The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2018

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Foreword

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is very common and a major cause of disability, hospital admission and premature death.

The criteria used to determine the presence of COPD vary and are responsible for differing estimates of prevalence. Separate studies from both Australia and New Zealand showed that 14% of Australians and 14.2% of New Zealanders aged 40 years or more had some degree of COPD using Global Initiative for Obstructive Lung Disease (GOLD) criteria (Toelle 2013, Shirtcliffe 2012). However using a different definition to identify cases, the prevalence of COPD was 9% in people aged 40 years or more (Shirtcliffe 2007). As the population ages it is likely more people will be affected by COPD.

The Australian Institute of Health and Welfare estimated that COPD was the fifth greatest contributor to the overall burden of disease, accounting for 3.6% of disability-adjusted life years (DALY) in 2003 (Australian Institute of Health and Welfare 2008). Chronic obstructive pulmonary disease ranks sixth among the common causes of death in Australian men and sixth in women (Australian Institute of Health and Welfare 2008). In New Zealand, it ranks fifth in both men and women (Ministry of Health 2010). The death rate from COPD among Indigenous Australians is five times that for non-Indigenous Australians. In New Zealand, the age standardised death rate for Māori (46.1 per 100,000) is more than double that for non-Māori (18.1 per 100,000). The disease costs the Australian community an estimated $8.8 billion annually in financial costs, including health and hospital costs, lost productivity, premature death and a low rate of employment (Access Economics Pty Limited for The Australian Lung Foundation 2008).

Chronic obstructive pulmonary disease is commonly associated with other chronic diseases including heart disease, lung cancer, stroke, pneumonia and depression.

Smoking is the most important risk factor for COPD. In 2011/12, 18.2% of Australian males and 14.4% of Australian females over the age of 18 years smoked daily (Australian Bureau of Statistics 2012). Smoking-related diseases have increased substantially in women, and death rates from COPD in women are expected to rise accordingly. Smoking is a leading cause of healthy years lost by Indigenous people both in Australia and New Zealand.

As with any chronic disease, optimum management of COPD requires health system reform in order that both anticipatory care (e.g. developing self-management capacity) and acute care (e.g. treating exacerbations) are planned for. It is beyond the scope of these guidelines to address all the health system reforms that may be required for chronic disease care. Such reforms will require changes of approach in micro-systems (e.g. a general practice or community physiotherapy service), in organisational structures and systems that coordinate care in regions (e.g. Primary Health Networks; Primary Health Care Organisations, Local Hospital Networks) as well as in national and state health policy making institutions.

Much can be done to improve quality of life, increase exercise capacity, and reduce morbidity and mortality in individuals who have COPD. This Australian and New Zealand guideline seeks to summarise current evidence around optimal management of people with COPD. It is intended to be a decision support aid for general practitioners, other primary health care clinicians, hospital based clinicians and specialists working in respiratory health. Published evidence is systematically searched for, identified, and reviewed on a regular basis. The COPD Guidelines Evaluation Committee meets four times a year and determines whether the reviewed evidence needs incorporation into the guideline.

The key recommendations are summarised in the "COPD-X Plan":

Case finding and **c**onfirm diagnosis,
Optimise function,
Prevent deterioration,
Develop a plan of care
Manage e**X**acerbations.

Professor Nicholas Glasgow (on behalf of the COPD Evaluation Committee), December 2011

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, a multidisciplinary group which meets to evaluate the current literature and undertake quarterly updates of the guidelines for the Australian and New Zealand context.

A medical librarian performs a systematic literature search for new papers in COPD, emphysema and chronic bronchitis, encompassing systematic reviews, clinical trials, cohort and case-control studies. Relevant papers are selected for review and 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. Following an approval process which invites review from the Thoracic Society of Australia and New Zealand (through the TSANZ Clinical Care and Resources Sub-Committee (CCRS) and consumer representatives, the updated guidelines are uploaded quarterly to the COPD-X website (https://copdx.org.au/).

Support for COPD-X

Ongoing 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. 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/.

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) levels of evidence and corresponding National Heart, Lung, and Blood Institute categories

NHLBI category	NHMRC level	Basis of evidence
A	I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
B	II	Evidence obtained from at least one properly designed randomised controlled trial.
C	III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
C	III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
C	III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel group.
C	IV	Evidence obtained from case series, either post-test or pre-test/post-test.

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
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

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
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.	II	Strong

Controlled oxygen delivery (0.5-2.0 L/min) is indicated for hypoxaemia in patients with exacerbations.	II	Strong
Non-invasive ventilation (NIV) is effective for patients with rising P_aCO_2 levels.	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)

C: Case finding and confirm diagnosis

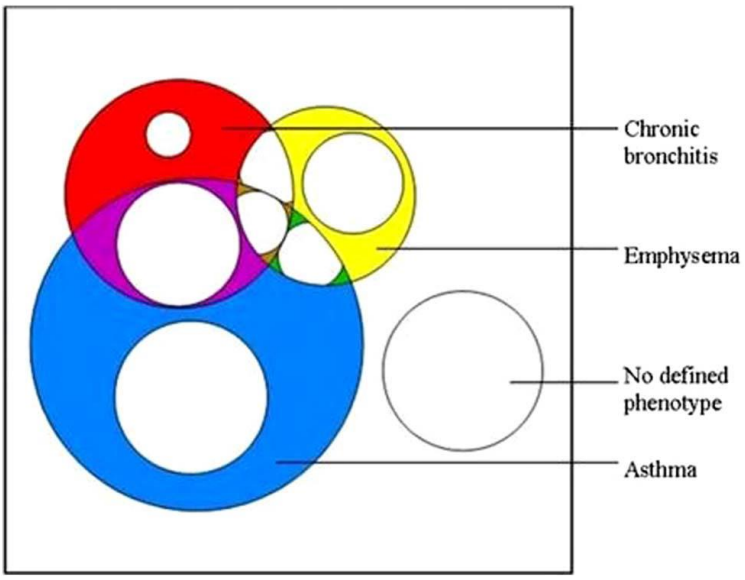
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation which is not fully reversible. The airflow limitation 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) 2018a). 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.

C1. Aetiology and natural history

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

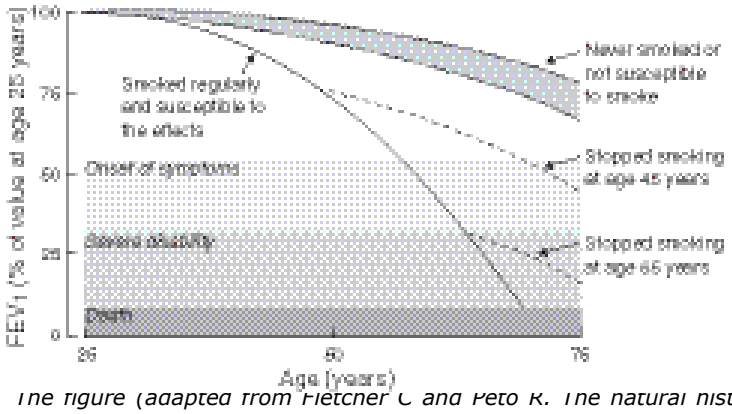
Cigarette smoking is the most important cause of COPD (Fletcher 1977, Burrows 1977, Matheson 2018). There is a close relationship between the amount of tobacco smoked and the rate of decline in forced expiratory flow in one second (FEV_1), although individuals vary greatly in susceptibility (Fletcher 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 smokers 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)

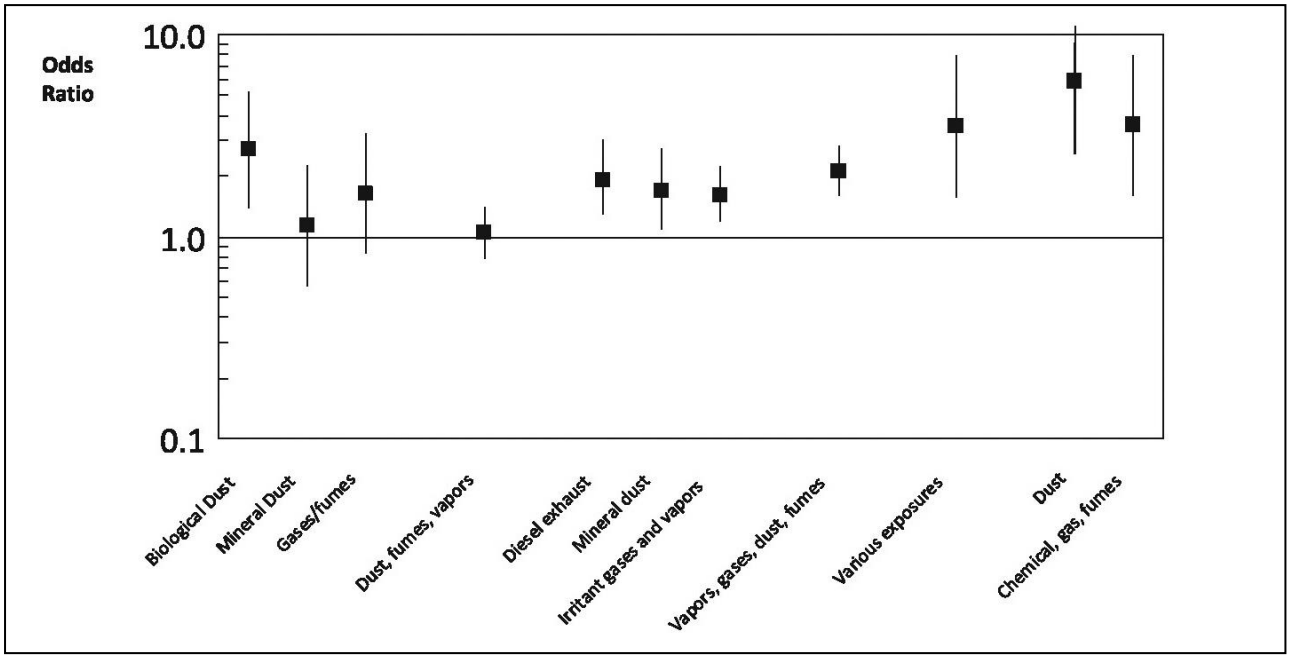


The figure (adapted from Fletcher C and Peto R. The natural history of chronic airflow obstruction. BMJ 1977;1:1645-1648 and reproduced with permission from the BMJ Publishing Group) shows the rate of loss of forced expiratory flow in one second (FEV_1) for a hypothetical, susceptible smoker, and the 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).

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) 2018a) (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. 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 rate 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). 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 mineral, 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



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]. Failure to achieve maximum lung function increases the risk of COPD in later life (Bui 2018, Lange 2015).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 Secondhand (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).

Box 2: Risk Factors for COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018a)

Genes
Exposure to particles
- Tobacco smoke
- Occupational dusts, organic and inorganic
- Indoor air pollution from heating and cooking with bio-mass in poorly vented dwellings
- Outdoor air pollution

Lung Growth and Development
Oxidative stress
Gender
Age
Respiratory infections
Previous tuberculosis
Socioeconomic status
Nutrition
Comorbidities

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 exerise 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 HRCT or a D_LCO <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, measured by the 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).

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 SGRQ and the 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 HRQoL instrument. However, the minimum clinically important difference in the total CAT score is unclear. The CAT is freely available in many languages (see http://www.catestonline.org/english/index.htm). 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

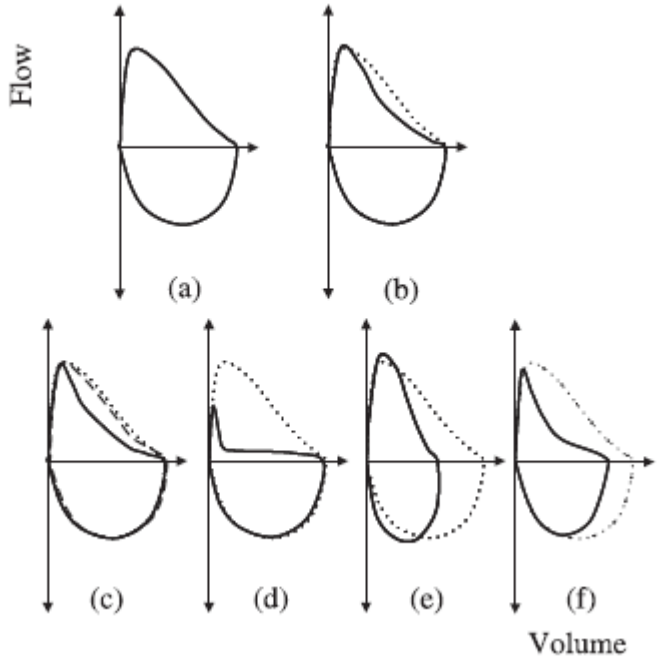
COPD is confirmed by the presence of persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.7$) [evidence level III-2, strong recommendation]

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 vs. 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). There is conflicting data comparing the two cut-offs regarding mortality and healthcare utilisation, however a

study (Bhatt 2014b) shows that the fixed cut-off of 0.7 identified more people with CT diagnosed emphysema.

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 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.

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. 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).

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. Lung Foundation Australia's *Position Paper: COPD case finding in community settings*, https://lungfoundation.com.au/resources/?search=COPD%20case%20finding 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.[†] 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).

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 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).

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

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

	MILD	MODERATE	SEVERE
Typical Symptoms	Few symptoms	Increasing dyspnoea	Dyspnoea on minimal exertion
	Breathlessness on moderate exertion	Breathlessness walking on level ground	Daily activities severely curtailed
	Recurrent chest infections	Increasing limitation of daily activities	Experiencing regular sputum production
	Little or no effect on daily activities	Cough and sputum production	Chronic cough
		Infections requiring steroids	
Typical Lung Function	FEV_1 ≈ 60-80% predicted	FEV_1 ≈ 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/wp-content/uploads/2018/09/Information-paper-Stepwise-Management-of-Stable-COPD-Aug2017.pdf

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 2017). 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.

COPD patients with 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 2017).

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 COPD patients 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 prevalence of severe homozygous (ZZ) alpha1 antitrypsin deficiency has been estimated at between 1/4,348 and 1/5,139 in European populations (Blanco 2006). Available data from 15 cohorts in Australia and New Zealand suggest that the prevalence of affected individuals is around 1/4000 (de Serres 2002). Although 75 to 85% of such individuals will develop emphysema, tobacco smoking is still the most important risk factor for COPD even in this group. Targeted screening suggests between 1.0 to 4.5% of patients with COPD have underlying severe α1-AT deficiency (American Thoracic Society/European Respiratory Society 2003). The index of suspicion should be high in younger

Caucasian patients with predominantly basal disease and a family history. The diagnosis can be made by measuring serum levels of alpha1 antitrypsin and if reduced, genotyping should be performed.

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 a number of 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 function 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[‡] 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 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.

[‡] 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

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 FVC. Ipratropium bromide improved quality of life, with a statistically 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 – 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 signifiant 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 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].

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, SGRQ or 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 vs. 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 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, vs. 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 (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).

***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, Wang 2016b) [evidence level I].

***Other combinations**:* In two 24-week RCTs, glycopyrrolate/formoterol improved FEV_1 compared to glycopyrrolate, formoterol, tiotropium or placebo (Martinez 2017). A LAMA/LABA fixed dose combination (containing glycopyrrolate 18 mcg and formoterol fumarate 9.6 mcg administered twice daily) delivered by Co-Suspension™ Delivery Technology MDI had similar safety and efficacy to that of its individual monocomponent MDIs in patients with moderate-to-very severe COPD (Hanania 2017). LAMA/LABA FDC MDI could be an option for patients with significant lung function impairment who are unable to generate adequate inspiratory flow through higher resistance devices.

***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 of LAMA/LABA combinations compared with monotherapies (Oba 2016) found that the fixed dose combinations provided benefits in lung function compared with their monocomponents, as well as in quality of life, with no increase in adverse outcomes. Combination therapy reduced moderate to severe exacerbations compared with LABA alone (HR 0.92, 95% CrI 0.73-0.93) but not compared with LAMA (HR 0.92, CrI 0.84-1.00). Effects on severe exacerbations were similar with both combination and monotherapies. Other network meta-analyses have also found benefits for LAMA/LABA fixed dose combinations, compared with their monocomponents (Calzetta 2017).

***Comparisons of LAMA/LABA vs 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 analysed 11 RCTs (9,839 patients) studying LAMA/LABA vs. ICS/LABA therapy (Horita 2017). Compared to ICS/LABA, LAMA/LABA resulted in a small reduction in the rate of exacerbations (OR 0.82, 95% CI 0.70 to 0.96), no significant change in mean SGRQ score (although there was a higher proportion achieving the MCID) and a small improvement in FEV_1 (mean difference 0.08 L, 95% CI 0.06 to 0.09). Pneumonia rates were lower, and there was no change in mortality. The studies were heterogeneous in study design and of relatively short duration, and the evidence was of low to moderate quality. Even with these limitations, this systematic review supports the use of LAMA/LABA fixed dose combinations over ICS/LABA inhalers, when initiating long-acting inhaled medicines. Further RCTs of ICS/LABA/LAMA in a single inhaler are awaited, to clarify their efficacy compared to LAMA/LABA. 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). Patients were permitted to continue with their usual COPD medications. There was no difference in exacerbation rates at 12 months. Based on the available evidence, theophylline cannot be recommended in COPD in the Australasian context [evidence level II].

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 number of randomised controlled trials of inhaled corticosteroids have been published and these have been combined in a systematic review (Yang 2012) [evidence level I], mainly involving patients without bronchodilator reversibility or bronchial hyper-responsiveness.

A meta-analysis of 38 studies (including 29 randomised controlled trials and nine observational studies) of inhaled corticosteroid use in COPD reported by Festic et al (Festic 2016), demonstrated similar increases in pneumonia risk, without associated increases in pneumonia-associated mortality or overall mortality; however ideally, further prospective studies which would systematically assess and monitor pneumonia as a pre-specified outcome are required. A post-hoc meta-analysis of data from a GSK trials registry (Pavord 2016) gave a small signal suggesting that patients with eosinophil counts <2% were at marginally increased risk of pneumonia events whether or not they were receiving inhaled corticosteroids. This may be the group who also derive least benefit from inhaled corticosteroids. Further prospective studies are awaited.

Inhaled corticosteroids, given as a single agent, decrease the exacerbation rate compared to placebo in studies longer than a year, with weighted mean difference of -0.26 exacerbations per participant, per year (95% CI -0.37 to -0.14, 2,586 participants). They also slow the rate of decline in quality of life, with the weighted mean difference in rate of change for the St George's Respiratory Questionnaire being -1.22 units/year (95% CI -1.83 to -0.60, 2,507 participants).

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 to 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 to 11.88, 2,333 participants) or a small statistically significant difference (pooled means analysis: 6.88 ml/year, 95% CI 1.80 to 11.96, 4823 participants, with the inclusion of the TORCH study (Calverley 2007, Yang 2012).

Any potential benefits of inhaled corticosteroids should be weighed against the potential risks of local oropharyngeal adverse effects and pneumonia. Local adverse effects include increased risk of oral candidiasis (OR 2.65, 95% CI 2.03 to 3.46, 5586 participants) and hoarseness or dysphonia (OR 1.95, 95% CI 1.41 to 2.70, 3267 participants) (Yang 2012). A meta-analysis of 43 COPD studies (26 fluticasone studies, n =21,247; 17 budesonide studies, n = 10,150) has demonstrated an increased risk of pneumonia with use of inhaled corticosteroids, when given as monocomponents or in combination inhalers (Kew 2014b). Non-fatal serious adverse pneumonia events (i.e. requiring hospital admission) were increased with fluticasone (OR 1.78, 95% CI 1.50 to 2.12) and budesonide (OR 1.62,

95% CI 1.00 to 2.62). There were no significant differences in serious adverse events or mortality when budesonide and fluticasone were compared indirectly. The risk of any pneumonia event was found to be higher with fluticasone than budesonide (OR 1.86, 95% CI 1.04 to 3.34), but this should be interpreted with caution due to differences in definitions of pneumonia in the trials. The authors recommended that safety concerns regarding increased pneumonia should be balanced against the benefits of reduced exacerbations and improved quality of life (Kew 2014b).

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].

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

COPD patients 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 COPD patients, the commencement of fluticasone (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 vs. 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).

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

A systematic review of inhaled corticosteroids vs. 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. Inhaled combination therapy

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 vs. 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% vs 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 vs. 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 (odds ratio 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 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], 1436 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 vs. 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 2014a). 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 COPD patients 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 COPD patients 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 vs. 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 is becoming available on the efficacy of multiple inhaled medications to guide the best combination that will optimise patient's lung function, improve symptoms and reduce exacerbations.

ICS/LABA plus LAMA: 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 systematic review incorporating this study concluded that the high and unbalanced withdrawal rate made interpretation of intervention effects difficult (Welsh 2013).

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; I2 = 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 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].

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 (2.15units SGRQ) and reduced rescue medications (less than one puff per day) (Frith 2015).

ICS/LABA/LABA – 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. The combination of beclometasone/formoterol/glycopyrronium is not currently available in Australia.

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 LAMA/LABA (indacaterol/glycopyrronium) (Papi 2018) [evidence level II]. Pneumonia rates were similar.

***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/LAMA/LABA - fluticasone furoate, umeclidinium and vilanterol) with dual therapies using the same molecules (ICS/LABA and LAMA/LABA), all administered once-daily via a 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.

In Australia, for initiation of triple therapy (ICS/LABA/LAMA) subsidised through the PBS, the patient must have a post-bronchodilator FEV1 <50% of predicted normal prior to therapy, AND must have a history of repeated exacerbations (2 or more) with significant symptoms despite regular bronchodilator therapy with a LAMA/LABA or an ICS/LABA OR the patient must have been stabilised on a combination of a LAMA, LABA and an ICS for COPD.

Harrison et al reviewed inhaled corticosteroid (ICS) prescription in 711 outpatients with spirometry-confirmed COPD at an Australian tertiary hospital and found that 52.4% of patients were prescribed an ICS despite a post-bronchodilator $FEV_1 \geq 50\%$ which is inconsistent with COPD-X recommendations (Harrison 2017). The study did not consider other guideline criteria such as recurrent exacerbations. Several UK GP database studies have demonstrated overprescribing of ICS in COPD (Brusselle 2015, Price 2014, White 2013). Price et al examined inhaler use in primary care in UK in over 3,000 patients

with spirometry confirmed COPD. Over 50% of patients who did not qualify for ICS based on GOLD guidelines were inappropriately prescribed ICS (Price 2014). Under treatment was reported in 17% of patients. A similar study, also in primary care in the UK reported over prescription of ICS in approximately 35% of patients (White 2013). Conversely, only 8% of patients were under treated. These studies highlight the importance of commencing bronchodilators as initial pharmacological therapy for patients with symptomatic COPD, before considering adding inhaled steroids in patients who have both moderate to severe airflow limitation (FEV_1 <50% predicted) and frequent exacerbations (two or more in the past year) (current PBS criteria).

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, but its role is controversial.

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 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=4528) (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, 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 Cox 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 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 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.

O4.3 Biologic therapies

Recent 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, but it is not known whether targeting interleukin-5 to reduce eosinophil activity can also affect clinical outcomes in COPD. A phase 2a trial of benralizumab, a humanized monoclonal antibody to interleukin-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). Pavord and colleagues have compared the interleukin-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 vs. 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.

The results of the current trials indicate that an eosinophilic subgroup of patients with COPD may benefit from biologic therapies, although it is noted that, although patients with current asthma were excluded, those with a past history of asthma or atopy were not. Further prospective studies are awaited.

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 to 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 to 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. 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].

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. These data support the recommendation to minimise the number of different devices prescribed in COPD patients.

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.

Lung Foundation Australia's Stepwise Management of Stable COPD available at https://lungfoundation.com.au/wp-content/uploads/2018/09/Information-paper-Stepwise-Management-of-Stable-COPD-Aug2017.pdf has images of asthma and COPD medicines on page 2. These are linked directly to the video and factsheets page on the Lung Foundation website via the Zappar app. The app allows the user to scan the images on either the hard copy or on-screen using their mobile device and the videos will automatically open on their device.

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].

Pragmatic pharmacist care programs may improve inhaler technique and refill adherence in patients with COPD (Tommelein 2014) [evidence level II].

O5.2 Inhaler adherence

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).

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 to 1.00) and cardiovascular disease (CVD) mortality (HR 0.48, 95% CI 0.26 to 0.88). Individuals who met the physical activity guidelines demonstrated the greatest reductions in all-cause (HR 0.56, 95% CI 0.45 to 0.69), CVD (HR 0.48, 95% CI 0.32 to 0.71) and respiratory mortality risk (HR 0.40, 95% CI 0.24 to 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 HRQoL, peripheral muscle function and exercise capacity, and, following rehabilitation, participants gain an enhanced sense of control over their condition (Bolton 2013, Coventry 2007, McCarthy 2015, Ries 2007, Alison 2017) [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 vs. 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 vs. 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, but there is also evidence of benefit from rehabilitation provided to in-patients, and in community and home settings where programs involve regular contact to facilitate exercise participation and exercise progression (McCarthy 2015, Ries 2007, Spruit 2013, Alison 2017). 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.

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**).

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. A 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 subanalysis 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).

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]. This finding is important because providing programs in community and home-based settings may overcome some of the barriers to program uptake and completion.

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 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 meta-analysis of data from 5 studies comparing supervised maintenance pulmonary rehabilitation programs with usual care showed a significant reduction in the risk of experiencing at least one respiratory-related hospital admission (risk ratio 0.62, 95% CI 0.47 to 0.81) (Jenkins 2018) although these findings were heavily influenced by one study (Guell 2017). Some form of regular exercise should be encouraged following completion of a pulmonary rehabilitation program to sustain the benefits gained (Alison 2017).

A list of pulmonary rehabilitation programs known to Lung Foundation Australia can be accessed at https://pulmonaryrehab.com.au/national-program-map/. 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 HRQoL, emotional function and the individuals' self-control over their condition following exercise training alone (McCarthy 2015, Ries 2007, Spruit 2013, Alison 2017) [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].

The recommendations for exercise training for people with COPD are based on the recommendations 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). 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.

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.

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 HRQoL in patients with COPD (Geddes 2008, Gosselink 2011) [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 (Beaumont 2018, Schultz 2018) [evidence level II]. 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 one 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 DLCO, expiratory muscle strength, exercise capacity (6MWD and VO2 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). 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 COPD patients 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 and health-related quality of life. 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 (Effing 2007) concluded that self-management education is associated with a significant reduction in the probability of at least one hospital admission when compared with usual care , which translates into a one-year Number Needed to Treat ranging from 10 (6 to 35) for individuals with a 51% risk of exacerbation to a Number Needed to Treat of 24 (16 to 80) for patients with a 13% risk of exacerbation. This review also showed a small but significant reduction in dyspnoea measured using the Borg 0-10 dyspnoea scale. However, the magnitude of this difference (weighted mean difference -0.53, 95% CI -0.96 to -0.10) is unlikely to be clinically significant. No significant effects were found in the number of exacerbations, emergency room visits, lung function, exercise capacity and days lost from work. Inconclusive results were observed in doctor and nurse visits, symptoms (other than dyspnoea), the use of courses of corticosteroids and antibiotics and the use of rescue medication. 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). The differences may be related to differences in the study populations, study context and extent of self-management support provided.

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, contact the Asthma Foundation (phone +64 4 499 4592; Internet address, http://www.asthmanz.co.nz).

People with COPD are vulnerable to developing symptoms of anxiety and depression, which then worsen quality of life and disability (Xu 2008, Eisner 2010b). Pulmonary rehabilitation has been associated with short-term reductions in anxious and depressive symptoms (Coventry 2007, Coventry 2013, Yohannes 2017). Additional intervention by mental health specialists will be required for clinically significant symptoms of anxiety or depression (Yohannes 2017).

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. 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.

The findings of this review do not support the widespread application of breathing exercises in the management of people with COPD. However, breathing exercises may have a role to improve exercise tolerance in selected individuals with COPD who are unable to undertake exercise training.

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.

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 [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.

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 vs. 37.9 ml, p<0.007) and 24 (mean 58.4 ml vs. -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 vs. -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 2016), 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 (6MWD) in all patients. Importantly, the increase in 6MWT 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 2016) 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 2016).

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). Vitamin D supplementation has been used in a small number of COPD trials. In an RCT using high-dose vitamin D (100,000 IU per month) administered over 1 year to 186 COPD patients, there was no improvement in exacerbation frequency, lung function, quality of life or mortality rate compared to placebo (Lehouck 2012) [evidence level II]. However, in the same trial, this vitamin D regimen resulted in a reduction in exacerbations in participants with severe vitamin D deficiency at baseline (Lehouck 2012) [evidence level III] and in an improvement in inspiratory muscle strength and oxidative metabolism compared to the placebo group, in patients undergoing pulmonary rehabilitation (Hornikx 2012) [evidence level III]. A prespecified subgroup analysis in a multi-centre study of COPD patients demonstrated that those participants (148 participants of a total of 240 COPD patients recruited from London clinics) who had baseline serum 25-hydroxyvitamin D levels below 50nmol/L had a 43% reduction in moderate and severe exacerbations when taking 3mg of vitamin D orally every 2 months, over a 12 month period (Martineau 2015) [evidence level III]. Vitamin D deficiency should be considered with a view to supplementary replacement in COPD patients.

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. bBody 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 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 dypsnoea 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 and alternative therapies

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

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 6MWT by -3.58 points (95% CI -4.27 to -2.90) on the Borg 0-10 dyspnoea scale and improved 6MWD by 46metres 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.

O7. Comorbidities

Cormorbid 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 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% vs. 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).

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 2.02-3.00, p<0.0001). This result was mainly driven by angina (OR 8.16) (Chen 2015) [evidence level III-2]. In addition, Feary's study 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].

CVD is an important cause of mortality and hospital presentations in COPD, even affecting those with mild disease. In addition to the high individual prevalences 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 1.25-3.69, 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. 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 on 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 beta-agonist and antimuscarinic bronchodilators and methylxanthines. More recently, 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, there are no proven adverse effects on safety. Despite being common clinical practice, there is less evidence about the safety of high dose, combined bronchodilator therapy in the setting of an 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) [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 0.95-6.0) and 3.2 (95% CI 1.3-8.1) in the intermediate and highest tertiles, respectively. The same authors reported that high sensitivity troponin T levels in stable COPD are associated with increased mortality risk in a prospective cohort study. Compared to the group with troponin T levels <5ng/L, adjusted HR were 1.7 (0.8-3.9) and 2.9 (1.2-7.2), for the groups with troponin T levels 5.1-13.9 ng/L and ≥ 14 ng/L, respectively (Neukamm 2016) [evidence level III-2].

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 PR 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's group (Abusaid 2009) [evidence level III-2] proposed a contributory role for diastolic dysfunction (DD) in an exacerbation of COPD. Their retrospective single centre cohort study reported that DD 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 (CAE) associated with an exacerbation of COPD. Using self-controlled case series methodology, they identified 25,857 COPD patients and their CAEs (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 CAE 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), 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 1.14 (1.07 - 1.21), and development of heart failure 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 substudy 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.

Barr and colleagues investigated a subgroup from the Multi-ethnic Study of Atherosclerosis (MESA): a multi-centre, prospective, cross-sectional study of cardiovascular disease (CVD). The group initially reported a linear relationship between extent of emphysema and impairment of LV 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 left ventricular ejection fraction. 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, increase in respiratory symptoms or change in 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. COPD symptoms are more pronounced during exertion and hence a recent study (Mainguy 2012) [evidence level II] has investigated dynamic lung function in GOLD stage II-III COPD patients during cardioselective beta-blocker treatment. This randomised, double blinded, placebo-controlled cross over trial compared inspiratory capacity (IC) at peak isotime exercise during endurance exercise testing as a measure of dynamic hyperinflation for treatment arms with bisoprolol (titrated to 10 mg) and titrated placebo. Included patients had no recognised indication for beta-blocker treatment and were randomised to treatment sequence. As expected, IC reduced with exercise; this effect was more pronounced in the bisoprolol arm -0.50 versus -0.41 ($p<0.01$). Exercise duration was non-significantly reduced in the bisoprolol arm, and the change was strongly correlated with the change in IC. However, the absolute difference was modest and of arguable clinical significance and so the group recommended that cardioselective beta-blockers not be withheld on this basis. Beta-blockers have duration-dependent effects, including effects on beta-receptor regulation, which are important in their efficacy for heart failure and may also be relevant in the airways. The 14 day beta-blocker treatment duration in this study was likely insufficient to fully demonstrate these effects. Despite a paucity of evidence to suggest harm, beta-blockers are still under-utilised in COPD for guideline-based indications such as systolic heart failure (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].

A number of observational studies also lend confidence to beta-blocker prescribing in COPD patients. Du et al's meta-analysis (Du 2016) of 15 observational cohort studies with follow up ranging from one to 7.2 years suggested that beta-blocker treatment was associated with reduced mortality risk (RR 0.72, 95% CI 0.63-0.83) and exacerbation risk (RR 0.63, 95% CI 0.57-0.71). Although there was significant heterogeneity amongst the included studies, sensitivity analysis to account for this did not change the outcome [evidence level III-2]. Beta-blocker treatment did not diminish the beneficial effects of inhaled treatments on post bronchodilator FEV_1 or COPD exacerbations. Prospective randomised controlled data is still needed (Dransfield 2018).

Acknowledging that, beyond improving survival, treatments used in COPD patients must not impair QOL. van Gestel's 2009 study (van Gestel 2009) [evidence level III-2] sought reasons for suboptimal beta-blocker prescription in terms of QOL. The surviving 469 COPD patients of their vascular surgery cohort were subsequently assessed via health-related QOL questionnaire (SF-36) at median follow up of 6.4 (2.9 to 9.3) years. A 70% response rate was achieved. Although 71% of patients were receiving beta-blockers at follow up, compared to 59% at baseline, neither beta-blocker treatment at baseline, nor at follow up, impacted significantly on QOL scores.

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

Interest in a potential disease-modifying role for HMG CoA reductase inhibitors (statins) in COPD is based upon established survival benefit in cardiovascular disease (CVD) as effective lipid-lowering drugs in combination with anti-inflammatory and antioxidant effects. Systematic reviews and meta-analysis have suggested beneficial effects of statin treatment in COPD (Dobler 2009, Janda 2009, Horita 2014). Horita's group performed meta-analysis for mortality outcomes in 10 cohort studies and reported a protective effect: HR 0.81 (0.75 – 0.86). Sensitivity analyses using subgroups and alternative modelling remained statistically significant, although the included studies were heterogeneous and publication bias was likely.

A prospective multicentre RCT explored the role of long-term simvastatin treatment (40mg/day) in exacerbation prevention in moderately severe COPD patients, who did not have any conventional indication for statin treatment (Criner 2014) [evidence level II]. The study was stopped prematurely, prior to attaining recruitment targets, due to futility. Whilst simvastatin treatment resulted in the expected improvements in dyslipidaemia, two consecutive interim analyses showed no beneficial effect on exacerbation rates or time to exacerbation in the study population as a whole, or in any subgroup.

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 cardiovascular disease (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 by Graat-Verboom (Graat-Verboom 2009) described an overall mean prevalence of osteoporosis of 35.1% (range 9-69%) with increasing odds ratios for osteoporosis associated with FEV_1, lower BMI and lower fat-free mass index. Patients with vertebral compression fractures, visualised on a lateral chest x-ray, had more frequent admissions, longer length of hospital stay, and increased mortality in the two years after admission (Pascual-Guardia 2017) [evidence level III-2].

Although, there is little evidence of a deleterious effect of inhaled corticosteroid at conventional doses (<2, 200 mcg/day) on fracture risk, triamcinolone was associated with reduced BMD in the Lung Health Study (Lung Health Study Research Group 2000) [evidence level II]. In a large study by Ferguson et al (Ferguson 2009) comparing the effects of salmeterol, fluticasone 1000 micrograms daily, the combination, or placebo, there was no increase in decline in bone mineral density over three years in active arms compared with placebo in the subgroup of patients whose bone density was measured [evidence level II]. Australian Guidelines on the prevention and treatment of osteoporosis, including corticosteroid-induced osteoporosis have been published (Sambrook 2002). Information on the current subsidies relevant to these drugs can be found at http://www.osteoporosis.org.au/treatment-options or on the website of the Pharmaceutical Benefits Scheme (www.pbs.gov.au) Higher doses of inhaled corticosteroids are associated with suppressed biochemical markers of remodelling but data on BMD and fractures at these doses are not available (Jones 2002) [evidence level I].

Despite the lack of evidence, management strategies in individuals taking long term corticosteroid therapy should include investigation of fracture risk including bone densitometry, assessment of vitamin D status, and other risk factors such as coexisting illnesses that may influence the skeleton (e.g. primary hyperparathyroidism). In individuals with low BMD at onset and in those taking more than 10-15mg of prednisolone per day or who have several risk factors for osteoporosis and whose BMD is <1.5 standard deviations below the young adult mean, treatment should be considered.

Evidence for fracture risk reduction is available for alendronate, risedronate, etidronate and parathyroid hormone. There is no evidence that calcitriol reduces fracture risk and some evidence to the contrary, so that the use of this drug is not recommended (Homik 2000). However, most patients in these studies did not have respiratory disease. Although calcium supplementation has not been demonstrated to reduce the risk of fracture in osteoporosis, a reduction in remodelling rate with some possible benefit in slowing bone loss is possible so calcium supplements are appropriate. Any deficiency of vitamin D should be corrected with supplements.

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 frail persons 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 deficit 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. 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).

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 (Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018b), 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 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 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 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 with hip fractures to emergency departments (Johal 2009). A large cohort study demonstrated a higher risk of hip fractures in patients with COPD in comparison to a matched non-COPD sample (hazard ratio 1.78; p<0.001). Moreover, patients who used inhaled bronchodilators and corticosteroids (n=10,362) had an even higher falls risk (HR 2.04, 95% CI 1.72 to 2.41, p<0.001) in comparison to those not using inhalers (n= 5,877, HR 1.63, 95% CI 1.40 to 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 to 6.66, p<0.005) (Yohannes 2016). Prospective studies have demonstrated a falls incidence rate in COPD of 1.17 to 1.20 falls/person-year, which is a considerably higher rate compared to that previously reported in healthy older adults (0.24 falls/person-year) (Oliveira 2015, Roig 2011).

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, polipharmacy (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). 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 fall 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 highlight the need for specific preventive interventions in this patient population. The importance of balance training has been increasingly recognised in COPD as an important falls 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 wakenings 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 apnoeas, 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 fiberoptic 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) (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 COPDGene 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 DLCO <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 followup, 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 to 1.9%), 3.6% (95% CI 3.6 to 3.7%) and 4.9% (4.9% to 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 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).

O7.12 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 work load achieved in patients with COPD (not necessarily with testosterone deficiency) maximal oxygen uptake and health related quality of life 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.

O7.13 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.

O7.14 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 COPD patients 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 indication 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 D_LCO 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 dihydropyrodine 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, 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 lead to an 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., dihydropyrodine 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

Lung volume reduction surgery (LVRS) involves resection of the most severely affected areas of emphysematous, non-bullous lung (Cooper 1995). This can improve lung elastic recoil and diaphragmatic function (Geddes 2000). The National Emphysema Treatment Trial 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 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 to 11.7 than for control, but long-term mortality favoured LVRS (OR 0.76, 95% CI 0.61 to 0.95) level 1. 96% of the patients contributing to the long term mortality data is from patients enrolled in the NETT study. The authors made note of high post-operative complications, especially persistent air leak and pneumonia.

A variety of nonsurgical techniques are currently under investigation. These include endobronchial one-way valves, self-activating coils, targeted destruction of emphysematous tissue, bypass tract airway stenting and transpleural ventilation.

Several randomised controlled trials examining endobronchial valves have been reported (Sciurba 2010, Herth 2012, Davey 2015, Klooster 2015, Wood 2014, Valipour 2016, Kemp 2017, Criner 2018). The Kemp and Criner trials are multicentre. The Kemp trial is the first multicentre trial. All trials recruited highly selected COPD patients with severe obstruction and gas trapping and excluded patients with significant hypercapnia ($PaCO_2$ > 50mmHg) and poor mobility (6MWD < 100m). Patients in the trials by Sciurba, Herth, Davey and Criner underwent pulmonary rehabilitation prior to randomisation. Only the Davey and Wood trials used a sham placebo bronchoscopy. Klooster, Valipour, Kemp and Criner excluded patients without intact interlobar fissures on CT chest and with collateral ventilation detected at bronchoscopy by the Chartis system. Valipour specifically recruited patients with homogeneous rather than upper lobe predominant emphysema.

All but the Wood trial reported improvements in FEV_1. Data on improvement in exercise outcomes was generally positive (Herth, Davey, Klooster, Valipour,,Kemp and Criner). Data on adverse events was significant. The Sciurba and Wood trials reported high hospital admissions for COPD exacerbations, Klooster reported an 18% pneumothorax rate, Valipour reported a 26% pneumothorax rate and Kemp reported that 29% of patients experienced a pneumothorax and that one patient died as a consequence. Criner reported a 27% pneumothorax rate and a 3% 45 day mortality rate (Criner 2018). By 12 months, 22% of patients in the Klooster trial required permanent valve removal (Klooster 2017).

The Klooster, Valipour, Kemp and Criner trials were the most thorough in excluding patients with collateral ventilation using both the intact lobar fissure on CT chest and the Chartis system during bronchoscopy. This may explain why these trials had the most impressive results with regards to lung function, quality of life and exercise improvements. The trials where the control arm used sham placebo bronchoscopy reported no difference between the study arms with respect to improvement in quality of life. Valves cannot yet be recommended as routine therapy and patients need to be informed of the short term mortality and complication rates. Davey recognises the high complication rates and appropriately calls for future trials to compare valve placement with surgical lung volume reduction (Davey 2015).

A small (n=45) non blinded randomised controlled trial comparing lung volume reduction coils to standard care showed significant improvement in quality of life, lung function and 6-minute walk distance at 90 days (Shah 2013). Of the 23 patients receiving the intervention, two sustained a pneumothorax. 22 patients from the control arm went on to receive endobronchial coils, with significant improvement in quality of life, 6-minute walk distance (and to a lesser degree lung function) at day 180 and 360 (Zoumot 2015). Deslee has reported on the largest randomised controlled trial (non-blinded) to date (Deslee 2014). 100 highly selected patients were randomised to usual care or bilateral coil placement. All patients had under gone pulmonary rehabilitation. The pre-specified primary end point of percentage of patients achieving a 54m improvement in 6-minute walk distance at 6 months was met (36% vs. 18% p=0.03). However, at 12 month follow up there was no significant difference in mean improvement in 6-minute walk distance. There were sustained improvements in spirometry and quality of life at 12 months. Pneumonia rates were far higher in the coil group (18% vs. 4% p=0.03) but pneumothorax rates were similar between the two groups. Cost effectiveness analysis found the treatment to be prohibitively expensive (12 month incremental cost effectiveness ratio was approximately $1,000,000 per QALY).

van Agteren performed a meta-analysis of endobronchial lung volume reduction surgery (van Agteren 2017) [evidence level I]. Results from 14 trials comprising almost 2,000 participants were analysed. The authors concluded that evidence for short-term (up to one year) improvements in disease status were most evident for studies testing endobronchial valves (five studies) and coils (three studies), including improvements in lung function and quality of life. The authors note a significant increase in adverse events. The odds ratio for an adverse event reported for trials examining endobronchial valves was 5.85 (95% CI 2.16-15.84) and the overall odds ratio for an adverse event amongst all endobronchial lung volume reduction techniques was 3.00 (95% CI 2.04-4.43). Pneumothorax rates of over 20% were reported in several endobronchial valve trials. It is important to note the authors' concerns regarding the lack of sham bronchoscopy and/or unclear status of blinding in some studies that may cause a risk of bias.

Herth et al (Herth 2016) performed an open label, multi centre, randomised controlled trial of staged, single lobe segmental steam thermal ablation on 70 patients with severe COPD and hyperinflation. All patients had undergone pulmonary rehabilitation and had a 6-minute walk distance over 140m. Patients with incomplete fissures and collateral ventilation were not excluded. At six months, there was a significant improvement in lung function and quality of life but not 6-minute walk distance. 24% of patients undergoing steam thermal ablation experienced a COPD exacerbation compared with 4% of controls. This procedure is not available in Australasia and its precise role is not yet clear, but as further long term data emerge this may be an option for patients with severe COPD and hyperinflation with collateral ventilation.

A non-blinded randomised controlled trial comparing endobronchial lung volume reduction using Emphysematous Lung Sealant (ELS) was terminated early due to loss of funding prior to the 12 month pre-specified endpoints (Come 2015). Limited data at 6 months showed significant improvements in spirometry, 6MWD, QoL and dyspnoea. However the complication rate was unacceptably high with increased hospitalisations (44% vs. 17%) and serious adverse events with two deaths in the intervention arm and no deaths in the control arm [evidence level II].

In summary, 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). This 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 http://anzcotr.org.au/v3custom/2017/anzcotr_2017.pdf 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 COPD patients having longer hospital and ICU stays than cancer patients. 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).

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). An integrated service model improved increased survival in patients with advanced lung disease (including COPD).

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.

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

There are no specific medications licensed for the treatment of breathlessness. 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).

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.

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.

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 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 Inspiratory muscle training Self-management education Breathing exercises e.g. pursed lip breathing, diaphragmatic breathing, timed breathing techniques * Use of walking aids Neuromuscular electrical muscle stimulation Chest wall vibration 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

***** May improve exercise tolerance as opposed to actual breathlessness

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 to 14.7) and for those who stopped during the period of follow-up 8.5 ml/year (95% CI 5.6 to 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 (on both SGRQ and CAT scores) and increased risk of severe exacerbations (OR 1.51, 95% CI 1.04 to 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]

A comprehensive review of smoking cessation in patients with respiratory diseases has been published by the European Respiratory Society (http://erj.ersjournals.com/content/erj/29/2/390.full.pdf) (Tonnesen 2007). A successful tobacco control strategy involves integration of public policy, information dissemination programs and health education through the media and schools. See the National Tobacco Strategy 2012-2018 (Commonwealth of Australia 2012). Smoking prevention and cessation programs should be implemented and be made readily available (World Health Organization 1999). Pharmacotherapies double the success of quit attempts (Cahill 2013). Behavioural techniques further increase the quit rate (Eisenberg 2008, Hartmann-Boyce 2014, Stead 2013b, Civljak 2013, Stead 2013a, Whittaker 2012, Cahill 2010, Stead 2005, Lancaster 2017) [evidence level I].

People who continue to smoke despite having pulmonary disease are highly nicotine dependent and may require treatment with pharmacological agents to help them quit (US Public Health Service 2000, Peters 2002). 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).

Smoking cessation has been shown to be effective in both sexes, in all racial and ethnic groups tested and in pregnant women (U.S. Department of Health and Human Services 1990). 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].

Brief counselling is effective (Lancaster 2017) [evidence level I] and every smoker should be offered at least this intervention at every visit (Fiore 2008). Comprehensive treatment of tobacco dependence involves providing both behavioural support and pharmacotherapy (Zwar 2014). 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 behavior 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 I]. Currently accepted best practice is summarised in the 5-A strategy: (Zwar 2014).

- **A**sk and identify smokers. Document smoking status in the medical record.
- **A**ssess the degree of nicotine dependence and motivation or readiness to quit
- **A**dvise smokers about the risks of smoking and benefits of quitting and discuss options
- **A**ssist cessation — this may include specific advice about pharmacological interventions or referral to a formal cessation program such as the Quitline
- **A**rrange follow-up to reinforce messages.

Cessation of smoking is a process rather than a single event, and smokers move between various stages of being *not ready (pre-contemplation), unsure (contemplation), ready (preparation), quitting (action)* and *possibly relapsing (maintenance)* before achieving long-term success. People at all stages can be offered assistance but advice tailored on the basis of the patient's readiness to quit (Zwar 2004). Brief interventions for smoking cessation involve opportunistic advice, encouragement and referral. Referral options are the Quitline (13 7848) and an accredited tobacco treatment specialist (aascp.org.au). Cessation rates increase with the amount of support and intervention, including practical counselling and social support arranged outside of treatment.

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/).

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.

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 2008) [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, inhaler, inhalator, lozenge, mouth spray and oral strip). 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. Up to date 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]. Health professionals should encourage smokers to use combined NRT if they are unable to quit using one NRT product alone, or experience cravings using only one form of NRT. Combination NRT can also be recommended as first line treatment.

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 to 4.27, NNT = 8, 95% CI 6 to 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 to 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).

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 to 7.87). Cytisine is not currently registered for use in Australia or New Zealand.

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 to 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 to 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 to 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 to 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 to 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. Before these products can be recommended for consumers, further research must be conducted on their safety and efficacy for smoking cessation. E-cigarettes can relieve cravings and symptoms of nicotine withdrawal as well as simulating the behavioural and sensory aspects of smoking. A small number of randomised controlled trials have suggested that e-cigarettes could have a role in cessation and harm reduction. A study in New Zealand found they had similar effects on six month cessation rates to nicotine patch among smokers wanting to quit (7.3% for e-cigarettes compared to 5.8% for patch) and rates were higher than for the participants randomised to non-nicotine containing e-cigarettes (3.6%). With such a large variety of e-cigarette products on the market and little data on their nicotine delivery, it is not known if their results can be generalised and further research is needed before recommendations for their use can be confidently made (Bullen 2013, Caponnetto 2013). Concerns about e-cigarettes include a lack of 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 third of the participants allocated to e-cigarettes in a clinical trial reported continued product use at 6 months, suggesting that they might have become long-term e-cigarette users (Bullen 2013). There are also concerns that e-cigarettes may potentially act as a gateway to smoking (Pepper 2014).

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.

Refer to the following web links for further information: http://www.firsnet.org/news-and-actions/30-firs-position-statement-on-e-cigarettes-launched-in-new-york-in-association-with-the-un-meeting-on-noncommunicable-diseases

Therapeutic Goods Administration provides information: https://www.tga.gov.au/community-qa/electronic-cigarettes

Lung Foundation Australia has a position statement about electronic cigarettes: https://lungfoundation.com.au/wp-content/uploads/2018/09/Information-paper-Inquiry-into-the-use-of-ecigarettes-and-personal-vaporisers-in-Australia-Mar2018.pdf

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).

Ex-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 2018) [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: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home.

P2.2 Pneumococcal immunisation

Pneumococcal immunisation is recommended for all patients with COPD. Pneumococcal immunisation with conjugated vaccines covering 13 virulent serotypes is highly effective in preventing vaccine-type invasive bacteraemic and non-bacteraemic community-acquired pneumococcal pneumonia in older adults (Bonten 2015). In contrast, the pneumococcal polysaccharide vaccine (covering 23 virulent serotypes) 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. Expert opinion is divided about whether to continue to advise use of the 23-valent polysaccharide vaccine or to replace its use with the far more effective conjugate vaccine. At present, the 23-valent polysaccharide vaccine is reimbursed for adults aged 65 years and over and recommended in the current context. Please see the link to The Australian Immunisation Handbook on the NHMRC's website for further details: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home.

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% vs. 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

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. Antibiotics

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 to 18) (Herath 2013). A 12 month randomised controlled trial of erythromycin 250mg bd in patients with moderate COPD found a significantly reduced risk of exacerbation with a rate ratio of 0.65 (95% CI 0.49-0.86) (Seemungal 2008) [evidence level II].

A 12 month randomised controlled trial of azithromycin 250 mg daily vs. placebo was undertaken in patients with COPD who were using supplemental oxygen, or had received a course of systemic corticosteroids for respiratory problems in the past year, or had visited an Emergency Department for a COPD exacerbation within the past year, or had been hospitalised for a COPD exacerbation within the past year (Albert 2011). The study found that azithromycin significantly increased the median time to the first exacerbation, reduced exacerbation rates, and improved quality of life in some patients [evidence level II]. However, hearing loss was more common in a small proportion of patients, and more macrolide-resistant organisms were seen. Patients had been excluded from the study if they had resting tachycardia, prolonged corrected QT interval or use of medications that could prolong this, or hearing impairment. It was not clear from the study to what extent participants had other treatment for their COPD maximised. Azithromycin 500mg, three times per week, over 12 months, was associated with an almost halving of exacerbations (RR 0.58, 95% CI 0.42-0.79) in severe COPD patients, with CT chest being performed to exclude bronchiectasis. Patients had at least three admissions in the preceding 12 months. While on azithromycin, 1 in 5 experienced diarrhoea. Macrolide resistance assessment was limited by small numbers of sputum samples, and no oral flora assessment, but with an unexplained greater resistance in the placebo group rather than the azithromycin group. No audiometry was included in the study (Uzun 2014) [evidence level II].

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.

Given the potential significant adverse effects of such regimens (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 antibiotic 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 to 0.83) and related hospitalisations (OR 0.64, 95% CI 0.51 to 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 to 22) to prevent one exacerbation and 30 (95% CI 22 to 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 to 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 Rratio 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 (odds ratio 0.86; 95% CI 0.79 to 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 to 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 2015 Cochrane Review (Poole 2015) included 34 trials involving 6,233 participants with COPD OR chronic bronchitis. The authors found treatment with mucolytics was associated with an increased likelihood of being exacerbation free during the period of study (OR 1.75, 95% CI 1.57 to 1.94) and calculated the number needed to treat with mucolytics for an additional beneficial outcome for an average of 10 months as eight (NNTB 8, 95% CI 7 to 10). Mucolytic use resulted in a reduction of 0.03 exacerbations per participant per month (mean difference (MD) -0.03, 95% CI -0.04 to -0.03) compared with placebo, that is, approximately one exacerbation every three years. These results however should be interpreted with care due to the very high heterogeneity (I^2 = 85%) and the smaller effect in more recent trials. The authors concluded that the use of mucolytics in patients with chronic bronchitis or COPD may produce a small reduction in exacerbations and small improvements in quality of life.

A double blind randomised controlled trial of erdosteine found that erdosteine reduced exacerbations by 19.4% (0.9 vs. 1.13 exacerbations /patient /year, p=0.01) largely due to an effect on mild events (Dal Negro 2017). Erdosteine also reduced exacerbation duration by 24.6% (9.55 vs. 12.63 days, p=0.023) and decreased use of reliever (p <0.001); however it did not affect quality of life or time to first exacerbation. In a subsequent meta-analysis of 10 RCTs involving 1,278 patients, that included the Dal Negro trial, 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 2018). 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).

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. No cost evaluation data were provided in this study.

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. 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 (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, -1.7) .

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 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).

P9. Regular review

Regular review, with objective measures of function and medication review, is recommended in the hope that this may reduce complications and the frequency or the severity (or both) of exacerbations and admissions to hospital. Please see comments in section D. A prospective trial in the primary care setting (Abramson 2010) randomised patients who had been prescribed inhaled medication to a) three monthly review and spirometry, b) usual care and spirometry before and after trial and c) usual care. This study did not show any significant improvement in quality of life or other health outcomes. Possible explanations for the negative results include limited power, few events and inclusion of doctor diagnosed obstructive lung disease as opposed to spirometry defined patients. Spirometry remains the gold standard for establishing the diagnosis of COPD.

P10. Oxygen therapy

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

Long term oxygen therapy 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. 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).

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 quality 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 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, O'Driscoll 2008) [evidence level I].

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. However, in patients who desaturate during exercise training, supplemental oxygen may be used with the aim of delaying the onset of dynamic hyperinflation and the associated dyspnoea (O'Donnell 1997, O'Donnell 2001), which in turn may permit patients to exercise at higher intensities and thus gain greater benefit from training (Emtner 2003). However, a systematic review of the small number of suitable studies reported to date does not allow firm conclusions regarding the use of supplemental oxygen during exercise training (Nonoyama 2007) [evidence level I].

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: Patients with hypoxaemia during sleep may require 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 is indicated for patients whose nocturnal arterial oxygen saturation repeatedly falls below 88%. Sleep apnoea should be excluded.

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

For patients with COPD who also have sleep apnoea or hypoventilation, ventilatory support with continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) may be more appropriate than oxygen therapy (for more details see Section X.3.2). A 2013 Cochrane meta-analysis comparing nocturnal NIV to standard care alone in patients with stable COPD and hypercapnia found no benefit. There was no significant change to gas exchange, exercise tolerance, quality of life, lung function, respiratory muscle strength or sleep efficiency (Struik 2013). The authors concluded that there is insufficient evidence to support widespread NIV use in stable COPD [evidence level I]. This meta-analysis included data from an Australian trial of hypoxaemic COPD patients with hypercapnia (n=144) randomised to long term oxygen therapy alone or with NIV. McEvoy et al found a small mortality benefit in the NIV group, at the expense of worse quality of life (McEvoy 2009) [evidence level II]. Mean pressures used were inspiratory positive airways pressure (IPAP) 13 cmH_2O, EPAP 5 cmH_2O. No significant reduction in $PaCO_2$ was observed.

In 2014 two further randomised controlled trials of long term NIV in patients with COPD were published. A major difference from the McEvoy trial is the significantly higher inspiratory positive pressures used. Kohnlein et al (Kohnlein 2014) randomised 195 patients with clinically stable, severe COPD and hypercapnia to NIV or usual care. Both groups were admitted to hospital every 3 months for 1 year for 'treatment optimisation'. NIV was titrated to target a reduction in $PaCO_2$ by 20% or achieve $PaCO_2$ of less than 48mmHg. There was a significant reduction in 1-year mortality. 12% mortality in the intervention group and 33% in the control group was reported; hazard ratio 0·24 (95% CI 0·11–

0·49; p=0·0004) [evidence level II]. Mean pressures used were IPAP 22cmH_2O, EPAP 5cmH_2O. Mean reduction in $PaCO_2$ was 7mmHg. In direct contrast to this finding, Struik et al 2014 found no mortality or exacerbation rate difference in a 12 month randomised controlled trial (n =201) of NIV and usual care in patients with severe COPD who had been admitted to hospital with an exacerbation of COPD and hypercapnia (Struik 2014). Mean pressures used were IPAP 19cmH_2O, EPAP 5cmH_2O. Mean reduction in $PaCO_2$ was 3.8mmHg.

In 2017, Murphy et al reported on a trial of long term NIV in patients who remained hypercapnic and hypoxic two to four weeks after resolution of respiratory acidosis due to an exacerbation of COPD (Murphy 2017). Murphy excluded patients with a BMI >35 kg/m_2 and patients with obstructive sleep apnoea. 116 patients were randomised to continuous home oxygen or continuous home oxygen plus home NIV. It should be noted that over 2,000 patients were screened for inclusion. Similar to Kohnlein, high NIV pressures were used with a median IPAP pressure of 24cmH_2O and a median EPAP pressure of 4cmH_2O. Median NIV adherence at 12 months was high at 7.6hrs. The 12-month risk of readmission or death was 63.4% in the home oxygen plus home NIV group vs. 80.4% in the home oxygen alone group, absolute risk reduction of 17.0% (95% CI 0.1-34%). There was no mortality difference at 12 months.

Comparison between the trials above is difficult as they used different treatment algorithms and NIV pressure settings. Furthermore, inclusion criteria and patient characteristics also differed significantly. For example, McEvoy et al performed a baseline diagnostic sleep study and excluded patients with OSA. A baseline PSG was not performed in the other trials. It is also unclear if the results from the Kohnlein trial are generalisable to an Australasian patient population given that all participants were electively admitted three monthly. The authors of a meta-analysis of 21 RCTs of domiciliary NIV trials concluded that domiciliary NIV does not reduce mortality in patients with stable COPD or in patients post admission for an exacerbation of COPD (Dretzke 2016). The trial by Murphy et al was not included in this meta-analysis. The authors noted significant differences in patient populations and trial designs.

With such significant heterogeneity of results, patient characteristics and methodology, it remains unclear if long term NIV should be universally recommended for patients with severe stable COPD and hypercapnia. The trial by Murphy et al demonstrates that in highly selected patients who remain hypercapnic and hypoxic several weeks after an episode of acute hypercapnic respiratory failure, home NIV delivered at very high pressures significantly reduces hospital re-admissions. Referral for specialist opinion at an institution with expertise in this area should be sought.

P12 Alpha1-antitrypsin deficiency

In a cohort of PiZZ and PiSZ individuals identified by the Swedish national neonatal alpha-1 antitrypsin (AAT) screening program in 1972–1974 and followed up regularly since birth, 4% of the PiZZ, 2% of the PiSZ and 12% of the control group were current smokers (P=0.008), and 17% of the PiZZ, 9% of the PiSZ and 21% of the control group had stopped smoking (Piitulainen 2017). PiZZ current smokers may have symptoms of COPD at the age of 37–40 years, whereas the never-smoking PiZZ and PiSZ individuals have normal lung function. In a single centre UK cohort of 482 untreated individuals with PiZZ, rates of annual decline of FEV_1 and gas transfer were highly variable at all stages of COPD severity, ranging from no decline to rapid decline in both never smokers and former smokers (Stockley 2016).

Tanash and colleagues compared mortality rates in 1,585 Swedish individuals with severe AAT deficiency with the 6,000 individuals randomly selected from the Swedish general population (Tanash 2017). The authors reported that individuals with AAT deficiency had lower survival rates compared with controls; however, the survival rate of never-smoking individuals with severe AAT deficiency identified by screening (rather than identified after presenting with respiratory symptoms) is similar to the never-smokers in the Swedish general population. This highlights the importance of smoking prevention in individuals with AAT deficiency.

A systematic review of three randomised controlled trials studying a total of 283 patients, concluded that there was a lack of evidence of clinical benefit from AAT augmentation therapy (Gøtzsche 2016) [evidence level I]. AAT augmentation therapy is not routinely available in Australia.

In the RAPID RCT, which contributed the majority of patients to the above systematic review, intravenous augmentation therapy was studied in 177 adults with COPD and severe AAT deficiency (serum level <11μM), FEV_1 35 to 70% predicted and no smoking in the prior six months (Chapman 2015). Intravenous AAT 60 mg/kg from pooled human plasma was given weekly in the intervention group, vs. matched placebo in the control group, for 24 months. Open label augmentation was then offered for a further 24 months. 10% of the intervention group withdrew prematurely, compared to 21% of the control group. The annual rate of lung density loss, measured by CT chest at total lung capacity (TLC), was statistically significantly less in the patients receiving AAT augmentation (mean –1.45 g/L per year, SE 0.23), compared to the placebo group (–2.19 g/L per year, SE 0.25), with a difference of 0.74 g/L per year (95% CI 0.06–1.42). There were no changes in annual rate of lung density loss when measured at a combination of TLC and FRC, or at FRC alone. There were no statistically significant differences in mortality, exacerbations, FEV_1 or adverse effects. Post-hoc exploratory analysis showed a reduced rate of lung density loss with higher trough serum AAT levels achieved. Benefits in patient-orientated outcomes were not demonstrated, although this study was not powered to show this.

A two year, open label extension trial of 140 patients who had participated in the previous trial (Chapman 2015) showed that the decrease in rate of lung density loss was maintained in patients who continued this dose of active AAT augmentation therapy, and was achieved by patients who started therapy during the extension trial (McElvaney 2017).

It is noted that the optimal dosing regimen has not yet been determined, but that in the trials described above patients underwent weekly intravenous infusions. The evidence to date demonstrates that AAT augmentation modifies the development of emphysema. It is unclear if AAT therapy improves clinical outcomes. Studies of cost-effectiveness have not yet been conducted.

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 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].

People with chronic conditions are often cared for by partners or family members. Significant psychological and physical consequences occur in carers of patients with chronic diseases. In populations where the patient's chronic disease is non-respiratory, there is evidence (Jones 1992) that the psychological health status of carers and patients is linked. One of the most effective means of improving the patient's functional and psychological state is pulmonary rehabilitation.

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 vs. 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). Although these domains are not specifically addressed in the following sections, they are directly relevant to each.

Disease management approaches in COPD include a number of the Chronic Care Model domains. A systematic review by Peytremann-Bridevaux (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, 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 Respiratory Questionnaire. There were also positive effects on exercise tolerance, hospital admissions and hospital days per person [evidence level I].

In a similar approach, a 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 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.

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, 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.

However, it is important to note that not all studies of disease management programs have shown benefit. Kruis et al (Kruis 2014) conducted a cluster RCT in 40 general practices in the Netherlands (1086 patients with COPD by GOLD criteria) of a multifaceted disease management intervention comprising multidisciplinary team of caregivers trained in motivational interviewing, setting up individual care plans, exacerbation management, implementing clinical guidelines and redesigning the care process. The intervention was compared to usual care. There was no difference in HRQoL. The differences in findings between studies may be related to variation in implementation of interventions. One of the differences between studies was the extent of emphasis on and uptake of physical activity/exercise training interventions.

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).

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: Most people visit a GP about once a year. 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").

D1.2 Other specialist physicians

COPD is an important co-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.

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 to 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 vs. 8.86±10.24 days, p≤0.001), greater improvement in mean Modified Medical Research Council Dyspnoea Scale (-0.1±0.6 vs. 0.2±0.6, p=0.003) and St George's Respiratory Questionnaire score (-6.9±15.3 vs. -0.1±13.8, p=0.003) compared with the UG (Ko 2017).

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). The prevalence of panic attacks and panic disorder in COPD are particularly high (Yellowlees 1987, Pollack 1996, Kunik 2005, Laurin 2007). 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 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 fiberoptic 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.

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 (see https://lungfoundation.com.au/wp-content/uploads/2018/09/Information-paper-COPD-Action-Plan-Mar2016.pdf for examples). 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. Self-management

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

A distinction can be made between 'self-management' and 'self-management support'. 'Self-management' is a normal part of daily living and involves the actions individuals take for themselves and their families to stay healthy and to care for minor, acute and long-term conditions. 'Self-management support' is the facility that healthcare and social-care services provide to enable individuals to take better care of themselves. The onus is on delivering training for self-management skills to individuals through a range of interventions (Osborne 2008).

A number of systematic reviews have been undertaken to evaluate the effect of self-management in COPD (See **Figure 5** for abbreviated table and **Appendix 6** for full table). Whilst these have consistently resulted in 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, Zwerink 2016).

A Cochrane review found self-management interventions 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. Earlier reviews have found reductions in both respiratory-related, ED and all-cause hospitalisations (Jonkman 2016b) as well as improved dyspnoea (Zwerink 2014), a reduction in urgent health care utilisation and improved exercise capacity measured by the 6MWD (Cannon 2016). However, reviews have also reported no differences in 6MWD, anxiety and depression, hospital admissions and mortality (Majothi 2015, Zwerink 2014, Cannon 2016, Jolly 2016, Jonkman 2016b). These systematic reviews should be interpreted with caution due to the methodological weaknesses of the studies and heterogeneity of the interventions and outcome measures.

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 (Jonkman 2016a) demonstrated that intervention duration, regardless of composition, displayed the strongest associated with reduction in all cause hospitalisations in COPD patients. Newham et al. identified that interventions targeting mental health were the most effective in improving HRQoL and reducing ED visits (Newham (2017).

In 2018, Aboumatar et al reported a RCT that recruited patients admitted to hospital with an acute exacerbation of COPD, or patients who had a previous diagnosis of COPD who were hospitalised and were receiving treatment for an increase in COPD symptoms (Aboumatar 2018). 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 exacerbations 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 fewer exacerbations at 6 months compared to usual care (difference, 0.68 (95% CI 0.22 to 1.15); P=0.004) and improvement in health status (difference −6.97 (95% CI −14.05 to 0.12); P=0.05).

COPD self-management programs overwhelmingly lead to improved health-related quality of life, with reduced exacerbations being a positive outcome of many studies. However, due to the heterogeneity of the study designs, setting and outcomes, we are unable to make recommendations regarding the essential elements of a COPD self-management program.

Written 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/wp-content/uploads/2018/09/Information-paper-COPD-Action-Plan-Mar2016.pdf. The Action Plan should be completed by the clinician and patient together and guides the patient in recognising when their symptoms change and what action they should take.

A systematic review by Howcroft et al. reported that supported use of COPD exacerbation action plans with a single short educational component reduced ED visits and hospital admissions (Howcroft 2016). The number needed to treat to reduce one hospital admission was 19. Studies that included an exercise program and longer education sessions were not included in this review. A subsequent RCT not included in this review confirmed a reduction in ED visits in patients who utilised an action plan (Zwerink 2016).

Figure 5: 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	6MWD	Respiratory-related mortality	Medication use	Urgent healthcare
Dickens et al., 2014	RCT	32 studies, database inception-2013	3941											☺
Zwerink et al., 2014	RCT, CCT	29 studies, 1995-2014	3688	☺	☺	☺	😐			☺	😐			
Majothi et al., 2015	RCT	9 studies, Moderate-severe COPD, database inception-2012	1466	☺	😐		😐	😐						
Cannon et al., 2016	RCT	25 studies, 1990-2016	4082	☺	😐				😐		☺			
Howcroft et al. 2016	RCT, quasi RCT	7 studies, Database inception -2015	1550	☺			😐	☺	😐				☺	
Jolly et al., 2016	RCT	173 studies, database inception-2012	n/a	☺	😐									
Jonkman et al., 2016	RCT	14 studies, 1985-2013	3282	☺	☺	☺	😐							
Lenferink et al., 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= randomised 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 Exacerbations and crises

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

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. 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.

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/wp-content/uploads/2018/09/Information-paper-COPD-Action-Plan-Mar2016.pdf.

A randomised controlled trial of 577 subjects with mild COPD, obtained from UK primary care COPD registers of 71 general practices evaluated a telephone health coaching programme which included the provision of a pedometer, written educational documents, diary, inhaler use education and encouragement of medication adherence (Jolly 2018). Most potential subjects did not respond to an invitation to participate. While there was no benefit on the primary outcome of quality of life as measured by the St George Respiratory Questionnaire, nor the secondary outcomes of anxiety and depression, other secondary outcomes of self-reported physical activity and inhaler usage did improve [evidence level II].

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 to 1.44). Furthermore, no differences were seen in health related quality of life, 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.

In contrast to the above studies, Segrelles et al., demonstrated that telehealth monitoring with daily tele-transmission of indices from home, including self-recorded oxygen saturation and peak expiratory flow rate (PEFR), by patients with severe LTOT dependent COPD, with monitoring for pre-determined 'red flag' deteriorations in indices by nurses, was associated with an approximate halving of emergency room visits, admissions, and hospital bed days (Segrelles Calvo 2014) [evidence level II]. Similarly, in a prospective randomised controlled study from Taiwan where 106 patients were randomised to usual care (including telephone calls) or telemedicine which involved accessing a website to record a range of daily variables with clinician access and intervention depending upon certain "flags", time to readmission was significantly greater in the telemedicine group (p=0.026) (Ho 2016).

A 12 month program of home-based telerehabilitation included both an exercise program at home (three times weekly) following a two month hospital-based pulmonary rehabilitation program as well as self management education, regular review by a team of health professionals via phone or Skype weekly, self monitoring of lung function and access to a helpline. This program was compared with a hospital-based pulmonary rehabilitation program twice weekly and to usual care. The control group had no initial pulmonary rehabilitation and both groups received sustained intensive pulmonary rehabilitation. Both home-based telerehabilitation and centre-based pulmonary rehabilitation reduced exacerbations and hospitalisations compared with usual care (mean$\pm$SD for exacerbations 1.7$\pm$1.7 vs. 1.8$\pm$1.4 vs. 3.5$\pm$1.8 respectively, $p<0.001$; hospitalisations 0.3$\pm$0.7 vs. 0.3$\pm$0.6 vs. 1.2$\pm$1.7 respectively, $p<0.001$). The home-based telerehabilitation group also had a lower rate of ED attendances in the 12 months of follow-up than the hospital-based group and usual care group

(0.5±0.9 vs. 1.8±1.5 vs 3.5±1.8 respectively, p<0.001). The home-based program was intensive and the results impressive, however a cost analysis was not included in the study (Vasilopoulou 2017). In an Australian study of telerehabilitation comparing 8 weeks of group exercise training thrice weekly with up to four remote participants, 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].

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 a randomised controlled trial, 470 COPD patients 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].

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).

D5. Treat anxiety and depression

Anxious and depressive symptoms and disorders are common comorbidities in people with COPD (Yellowlees 1987, Kunik 2005, Ng 2007, Xu 2008, Eisner 2010b) and have a range of negative impacts [evidence level I]

Anxiety symptoms in COPD are associated with worse quality of life (Giardino 2010, Blakemore 2014), self-management (Dowson 2004) and exercise performance (Eisner 2010b), and with increased medical symptom reporting (Katon 2007), exacerbations (Laurin 2012), hospitalisations (Yellowlees 1987, Gudmundsson 2005, Livermore 2010), length of hospitalisations (Xu 2008), medical costs (Katon 2007, Livermore 2010), and mortality (Celli 2008). 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 promising evidence from a number of small randomised controlled trials that cognitive behaviour therapy can treat anxiety symptoms in COPD (de Godoy 2003, Hynninen 2010, Livermore 2010, Yohannes 2017), prevent the development of panic attacks, panic disorders (Livermore 2010) and reduce ratings of dyspnoea (Livermore 2015, Yohannes 2017). The health service burden associated with anxiety in COPD is well established. A nurse-delivered minimalist version of Cognitive Behaviour Therapy facilitated by the use of laminated cards and delivered in 1-2 home visits of 20-60 minute duration, provided clinically and statistically significant improvements in the Hospital Anxiety Depression Scale (HADS) and also the CRQ Mastery scale, in the intervention arm (n=22) compared to the control arm (n=22), when followed up at 3 months (Bove 2016). In a trial of 28 patients undergoing pulmonary rehabilitation with a three month follow up, cognitive behaviour therapy showed a short term improvement in fatigue, stress and depression and anxiety scores, thus demonstrating a non-pharmacological intervention with important positive outcomes, although the follow up of 3 months is short and unknown if the benefits are sustained (Luk 2017).

A record linkage study in Canada found that elderly COPD patients prescribed benzodiazepines 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).

This retrospective cohort study of 80,088 U.S. Medicare recipients demonstrated 34% higher 30 day readmission rate in COPD patients who had depression, and 43% higher with anxiety (Singh 2016b). These and other co-existing psychological disorders were associated with being less likely to have follow up appointments, and more 30 day readmissions (23.8% vs. 16.25%). Although this study design has the potential for confounding by severity of disease, it is noteworthy that these relationships with readmissions were much higher than index admission ICU length of stay, or need for the use of mechanical ventilation, which supports the case that depression and anxiety are important independent predictors of readmission.

SSRIs (such as sertraline) have been recommended as better first line pharmacological therapies for anxiety in COPD. Psychiatrists can advise on the most appropriate medications for particular patients (Shanmugam 2007). 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 2014, Alexopoulos 2016).

People with COPD are not only at high risk of depressive symptoms and mood disorders but are at higher risk than people with other chronic conditions (Ng 2007, Omachi 2009). When depressive symptoms are comorbid with COPD they are associated with worse health related quality of life (Ng 2007, Omachi 2009, Hanania 2011, Blakemore 2014) and difficulty with smoking cessation(Ng 2007), and with increased exacerbations (Laurin 2012), hospitalisations (Bula 2001, Xu 2008, Hanania 2011, Iyer 2016), length of hospitalisations (Ng 2007), medical costs (Bula 2001), and mortality (Bula 2001, Ng 2007). Depression may also influence decisions about end of life issues (Stapleton 2005). As is the case for anxiety symptoms in COPD, there is evidence from small, randomised controlled trials that depressive symptoms can be decreased by cognitive behaviour therapy (de Godoy 2003, Hynninen 2010). Mindfulness-based cognitive therapy in conjunction to pulmonary rehabilitation also improved depressive symptoms compared to pulmonary rehabilitation alone (Farver-Vestergaard 2018).

Evidence for the effectiveness of particular antidepressant medications for mood disorders in COPD is still limited, with a few small, randomised controlled trials conducted (Argyropoulou 1993, Lacasse 2004, Eiser 2005, He 2016). Treatment with antidepressants can be complicated by poor tolerance of side effects such as sedation, which may cause respiratory depression (Evans 1997). As with anxiety symptoms, psychiatrists can advise on which pharmacological treatments may be most appropriate for patients.

However, the existing evidence still 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 utilised in numerous studies of people with COPD (Gudmundsson 2005, Ng 2007, Xu 2008, Livermore 2010, Eisner 2010b, Bock 2017). Another screening option is the Patient Health Questionnaire (PHQ), which screens for symptoms of the most commonly 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, contact the Asthma and Respiratory Foundation of New Zealand (phone +64 4 499 4592; Internet address, http://www.asthmanz.co.nz).

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 0–9.6) 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 IL-15 and 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 vs. 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).

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). Other causes include left ventricular failure and pulmonary embolus. 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.

A systematic review comprising of seven trials with a total of 880 patients who were hospitalised with an exacerbation of COPD and underwent a CT pulmonary angiogram found that 16% had a pulmonary embolism (Aleva 2017). There was large variation in the prevalence of pulmonary embolism between studies; 3% to 29%. Only one third of patients had small isolated sub segmental pulmonary embolism. Based on the high prevalence of pulmonary embolism, this diagnosis should be considered in patients presenting with an exacerbation of COPD when signs of an infection are absent and chest pain and cardiac failure are present.

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 to 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/wp-content/uploads/2018/09/Information-paper-COPD-Action-Plan-Mar2016.pdf). 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 hospitalization (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 hospitalisations.

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."	**36% improvement** (OR 0.64, 95% CI 0.51 to 0.82 NNT 30, 95% CI 22 to 61)	P5.1 *Barr 2005*
	"… tiotropium was more **effective in preventing COPD exacerbations leading to hospitalisation** [compared to a range of other LABAs]"	**14% improvement** (OR 0.86, 95% CI 0.79 to 0.93)	P5.2 *Chong 2012*
Aclidinium	"…Aclidinium resulted in marginal improvements in quality of life and FEV1, 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 2014a*
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 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

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 …"	**45% improvement** (HR 0.55, 95% CI 0.35 to 0.88)	X3.8 *Casas 2006*
	"Adherence to inhaled medications regimes is associated with **reduced risk of death and admissions to hospital** due to exacerbations in COPD..."	**44% improvement** (RR 0.56, 95% CI 0.48 to 0.65)	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 8 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 to 0.99) [evidence level I]. There was no significant difference in mortality (risk ratio = 0.65, 95% CI 0.40 to 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).

Arterial blood gases: Arterial blood gas levels should be measured if the FEV_1 is less than 1.0 L or less than 40% predicted, or if percutaneous oxygen saturation is less than 90% in the presence of adequate peripheral perfusion or cor pulmonale. 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 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 yrs) 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% vs. 5.8%, p<0.001). Severity of dypsnoea 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 to 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). 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). High doses of beta-agonists may induce hypokalaemia and predispose to cardiac arrhythmias.

A small (n=30) single centre pilot randomised controlled trial performed in New Zealand (Mukerji 2015) 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 to 27.7, 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 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 to 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.

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.

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

Exacerbations with clinical features of infection (increased volume and change in colour of sputum and/or fever) benefit from antibiotic therapy [evidence level II, 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].

A 2012 Cochrane systematic review (Vollenweider 2012) found a reduction in treatment failure in patients with severe exacerbations who were treated with antibiotics (RR 0.77; 95% CI 0.65 to 0.91; I2 = 47%). Treatment failure was defined as lack of improvement in symptoms, deterioration, need for further antibiotics or death due to exacerbation. A reduction in mortality (data from one trial only) and a reduced length of stay was only seen in patients admitted to ICU. Patients treated with antibiotics experienced higher rates of diarrhoea (OR 2.62; 95% CI 1.11 to 6.17). No significant benefit for treatment failure in outpatients was found when analysis was restricted to currently available antibiotics (RR 0.80; 95% CI 0.63 to 1.01; I^2 = 33%). 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].

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 to 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 2016a).

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 2014) recommend the use of oral agents such as amoxycillin or doxycycline.

If patients do not respond to the above antibiotics, or if resistant organisms are suspected, amoxycillin–clavulanate could be prescribed. If pneumonia, Pseudomonas or staphylococci are suspected, appropriate antibiotics should be used.

Typically, a course of treatment should be at least five days. A response is usually seen within three to five days, and a change of antibiotic should be considered if the response is unsatisfactory. An historical population-based cohort study (Roede 2008) [evidence level III-2] 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).

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 to 3.2, NNT = 7, 95% CI 4 to 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.

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]. Nonetheless, a recent retrospective study of patients with exacerbations of COPD admitted to a New South Wales hospital between 2011 and 2013 found that oxygen concentrations of greater than 28% were still delivered to the majority of patients, both in the ambulance and the emergency department (Susanto 2015). Similarly, 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 to 88.3%) (Chow 2016). 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 $paCO_2$ 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 $PaCO_2$ 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 to 0.76); NNT 12 and decreases the risk of needing endotracheal intubation by 65% (RR 0.36, 95% CI 0.28 to 0.46; NNT 5) (Osadnik 2017). This benefit is similar for patients with mild acidosis (pH 7.30 to 7.35) vs. 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). The optimal location for provision of NIV should be determined by local experience and availability of expertise.

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 to 0.79), reduced ventilator-assisted pneumonia (RR 0.29, 95% CI 0.19 to 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 to 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. Jennings 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].

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 (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. The 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 health-related quality of life and exercise capacity in the short-term (median of five months for health-related quality of life and a median of three months for exercise capacity). Pulmonary rehabilitation

also reduced hospital readmissions (pooled odds ratio 0.44, 95% CI 0.21 to 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 to 1.67).

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), large benefits for health-related quality of life and exercise capacity were found. In contrast, no statistically significant reduction in hospital readmissions was found (odds ratio 0.30, 95% CI 0.07–1.29, n=187 participants), most likely due to the small sample. 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) (Puhan 2016).

Information about pulmonary rehabilitation including a list of programs known to Lung Foundation Australia can be accessed at https://lungfoundation.com.au/patients-carers/get-support/lung-disease-and-exercise/pulmonary-rehabilitation/. 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**). 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.

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 to 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 is 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 2016) 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 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.

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	200mcg	4-6-hourly	MDI/spacer
	Terbutaline	500mcg	6-8-hourly	DPI
	Salmeterol	50mcg	12-hourly	MDI/DPI
	Formoterol	12mcg	12-hourly	MDI/DPI
	Antimuscarinic (Anticholinergic)			
	Ipratropium	40-80mcg	6-8-hourly	MDI/spacer
	Tiotropium	18mcg	24-hourly	DPI
	Corticosteroid			Inhaled
	Beclometasone (small particle)	400-800mcg/day		MDI/spacer
	Budesonide	800-1600mcg/day		DPI
	Fluticasone	500-1000mcg/day		MDI/DPI
	Ciclesonide	80-320mcg/day		MDI – spacer not recommended

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 cheap, 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 accurate and 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)	• Breath-activated solution for inhalation. The cartridge is inserted and primed before first use of the Respimat. To deliver the inhalation, the clear based 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.
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 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.
- Extrasoft 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)(Cazzola 2015b)

Health Status measures

PROM	Purpose	Domains	No. items	Reliability	Validity	MCID
SGRQ	Assess health status impairment in airways disease(COPD, Asthma, Bronchiectasis)	Symptoms, activity, impacts	50	✔	✔	4 units
SGRQ-C	Assess health status in COPD – weakest items removed	Symptoms, activity, impacts	40	✔	✔	4 units
CRQ (short form also available)	HR QOL 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
CAT	Quantifies symptom burden of COPD, health status measurement	Energy, Sleep, confidence, activities, breathlessness, chest tightness, phlegm, cough	8	✔	✔	2 units

Symptom measures

PROM	Purpose	Domains	No. items	Reliability	Validity	MCID
MMRC	Disability from COPD related to breathlessness	Uni-dimensional	1 - 5 point scale	✔	✔	~ 1, but limited data
Baseline and Transitional Dyspnea Indices BDI-TDI	Measurement of dyspnea based on ADLs	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

Exacerbations

Patient Reported Outcome Measure (PROM)	Purpose	Domains	No. items	Reliability	Validity	MCID
EXACT-PRO	Evaluates frequency, severity and duration of an AE COPD (Daily)	Breathlessness, cough and sputum, chest symptoms	14	✔	✔	Not yet established
EXACT - 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(breathless-ness) 1 point Δ(cough & sp) 1 point Δ(chest symptoms)

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
Dickens et al., 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 et al., 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 et al., 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 et al., 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 et al. 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 et al., 2016	RCT	173 studies, database inception-	n/a	To identify the most effective components of interventions to	Include 3+ components e.g. structured group-based PR programs (to teach self-management skills); educational self-management interventions delivered in an	☺	😐		

		2012		facilitate self-management of health care behaviours	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 et al., 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 et al., 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.

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Glossary of Terms

6MWD	6-Minute Walk Distance
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
EPC	Extended Primary Care
ERV	Expiratory Reserve Volume
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
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
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
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
TLC	Total Lung Capacity
WMD	Weighted Mean Difference

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