observational cohort study demonstrated that ward-based NIV (managed by respiratory medical and nursing staff) compared with high dependency unit (HDU) and ICU-based NIV achieved equivalent clinical outcomes and was substantially more cost-effective (Parker 2018). These findings were replicated in a similar but retrospective study based in a teaching hospital in China (Hong 2020). The optimal location for provision of NIV should be determined by local experience and availability of expertise.

Hartley et al used a derivation cohort of 489 patients to derive a mortality prediction score for patients with an exacerbation of COPD and hypercapnic respiratory failure receiving NIV. The NIVO score was then validated in a group of 733 patients from across 10 hospitals in England and Wales. The NIVO score consisted of 6 measures that should be available at the bedside (see below). The area under the curve form predicting mortality was 0.79. The score also allowed for mortality risk stratification - see table below. The NIVO score performed better in this patient group than all other mortality prediction scores tested. Use of this score may assist clinicians, patients and their carers in making decisions regarding acute non-invasive ventilation (Hartley 2021) [evidence level III].

X3.2.1 Humidified nasal high flow therapy (hNHF)

Humidified nasal high flow therapy (hNHF) delivering flows of up to 60 L/minute has been used successfully for the management of acute hypoxaemic respiratory failure, while in acute exacerbations of COPD associated with hypercapnia and acidemia, NIV is accepted as standard of care.

In a multi-centre Italian study of hNHF (Cortegiani 2020), (Optiflow and MR850 or Airvo) patients (n=80) with mild-moderate AECOPD and hypercapnia (PaCO2 > 55mmHg, pH 7.25-7.35) before support were randomised to receive NIV or hNHF, with oxygen titrated to oxygen saturations of 88-92%. hNHF was statistically non-inferior to NIV as initial ventilatory support in reducing PaCO2 at 2 hrs (-6.8mmHg HFNT $\pm$ 8.7, v -9.5 mmHg $\pm$8.5), p=0.4, considering a non-inferiority margin of 10 mmHg. However, by 6 hours 32% of patients in hNHF group had switched to NIV due to worsening or no improvement of respiratory failure; n=1 due to intolerance, while from the NIV group only one patient switched to hNHF due to intolerance and one to invasive ventilation. The authors of this study concluded that further trials with a superiority design examining patient related outcome measures are needed. NIV remains standard of care at present as it has been consistently shown to reduce mortality [evidence level I].

In a multi-centre RCT of patients from 16 hospitals in China admitted with AECOPD and mild hypercapnia (pH ≥7.35 and PCO2>45mmHg) there was no difference in the primary outcome of proportion of patients needing intubation in the HFNC group (AirVo2 started at 25L/min and increased to maximal tolerance with maximal humidification and maintaining SPO2 90-95%) versus the controlled oxygen group (low flow oxygen at 1-5L/min to maintain SPO2 90-95%). There was no difference between the groups in rate of treatment failure (15.8% versus 14.5%) and the most common reason for treatment failure in the HFNC group was intolerance, whereas in the controlled oxygen group it was need for NIV. The numbers of patients upgraded to NIV in both groups were comparable. However, the median duration from randomisation to commencement of NIV was longer in the HFNC group. Patients in the HFNC group had longer lengths of stay (9 v 8 days) and increased treatment costs (by 14.6%) compared to those on controlled oxygen therapy (Xia 2022) [evidence level II].

Overall, taking together the results of these two studies, there was no clear benefit to the use of HFNC in these patients hospitalised with mild-moderate exacerbations of COPD, and potential for harm.

X3.3 Invasive ventilation (intubation)

NIV is contraindicated in patients who are unable to protect their airways, are not spontaneously breathing or who have severe facial injury or burns (Esteban 2000). Relative contraindications (situations where NIV may be less effective) include life-threatening refractory hypoxaemia (PaO_2 < 60 mmHg, or 8 kPa on 100% inspired oxygen), bronchiectasis with copious secretions, severe pneumonia, and haemodynamic instability. These patients may require intubation. Patients who need mechanical ventilation have an inpatient mortality of up to 39% (Wildman 2009). A multi-centre Spanish study (Rivera-Fernandez 2006) that followed surviving patients for 6 years found that subsequent mortality was related to age, Acute Physiology and Chronic Health Evaluation (APACHE) score and quality of life. Although quality of life deteriorated over time, 72% of the survivors remained self-sufficient [evidence level III-2]. A multi-centre UK study (Wildman 2009) that followed surviving patients up to 180 days found that 80% rated their quality of life unchanged compared to pre-admission and 96% would elect to receive the same treatment again under similar circumstances. Overall patients' functional capacity was slightly reduced at 180 days, but broadly predicted by, pre-admission function. Doctors' prediction of survivors' quality of life was pessimistic and agreed poorly with their patients rating.

Weaning from invasive ventilation can be facilitated by the use of non-invasive ventilation. In a Cochrane meta-analysis of patients with predominantly COPD, the use of non-invasive ventilation for weaning resulted in decreased mortality (RR 0.55, 95% CI 0.38-0.79), reduced ventilator-assisted pneumonia (RR 0.29, 95% CI 0.19-0.45), reduced length of stay in ICU (WMD -6.27 days, 95% CI -8.77 to -3.78) and reduced hospital length of stay (WMD -7.19 days, 95% CI -10.8 to -3.58) (Burns 2013).

The patient's wishes regarding intubation and resuscitation should ideally be documented before an admission for management of respiratory failure. Patients who require ventilatory support during exacerbations of COPD may have impaired control of breathing or apnoeas during sleep, even when well. Therefore, performing a diagnostic sleep study when the patient's condition is stable should be considered. Narcotic analgesics and sedatives should be avoided, as these may worsen ventilatory failure and hasten the need for positive pressure ventilation.

X3.4 Clearance of secretions

Patients who regularly expectorate sputum or those with tenacious sputum may benefit from airway clearance techniques (ACTs) during an exacerbation. However, the choice of ACTs during exacerbations requires careful consideration as these episodes result in worsening of airflow limitation and lung hyperinflation, which lead to acute increases in dyspnoea. Patients are also likely to experience significant physical fatigue during an exacerbation and this impacts on the choice of ACT. A Cochrane Systematic Review of 9 trials examined the efficacy of ACTs in patients experiencing an exacerbation of COPD (Osadnik 2012). The use of ACTs was associated with a significant short-term reduction in the need for increased ventilatory assistance (odds ratio 0.21, 95% CI 0.05-0.85, data from 4 studies involving 171 patients) NNT 12, 95% CI 10-66 [evidence level I], the duration of ventilatory assistance (mean difference of -2.05 days, 95% CI -2.60 to -1.51 compared to control, data from 2 studies of 54 patients) [evidence level I] and hospital length of stay (mean difference -0.75 days, 95% CI -1.38 to -0.11 compared to control, data from one study of 35 patients) [evidence level II]. Airway clearance techniques that utilised positive expiratory pressure (PEP) tended to be associated with a greater reduction in the need for increased ventilatory assistance and hospital length

of stay compared to non-PEP based ACTs however the difference was not significant.

With the exception of chest wall percussion, which has been associated with a decrease in FEV_1 and one report of vomiting during treatment involving a head-down tilt position ACTs were not associated with serious adverse effects (Hill 2010, Tang 2010, Osadnik 2012) [evidence level I]. Airway clearance techniques applied during an exacerbation do not appear to improve measures of resting lung function or produce any consistent changes in gas exchange (Osadnik 2012) [evidence level I]. However, the limitations of the studies included in the systematic reviews (i.e. considerable diversity in patients' characteristics and application of specific techniques, small sample sizes in some of the studies, large variety of outcome measures) limited the ability to pool data for meta-analysis. A multicentre RCT that involved 90 patients hospitalised with an exacerbation of COPD investigated whether the addition of PEP therapy to usual medical care that included a standardised physical exercise training regimen improved symptoms, QoL and incidence of future exacerbations (Osadnik 2014). Individuals in this study were characterised by evidence of sputum expectoration or a history of chronic sputum production with over 50% of those recruited expectorating purulent sputum, however individuals with primary bronchiectasis were excluded. The authors found no significant between group differences in symptoms or quality of life assessed over a 6-month period following hospital discharge. The incidence of exacerbations during the follow-up period was low and similar in both groups. The findings of this study (Osadnik 2014) do not support a routine role for PEP therapy even in patients with purulent sputum who are hospitalised for an exacerbation of COPD.

Given the negative impact that exacerbations have on symptoms such as dyspnoea and fatigue, it is important to decide whether performing ACT is appropriate, and if so, choosing the most appropriate technique during this time. The choice of ACT should be guided by a physiotherapist experienced in this type of clinical presentation.

X3.5 Develop post-discharge plan and follow-up

The aim is to relieve hypoxaemia and obtain improvement in clinical signs and symptoms.

- ***Clinical examination:*** Reduction in wheeze, accessory muscle use, respiratory rate, distress.
- ***Gas exchange:*** Arterial blood gas levels and/or pulse oximetry levels should be monitored until the patient's condition is stable (SpO_2 88 to 92%).
- ***Respiratory function testing:*** FEV_1 should be recorded in all patients after recovery from an exacerbation.
- ***Discharge planning:*** Discharge planning should be commenced within 24–48 hours of admission.

As individual non-pharmacological interventions have shown some promise in reducing COPD admissions, diverse attempts have been made at "bundling" various combinations of these interventions. A large Canadian cohort study of hospitalised COPD patients compared those exposed (n=796) to a bundled intervention (inhaler device technique, follow up with primary care, medication optimization, written discharge management plan, referral to pulmonary rehabilitation, comorbidities and frailty screen, and smoking cessation) to patients not exposed (n=3344). The bundled intervention resulted in an 83% reduced risk of 7-day readmission (RR 0.17, 95% CI 0.07-0.35) and 26% reduced risk of 30-day readmission (RR 0.74, 95% CI 0.60-0.91). There was no difference in 90-day readmissions. The transition bundle however was also associated with a 7.3% (RR 1.07, 95% CI 1.0-1.15) relative increase in length of stay and a 76% (RR 1.76, 95% CI 1.53-2.02) greater risk of a 30-day ED revisit. Within this cohort was a nested RCT where patients exposed to the bundled intervention were randomised to a case coordinator (n=392) in addition to the bundled intervention versus the bundled intervention only (n=404). There was no difference in readmission between these groups, although 7.6% more patients in the care co-ordinator group visited their primary care physician within 14 days of discharge. The care co-ordinator did not provide ongoing case management beyond contact

between 48 to 72 hour and 7 to 10 days after discharge (Atwood 2022) [evidence level III-2]. These data highlight the importance of COPD discharge bundles.

Jennings et al (2015) randomised 173 patients admitted to hospital with an exacerbation of COPD to usual care or a pre-discharge care bundle. The care bundle included smoking cessation counselling, screening for gastroesophageal reflux disease and depression or anxiety, standardised inhaler education, and a 48-h post-discharge telephone call. The intervention did not reduce 30 or 90-day COPD readmission rates. Where bundles have omitted proven components such as pulmonary rehabilitation, there has been no benefit for readmissions (Jennings 2015) [evidence level II]. A Tasmanian retrospective cohort study by Njoku et al (2022) demonstrated that being male (odds ratio [OR] 1.49, 95% CI 1.06–2.09), or Indigenous (OR 2.47, 95% CI 1.31–4.66) and living in a lower socioeconomic region (OR 1.80, 95% CI 1.20–2.69) were risk factors for 30-day readmission (Njoku 2022) [evidence level III-B]. Efforts to find effective interventions are needed particularly for those at high risk of readmission.

Supportive discharge care, sometimes known as transitional care, has been demonstrated to reduce COPD admissions (OR 0.60, 95% CI 0.42-0.85) and all cause re-admissions (OR 0.72, 95% CI 0.53-0.98), with greatest likelihood of success with greater intervention duration (longer the better), use of phone calls, and multidisciplinary professional involvement (Ridwan 2019) [evidence level I].

X3.6 Pulmonary rehabilitation

Consider pulmonary rehabilitation at any time, including during the recovery phase following an exacerbation [evidence level I, strong recommendation]

Exacerbations of COPD are characterised by worsening dyspnoea and fatigue, decreased exercise tolerance and a reduction in health-related quality of life (HRQoL) (Seemungal 2000, Spencer 2003). Individuals are typically less active following hospitalisation for an exacerbation of COPD and this low level of activity may persist for several weeks (Pitta 2006). Quadriceps muscle strength is often reduced during an exacerbation and may be a contributor to inactivity (Spruit 2003).

Pulmonary rehabilitation should be offered to people with COPD following hospitalisation for an exacerbation of COPD. A systematic review of 17 studies (Puhan 2016) reported the effects of pulmonary rehabilitation in 1,477 participants who were in the recovery phase of a recent hospitalisation for an exacerbation of COPD. Rehabilitation was commenced between two days and two weeks after the exacerbation, and was provided in inpatient, outpatient, and home settings, with a program duration between four days and six months. Pulmonary rehabilitation significantly improved HRQoL and exercise capacity in the short-term (median of five months for HRQoL and a median of three months for exercise capacity). Pulmonary rehabilitation also reduced hospital readmissions (pooled odds ratio 0.44, 95% CI 0.21- 0.91, n=810 participants). The follow-up period for collection of hospitalisation data ranged from three to 18 months, with a median duration of nine months. There was no significant effect on mortality (pooled odds ratio 0.68, 95% CI 0.28- 1.67). In another systematic review (Ryrso 2018), early supervised pulmonary rehabilitation (initiated within four weeks after a COPD exacerbation) reduced mortality (four studies, RR=0.58, 95% CI 0.35-0.98) after the end of treatment. There was no effect of early supervised pulmonary rehabilitation on mortality over the longer-term, most likely due to the small sample (three trials, 127 participants) [evidence level I].

In the Australian and New Zealand health care context, inpatient pulmonary rehabilitation is not easily accessible, whereas access to outpatient pulmonary rehabilitation is more feasible. Accordingly, the authors of the Australian and New Zealand Pulmonary Rehabilitation Guidelines (Alison 2017) performed a meta-analysis of five outpatient pulmonary rehabilitation studies (program duration 6-12 weeks), commenced within two weeks of hospital discharge. Consistent with the Puhan review (Puhan

2016) and confirmed by the Ryrso review (Ryrso 2018), large benefits for HRQoL and exercise capacity were found. Importantly, no adverse events were reported. Overall, the Australian and New Zealand Pulmonary Rehabilitation Guidelines recommend that outpatient pulmonary rehabilitation is provided after an exacerbation of COPD, commencing within two weeks of hospital discharge (weak strength of recommendation, moderate quality of evidence) (Alison 2017). The Ryrso review (Ryrso 2018) reported a decrease in the number of COPD-related hospital admissions in the three to 12 months following early supervised pulmonary rehabilitation programs initiated after discharge (RR=0.41, 95% CI 0.11-1.47), and no difference in the drop-out rate between early supervised pulmonary rehabilitation and usual care. Given the personal and health-system benefits of pulmonary rehabilitation commenced shortly after an exacerbation, it is important to have appropriate screening and referral processes to increase participation in early pulmonary rehabilitation.

Information about pulmonary rehabilitation including a list of programs known to Lung Foundation Australia can be accessed on the website. The individual contact details can be obtained by calling the Lung Foundation's Information and Support Centre (free-call 1800 654 301).

X3.7 Discharge planning

Patients with COPD discharged from hospital following an exacerbation should receive comprehensive follow-up led by the primary healthcare team [evidence level I, strong recommendation].

Discharge planning involves the patient, external lay and professional carers, the multidisciplinary hospital and community team and the patient's regular GP. It should commence on admission and be documented within 24–48 hours (see **Box 14**).

Lung Foundation Australia has developed the Managing COPD Exacerbation Checklist available at: https://lungfoundation.com.au/resources/?search=managing%20a%20copd%20exacerbation%20checklist which provides guidance on managing a patient at three stages – in hospital; prior to leaving hospital; and on an ongoing basis 1-4 weeks post-discharge (See **Figure 8**).

Appropriate patient education and attention to preventive management are likely to reduce the frequency of further exacerbations. Assessment of social supports and domestic arrangements are critical in discharge planning. Medicare items support aspects of discharge planning. See http://www.health.gov.au/internet/main/publishing.nsf/Content/mbsprimarycare-chronicdiseasemanagement-qanda

A discharge pack, which includes general information about COPD, advice on medication use and written instructions on use of inhalation and oxygen devices, if appropriate, as well as a plan for management of worsening symptoms, should be provided. The GP (and respiratory outreach program, if available) should be notified during the patient's admission. A case conference involving the multidisciplinary team and GP may assist successful transition to the community. Medicare Benefits Schedule Enhanced Primary Care item numbers may be claimed for "participation in a case conference" and "contribution to a care plan" (see Section D).

Before discharge, referral to a comprehensive pulmonary rehabilitation program should be considered.

Box 14: Criteria for discharge

Suggested criteria for a patient's readiness for discharge include:

- The patient should be in a clinically stable condition and have had no parenteral therapy for 24 hours
- Inhaled bronchodilators are required less than four-hourly
- Oxygen delivery has ceased for 24 hours (unless home oxygen is indicated)
- If previously able, the patient is ambulating safely and independently, and performing activities of daily living
- The patient is able to eat and sleep without significant episodes of dyspnoea
- The patient or caregiver understands and is able to administer medications
- Follow-up and home care arrangements (e.g., home oxygen, home-care, Meals on Wheels, community nurse, allied health, GP, specialist) have been completed.

A meta-analysis which included an appraisal of four RCTs across three countries and which demonstrated that the use of COPD discharge bundles reduced hospital readmissions by 20% showed no demonstrable benefit in terms of LOS or mortality (Ospina 2017). Outpatient follow-up was found to be a core element to reduce re-admissions.

A systematic literature review of 13 evidence based clinical pathways used in either primary care or hospital settings across 10 countries has demonstrated a reduction in COPD re-admissions by 34% (OR 0.66, 95% CI 0.49-0.88) [evidence level I], although with little reduction in length of stay. Studies with longer follow ups appeared more likely to detect benefits (Plishka 2019).

Figure 8: Managing a COPD Exacerbation Checklist

X3.8 Support after discharge

Follow-up at home after discharge from hospital may extend the continuum-of-care process begun within the acute environment and supported discharge programs are now well established. Such programs are generally short term in nature and have clear criteria for which patients are suitable. Compared to more traditional in-patient management, supported discharge programs are associated with shorter length of stay and lower 90-day mortality, with little difference in readmission rate (Kastelik 2012), confirming the safety of such an approach. Over the longer term, an integrated approach involving a discharge plan shared with the primary care team together with access to a case manager through a web-based call centre has been shown to reduce re-admissions for COPD exacerbations compared to usual care (Casas 2006) [evidence level II]. Although a systematic review of structured, planned, post-discharge support found evidence for a reduction in readmissions at 30 days, the study was unable to identify a single intervention 'package' that could be recommended (Pedersen 2017). Notably, a study of supported self-management following discharge, which combined home visits to empower participants to manage their COPD independently and case management to facilitate prompt and appropriate access to care (not included in the above-mentioned systematic review), did not find any significant benefit on COPD admissions or death when compared to usual care (hazard ratio 1.05, 95% CI 0.08-1.38) (Bucknall 2012). Not only do many of these studies have different outcomes, but many were conducted in Europe and their applicability to the Australasian setting is not known. Telephone follow-up may be a way of systematically extending support to patients and increasing their coping strategies at home, but the outcomes of this intervention have not been studied systematically.

X3.9 Clinical review and follow-up

There are no randomised clinical trials that have addressed the best method for follow-up (Sin 2002). It is recommended that the first review after a hospital admission should be by the GP and within seven days of discharge (**Box 15**). Chronic cough and sputum production are associated with an increased risk of further exacerbation (Burgel 2009) [evidence level III-2] and these patients may warrant closer monitoring. A decision about the requirement for specialist review should be made at the time of discharge. Follow-up care allows further discussion of self-management plans and future monitoring (Sin 2002).

Box 15: Follow-up – initial and subsequent

- Assessment of the patient's coping ability and strategies
- Measurement of FEV_1 and performance status
- Reassessment of medication adherence and techniques with inhalation devices
- Review of immunisation status (influenza and pneumococcal)
- Assessment for long-term oxygen therapy (may require reference to specialist facility)
- Consideration of referral for pulmonary rehabilitation
- Assessment of risk of osteoporosis and management
- Smoking cessation — counsel and/or refer
- Assess nutritional status (frequent small meals reduce dyspnoea)

X4. Uptake and impact of guidelines for exacerbations

Although there are many COPD guidelines around the world, there has been little evaluation of their uptake into clinical practice, or their impact on clinical outcomes. A study of the compliance to COPD-X (Gerber 2018) recommendations in 381 COPD patients attending the EDs of two hospitals within one local Australian health service, has demonstrated moderately satisfactory results, with compliance to individual recommendations of the order of 74 to 90%, and to the whole list of recommendations of 49%, indicating some room for further improvement. Highest levels of compliance were seen in the most severe COPD cases. This study did not show a reduction in LOS with greater compliance; however this analysis did not adjust for severity.

A retrospective study of 134 patients admitted with an exacerbation of COPD at an Australian tertiary hospital demonstrated poor adherence to COPD-X recommendations for managing exacerbations. Controlled oxygen therapy to achieve SpO2 88-92% was provided in 42% of cases and referral to pulmonary rehabilitation was made in only 17.9% of cases. Furthermore, smoking cessation counselling was provided to 40% of patients and a review of immunisation status only occurred in 2% of cases (Sha 2020).

A European study found that hospitalised COPD patients with an exacerbation received on average only 41% of key diagnostic, pharmacological and non-pharmacological recommendations from clinical guidelines, including low uptake of provision of smoking cessation advice (3%), inhaler technique education (11%) and referral to pulmonary rehabilitation (29%) (Seys 2017).

An audit of COPD patients in the Outpatient respiratory clinics of 59 Spanish hospitals (Calle Rubio 2017) demonstrated that clinical practice, at least as recorded in the case notes, fell well short of recommendations in GOLD and Spanish national guidelines for COPD.

A prospective cohort study of 415 patients with an exacerbation of COPD who presented at 46 EDs in 5 Asia-Pacific countries, 65% of these arriving by ambulance, and 78% of those being admitted to hospital, of which 7% to an ICU and median LOS 4 days highlights the public health and acute care hospital burden of COPD exacerbations (Kelly 2018). Clinical management findings against COPD-X benchmarks are to be interpreted with caution as they are based on case-note audit but were indicative of excessive use of uncontrolled oxygen therapy and a suboptimal use of a combination of inhaled corticosteroid/bronchodilator therapy, arterial blood gas measurement and also treatment with non-invasive ventilation.

An audit of 801 patients with COPD who presented to 66 European and 46 Australasian participating emergency departments (ED) with breathlessness demonstrated a low adherence to COPD-X and GOLD guideline management recommendations with respect to the use of systemic corticosteroids and antibiotics, especially in the European sites (Kelly 2019). Use of non-invasive ventilation when indicated was equally low in both regions. The authors propose novel use of care bundles and supportive clinical support systems in EDs to reduce the evidence–practice gap.

A tertiary hospital in Israel introduced an electronic clinical decision support tool for use in COPD patient discharge and reported a very significant increase in adherence to guidelines with respect to prescription of appropriate inhalers, recommendations regarding vaccination and smoking cessation as well as follow up in outpatient clinics (Epstein 2019).

Appendices

Appendix 1. Use and doses of long-term inhaled bronchodilator and corticosteroids determined in response trials

Response	Drug	Dose (mcg)	Frequency	Delivery
Improved airway function Improved exercise capacity Reduced breathlessness Improved quality of life				
	beta-agonist			
	Salbutamol	100-200mcg	4-6-hourly	MDI/spacer
	Salbutamol	200-400mcg	4-6 hourly	DPI
	Terbutaline	500-1500mcg	6-8-hourly	DPI
	Salmeterol	50mcg	12-hourly	MDI/DPI
	Formoterol	12mcg	12-hourly	MDI/DPI
	Indacaterol	150-300mcg	24-hourly	DPI
	Antimuscarinic (Anticholinergic)			
	Ipratropium	42-84mcg	6-8-hourly	MDI/spacer
	Tiotropium	18mcg	24-hourly	DPI
	Tiotropium	2.5mcg	24-hourly	Respimat
	Glycopyrronium	50mcg	24-hourly	DPI
	Corticosteroid			Inhaled
	Beclometasone (small particle)	50-200mcg/day	12-hourly	MDI/spacer
	Budesonide	400mcg	12-hourly	DPI
	Fluticasone propionate	250-500mcg/day	12-hourly	MDI/DPI
	Fluticasone furoate	100mcg/day	12-hourly	DPI
	Ciclesonide	80-320mcg/day	24-hourly	MDI/spacer

MDI=metered dose inhaler. DPI=dry powder inhaler.

Appendix 2. Explanation of inhaler devices

Delivery system	Available products	Considerations
Metered dose inhaler (MDI)	Ventolin, Asmol, Airomir, Epaq (salbutamol 100mcg); Atrovent (ipratropium bromide 21mcg); Qvar (beclometasone 50mcg, 100mcg); Alvesco (ciclesonide 80mcg, 160mcg); Flixotide (fluticasone 50mcg, 125mcg, 250mcg); Serevent (salmeterol 25mcg); Seretide (salmeterol 25mcg and fluticasone 50mcg, salmeterol 25mcg and fluticasone 125mcg, salmeterol 25mcg and fluticasone 250mcg); Symbicort Rapihaler (budesonide 200 mcg and formoterol 6 mcg)	• MDIs should be used with a spacer device, as some people have difficulty coordinating the release of medication with inhalation.
Spacers	Aerochamber Breath-A-Tech Fisonair Nebuhaler Volumatic	• The spacer chamber acts as a reservoir for the aerosol released from an MDI. The patient can then inhale from this chamber without having to coordinate the release of the medication. • Use of spacers with inhaled corticosteroids reduces adverse effects of oral candidiasis and hoarseness, as well as optimising medication delivery. • MDI with spacer is as effective as a nebuliser if an equivalent dose is taken; 10-15 puffs of 100mcg salbutamol MDI via a spacer is therapeutically equivalent to a 5mg salbutamol nebule. • Spacers are cost effective, portable, easily cleaned and maintained, do not require electricity and are simple and quick to use. • A small volume spacer is preferable when the vital capacity is less than 1.5 L.
Autohaler	Airomir (salbutamol 100mcg); Qvar (beclometasone 50mcg, 100mcg)	• Breath-activated MDI containing 200 doses of medication. • Use can improve lung deposition in patients with poor MDI inhaler technique. As the patient starts a slow, deep breath through the mouthpiece, a flap valve is triggered, and the dose automatically releases.
Dry powder inhalers (DPI)		

Accuhaler	Serevent (salmeterol 50mcg); Flixotide (fluticasone propionate 100mcg, 250mcg, 500mcg); Seretide (salmeterol 50mcg and fluticasone propionate 100mcg, salmeterol 50mcg and fluticasone propionate 250mcg, salmeterol 50mcg and fluticasone propionate 500mcg)	• Breath-activated multi-dose DPI containing 60 individually sealed doses. A dose counter shows the number of doses remaining. It gives consistent drug delivery over a range of inspiratory flow rates (30-120 L/minute). • Lactose powder is combined with the active medication for patients to taste and reassure them that they have inhaled a dose.
Aerolizer	Foradile (formoterol 12mcg)	• Breath-activated single-dose powder inhaler that comes with a sheet of 60 capsules in push-out foil sheet. One capsule is loaded into the inhaler and pierced before inhaling. • Gives consistent drug delivery over a range of inspiratory flow rates.
Turbuhaler	Bricanyl (terbutaline 500mcg); Pulmicort (budesonide 100mcg, 200mcg, 400mcg); Oxis (formoterol 6mcg, 12mcg); Symbicort (formoterol 6mcg and budesonide 100mcg, formoterol 6mcg and budesonide 200mcg, formoterol 12mcg and budesonide 400mcg)	• Breath-activated multi-dose inhaler, containing 60 (Oxis, Symbicort) or 200 (Pulmicort, Bricanyl) doses; ensures delivery without the need to coordinate inspiration with drug release. • Dose delivery is halved if the patient cannot produce inspiratory flow above 30 L/min. Very few patients with COPD cannot produce a rate of >60 L/min. • Produces very fine powder, so patients often don't taste anything. • Dose indicator shows when there are 20 doses remaining, and then when the inhaler is empty (it contains a drying agent that can be heard when the inhaler is shaken, which can be misinterpreted as available medication).
HandiHaler	Spiriva (tiotropium 18mcg)	• Breath-activated dry powder inhaler. A capsule containing tiotropium is dropped into the HandiHaler, and pierced by pressing a button. The patient then inhales through the mouthpiece for effective drug delivery. Studies have shown that patients with a wide range of disease severity are able to generate sufficient inspiratory airflow (as low as 20 L/min) to evacuate the powder from the capsule.
Breezhaler	Onbrez (indacaterol 150mcg, 300 mcg) Seebri (glycopyrronium 50mcg) Ultibro (indacaterol 110 mcg/glycopyrronium 50 mcg)	• Breath-activated single-dose powder inhaler • Capsules come in foil packs containing 30 capsules in a cardboard carton • Breezhaler inhalation device allows oral inhalation of the content of the capsule shell. One capsule is loaded into the inhaler and pierced before inhaling. • Gives consistent drug delivery over a range of inspiratory flow rates.

Genuair	Bretaris (aclidinium 322 mcg/ dose) Brimica (aclidinium 340 mcg/formoterol 12 mcg)	• Breath activated multi-dose DPI (containing 30 or 60 doses) with an integral dose indicator, a green dosage button and a coloured control window. Before inhaling the dose, the green button should be pressed all the way down and then released. The coloured control window changes to green suggesting the dose is ready for inhalation. If the full dose is inhaled correctly, the control window turns red. Genuair is equipped with a dose indicator, displaying intervals of 10 (60, 50, 40, 30, 20, 10, 0). When a red striped band appears in the dose indicator, only a few doses are left in the device. Bretaris Genuair also contains lactose.
Ellipta	Breo (fluticasone furoate 100 mcg and vilanterol trifenatate 25 mcg)	• Breath activated multi-dose DPI containing 14 or 30 doses. The active substances are in separate blisters in powder form inside the device. It has a dose counter; when fewer than 10 doses are left, half of the dose counter shows red.
Soft mist inhaler	Spiriva Respimat (tiotropium 2.5 mcg) Spiolto Respimat (tiotropium 2.5 mcg/olodaterol 2.5 mcg)	• Push button activated solution for inhalation. The cartridge is inserted and primed before first use of the Respimat. To deliver the inhalation, the clear base is turned until it clicks, the cap is opened, and the patient closes their lips around the mouthpiece. The dose-release button is pressed, and the mist is inhaled with a slow, deep breath, then a breath hold. A dose indicator shows a low number of doses left, and the inhaler locks when empty. May be suitable for patients with poor inspiratory effort.
Nebulisers	Most nebulisers are electric. Some ultrasonic nebulisers are battery operated. These models are not heavy duty but are ideal for travelling. There are also 12-volt pumps that plug into a car cigarette lighter. Use of inhaled corticosteroids requires a high-flow, heavy- duty pump.	• Corticosteroid or ipratropium bromide aerosol should not be allowed to enter the eyes to avoid the risk of adverse effects such as glaucoma or urinary outlet obstruction. Patients should be advised to wipe their face dry after using the nebuliser to remove medication from the skin. • Ipratropium can be combined with beta-agonist, but not with corticosteroid.

The products listed may not all be subsidised under the Pharmaceutical Benefits Scheme for use in COPD.

Appendix 3. Long term oxygen therapy (McDonald 2016a)

Initiating oxygen therapy

- Before introducing oxygen therapy, ensure optimal treatment of the pulmonary disorder while monitoring improvement with objective tests such as FEV_1 and forced vital capacity (FVC). Treatment may include maximum therapy for airway obstruction, attention to nutrition and bodyweight, an exercise rehabilitation program, control of infection, and treatment of cor pulmonale.
- In patients selected for oxygen therapy, assess the adequacy of relief of hypoxaemia (PaO_2 > 60 mmHg, or 8 kPa; SpO_2 > 90%) and/or improvement in exercise capacity or nocturnal arterial oxygen saturation while using a practical oxygen delivery system.

What the patient needs to know

- Patients receiving oxygen therapy in the home, and their carers, should have the use clearly explained. That is, hours of use and flow rate, and any need to vary flow rates at given times. The equipment and its care, including how to obtain servicing or **replacements**, needs to be explained. The dangers of open flames (especially cigarettes, gas heaters and cookers) need to be emphasised.
- Flow should be set at the lowest rate needed to maintain a resting $PaO_2$of 60 mmHg (8kPa) or SpO_2 > 88%. For patients with COPD, 0.5–2.0 L/min is usually sufficient. Flow rate should be increased by 1 L/min during exercise.
- Humidifiers are generally not needed at oxygen flow rates below 4 L/min.
- Extra soft nasal prongs are recommended for continuous oxygen use, but may become uncomfortable at flow rates over 2–3 L/min and in the long term. Facemasks may be preferred for at least some of the time, although there are dangers of rebreathing exhaled CO2 at flow rates below 4 L/min.

Review

- Reassess 4–8 weeks after starting continuous or nocturnal oxygen therapy, both clinically and by measurement of PaO_2 and $PaCO_2$, with and without supplementary oxygen. A decision can then be made as to whether the treatment has been properly applied and whether it should be continued or abandoned.
- Patients on intermittent oxygen therapy should also be reassessed periodically. The review can be undertaken by appropriately trained staff using a pulse oximeter to confirm hypoxaemia (SpO_2 < 88%) at rest or during daily activities. They should also check compliance with therapy and smoking status.
- Review at least annually or more often according to the clinical situation.

Dangers

- Supplementary oxygen in patients with increased arterial $PaCO_2$ may depress ventilation, increase physiological dead space, and further increase arterial $PaCO_2$. This is suggested by the development of somnolence, headache and disorientation.
- In long-term oxygen therapy, the increase in arterial $PaCO_2$ is usually small and well tolerated. However, serious hypercapnia may occasionally develop, making continued oxygen therapy impractical. Risk appears greater during exacerbations of disease or if the flow of oxygen is increased inappropriately.
- Sedatives (particularly benzodiazepines), narcotics, alcohol and other drugs that impair the central regulation of breathing should not be used in patients with hypercapnia receiving oxygen therapy.

Choosing the right method (see Adult Domiciliary Oxygen therapy Clinical Practice Guideline for further details)

Domiciliary oxygen therapy can be delivered via the following systems:

- ***Stationary oxygen concentrators:*** These floor-standing electrically driven devices work by extracting the nitrogen from room air by means of molecular sieves and deliver a continuous flow of oxygen at the outlet. The percentage of oxygen is around 90 to 95% depending on the model used. A back-up standard D-size oxygen cylinder is often supplied in case of concentrator breakdown or power failure. Users may claim a rebate on their electricity account.

- **Portable oxygen concentrators:** These are small, lightweight portable oxygen concentrators (POC) that are powered by the household electrical supply or via a car battery or rechargeable battery which makes them suitable for ambulatory use. Some models have been approved by some of the commercial airlines. Two types are available, those that are only capable of delivering pulsed oxygen (these are generally smaller and lighter in weight) and those that can deliver both pulsed and continuous flow oxygen. The performance specifications of the different models of POCs vary considerably and for patients with high oxygen needs, some POCs may not achieve a sufficient concentration of inspired oxygen to meet the patient's needs during exercise.

- **Cylinders:** These contain compressed oxygen gas and deliver 100% oxygen at the outlet. Portable lightweight cylinders are available. Electronic conservation devices are often supplied to deliver oxygen predominantly during inspiration and therefore avoid wastage. Demand flow devices are the most common and deliver a pre-set volume or bolus of oxygen in early inspiration. Use of such devices results in up to a fourfold reduction in oxygen consumption. Reservoir-style conservers (i.e. nasal cannulae with an integrated pendant shaped reservoir) are a cost-effective alternative.

The prescription should always specify:

- the source of supplemental oxygen;
- method of delivery;
- duration of use; and
- flow rate at rest, during exercise and during sleep.

There is no significant difference in the quality of oxygen delivery among the above methods. However:

- Concentrators are cheaper than cylinders if use is equivalent to or more than three E-size cylinders per month.
- Concentrators can be wheeled around the home but are heavy (about 21–26 kg) and are difficult to move up stairs and in and out of cars.
- Concentrators cannot be used for nebulisation, as the pressure delivered is too low (35–63 kPa, compared with 140 kPa for nebuliser pumps).
- If the anticipated need is for longer than three years, it is cheaper to buy than to rent a unit. The units usually have a five-year guarantee. However, public funding is available for pensioners and Health Care Card holders, subject to means testing.

Appendix 4. Strategies that may assist in reminding people to reduce sedentary time

TV viewing	During each advertisement break, stand up and go for a short walk around your house.
Reading	At the end of each book chapter or after a few pages of the newspaper, stand up and go for a short walk around your house.
Transport	Stand up whilst waiting for a bus or train.
Daily tasks	When ironing, put items away in multiple small trips rather than putting everything away once you have finished.
Computer use	Consider setting an alarm (e.g. on your phone) to remind you to stand up every 30 minutes.
Phone use	Consider standing up to use your phone. Go for a short walk around your house after you finish using your phone to call / text someone.

Appendix 5. Table of Minimum Clinically Important Differences (MCID) for COPD (Cazzola 2015b)

Health Status measures

Patient Reported Outcome Measure (PROM)	Purpose	Domains	No. items	Reliability	Validity	MCID
St George's Respiratory Questionnaire (SGRQ)	Assess health status impairment in airways disease (COPD, Asthma, Bronchiectasis)	Symptoms, activity, impacts	50	✔	✔	4 units
St George's Respiratory Questionnaire-COPD (SGRQ-C)	Assess health status in COPD – weakest items removed	Symptoms, activity, impacts	40	✔	✔	4 units
Chronic Respiratory Questionnaire (CRQ) (short form also available)	health-related quality of life in chronic respiratory disease	Mastery, fatigue, emotional function and dyspnoea	20	✔	✔	0.5 units
Clinical COPD Questionnaire (CCQ)	Health status assessment in a primary care setting	Symptoms, functional state, mental state	10	✔	✔	0.4 units
COPD Assessment Test (CAT)	Quantifies symptom burden of COPD, health status measurement	Energy, Sleep, confidence, activities, breathlessness, chest tightness, phlegm, cough	8	✔	✔	2 units

Symptom measures

Patient Reported Outcome Measure (PROM)	Purpose	Domains	No. items	Reliability	Validity	MCID
Modified Medical Research Council (MMRC)	Disability from COPD related to breathlessness	Uni-dimensional	1 - 5-point scale	✔	✔	~ 1, but limited data
Baseline Dyspnoea Index (BDI) Transitional Dyspnoea Index (TDI)	Measurement of dyspnoea based on activities of daily living	BDI: functional impairment, magnitude of task, magnitude of effort	BDI 3 TDI 3	✔	✔	1 unit in TDI
The Breathlessness Cough and Sputum Scale (BCSS)	Tracks severity of resp symptoms and evaluate efficacy in clinical trials - COPD	Breathlessness, cough, sputum	3	Acceptable	Acceptable	>1 substantial .6 mod .3 small
Dyspnoea 12	Current level of breathlessness severity	Uni-dimensional	12	✔	✔	Not yet established

1 **Exacerbations**

Patient Reported Outcome Measure (PROM)	**Purpose**	**Domains**	**No. items**	**Reliability**	**Validity**	**MCID**
The **EXA**cerbations of **C**hronic Pulmonary Disease **T**ool (EXACT®)	Evaluates frequency, severity and duration of an AE COPD (Daily)	Breathlessness, cough and sputum, chest symptoms	14	✔	✔	Not yet established
Evaluating Respiratory Symptom (E-RS®)	Derivative instrument of the EXACT, designed to address the need for a standardized daily diary to assess respiratory symptoms in patients with stable COPD	Breathlessness, cough and sputum, chest symptoms	11	✔	✔	3 point Δ(total score) 2 point Δ(breathlessness) 1 point Δ(cough & sp) 1 point Δ(chest symptoms)

2

Appendix 6: Table of Systematic Reviews Evaluating the Effect of Self Management in COPD

Authors	Design	Studies included	Participants n=	Aims	Intervention	HRQoL	All-cause hospitalisations	Respiratory-related hospitalisations	Mortality	ED presentations	Anxiety & depression	Dyspnoea	6MWD	Respiratory-related mortality	Medication use	Urgent healthcare
Dickens 2014	RCT	32 studies, database inception-2013	3941	To examine the characteristics of complex interventions intended to reduce the use of urgent and unscheduled healthcare among people with COPD	Multiple components and/or professionals, individual, group, phone or computer. Including education, rehabilitation, psychological therapy, social intervention, organisational intervention (e.g. collaborative care or case management), psychological drug trials. Simple interventions, e.g. new treatment for underlying long-term condition, compared to treatment as usual excluded											☺
Zwerink 2014	RCT, CCT	29 studies, 1995-2014	3688	To assess the efficacy of self-management interventions for individuals with COPD	Structured interventions aimed at improvement of self-health behaviours and self-management skills. Interventions required at least an iterative process of interaction between participant and healthcare provider, and ideally included formulation of goals and provision of feedback. Interventions with < 2 contact moments were excluded.	☺	☺	☺	😐			☺	😐			

Majothi 2015	RCT	9 studies, Moderate-severe COPD, database inception-2012	1466	To evaluate the effect of COPD self-management following admission to hospital	1+ components commonly included in self-management interventions, e.g. action plans, exercise, education, inhaler technique, bronchial hygiene and breathing techniques, stress management and relaxation, nutritional programs, patient empowerment, support groups and telecare, provided in hospital or community setting with a usual care, control, sham intervention or other self-management intervention comparator.	😊	😐		😐	😐						
Cannon 2016	RCT	25 studies, 1990-2016	4082	To analyse the outcome of self-management RCTs and their impact upon COPD patients' health outcomes using meta-analysis	Self-management intervention including at least 4 of the following: Exacerbation action plan, COPD education, medication information, management of exacerbations, management of stress and/or anxiety, nutritional guidance, exercise program/information, or managing a healthy lifestyle.	😊	😐				😐		😊			
Howcroft 2016	RCT, quasi RCT	7 studies, Database inception -2015	1550	Compare COPD exacerbation action plans with a single short educational component + ongoing support directed at use of action plan	Action plan with a single educational component of short duration allowing time for the clinician to personalise plan. Ongoing support delivered by phone or direct contact. Studies with broader self-management support interventions, e.g. education in multiple sessions over a longer period or exercise programmes, with or w/out an action plan were excluded. Active intervention was compared to 'usual care'.	😊			😐	😊	😐				😊	

Jolly 2016	RCT	173 studies, database inception-2012	n/a	To identify the most effective components of interventions to facilitate self-management of health care behaviours	Include 3+ components e.g. structured group-based PR programs (to teach self-management skills); educational self-management interventions delivered in an outpatient setting or at home, sometimes with telephone follow-up; integrated disease management with multidisciplinary input and often some element of monitoring by health professionals; exercise-only interventions (with some dyspnoea management) and respiratory muscle training using threshold devices.	😊	😐									
Jonkman 2016	RCT	14 studies, 1985-2013	3282	Determine if self-management programs were associated with better outcomes and if any subgroups benefit more	Interventions providing information to patients and including 2+ of: stimulation of sign/symptom monitoring; education in problem solving skills, i.e. self-treatment of acute exacerbations and stress/symptom management; smoking cessation; and stimulation of medical treatment adherence; physical activity; or improving dietary intake. Components aimed at enhancing the patient's active role and responsibility.	😊	😊	😊	😐							
Lenferink 2017	RCT	22 studies, 1995-2017	3854	To evaluate the efficacy of COPD-specific self-management interventions that include an action plan for exacerbations	Must include a written action plan for AECOPD and an iterative process between participant and healthcare provider(s) in which feedback was provided.	😊	😐	😊	😐	😐		😐		☹		

Table 😊= improved, 😐= no change, ☹= worsened., grey shading indicates outcome was not analysed. HRQoL= health-related quality of life, 6MWD= 6-minute walk distance, RCT= randomised controlled trial, CCT= controlled

clinical trials, COPD= chronic obstructive pulmonary disease, ED= emergency department, PR = pulmonary rehabilitation.

List of Figures

List of Boxes

Glossary of Terms

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AAT	Alpha-1 Antitrypsin
ABG	Arterial Blood Gas
ACT	Airway Clearance Techniques
ADO	Age, Dyspnoea score and Obstruction
BODE	Body mass index, degree of Obstruction as measured by FEV_1, Dyspnoea score and Exercise capacity
CAT	COPD Assessment Test
CBT	Cognitive Behaviour Therapy
CCQ	Clinical COPD Questionnaire
CI	Confidence Interval
CrI	Credible Interval
CPAP	Continuous Positive Airway Pressure
CRQ	Chronic Respiratory Disease Questionnaire
CVD	Cardiovascular Disease
D_LCO	Diffusing Capacity of Lung for Carbon Monoxide test
DPI	Dry Powder Inhaler
EPC	Extended Primary Care
ERV	Expiratory Reserve Volume
FeNO	Exhaled nitric oxide fraction
FEV_1	Forced Expiratory Volume in 1 Second
FFM	Fat Free Mass
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
HADS	Hospital Anxiety and Depression Scale
HFNC	High Flow Nasal Cannula
HR	Hazard ratio
HRCT	High Resolution Computed Tomography
HRQoL	Health-related quality of life
IC	Inspiratory Capacity
IPAP	Inspiratory Positive Airway Pressure
ISWD	Incremental Shuttle Walk Distance
LOS	Length of Stay
LTOT	Long Term Oxygen Therapy
MCID	Minimum Clinically Important Difference
MDI	Metered Dose Inhaler
mMRC	Modified Medical Research Council Dyspnoea Scale
NHF	Nasal High Flow
NIV	Non-Invasive Ventilation
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NNTB	Number needed to treat for an additional beneficial outcome
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
PBS	Pharmaceutical Benefits Scheme
PEP	Positive Expiratory Pressure
PHT	Pulmonary Hypertension

pMDI	Pressurised Metered Dose Inhaler
RCT	Randomised Controlled Trial
RR	Relative Risk/ Rate Ratio
SD	Standard Deviation
SES	Socioeconomic Status
SGRQ	St George's Respiratory Questionnaire
SGRQ-C	St George's Respiratory Questionnaire-COPD
TB	Tuberculosis
TLC	Total Lung Capacity
WMD	Weighted Mean Difference

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