

BEST-PRACTICE EVIDENCE BASED MEDICINE FOR THE EFFECTIVE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Signed.....

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Date 17/07/2019

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“I get by with a little help from my friends.” - The Beatles

Abbreviations

95% CI	95% confidence interval
A1	Author one
A2	Author two
ACTRN	Australian New Zealand Clinical Trials Registry number
ACTs	Airway clearance techniques
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AR	Augmented reality
BCW	Behavioural change wheel
CALHN	Central Adelaide Local Health Network
COM-B	Capability, opportunity, motivation and behaviour
COPD	Chronic Obstructive Pulmonary Disease
COPD-X	The Australian and New Zealand guidelines for the management of COPD
CPG	Clinical practice guideline
DALYs	Disability adjusted life years
DOI	Digital Object Identifier
e.g.	Exempli gratia (for example)
EMR	Electronic medical record
FEV ₁	Forced expiratory volume in one second
GMP	General Medicine Physician
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
HIV	Human immunodeficiency virus

HR	Hazard ratio
HREC	Human research ethics committee
i.e.	Id est (in other words)
ICS	Inhaled corticosteroids
IF	Impact Factor
IM	Intervention mapping
LABA	Long acting β 2-against
LAMA	Long acting muscarinic agent
LFA	Lung Foundation Australia
MD	Mean difference
mg	Milligrams
ml	Millilitre
N/A	Not Applicable
n=	Number =
NHMRC	National Health and Medical Research Council
NICE	The National Institute for Health Care and Excellence
NIV	Non-invasive ventilation
NNT	Number needed to treat
NRT	Nicotine replacement therapy
NS	Not significant
OR	Odds ratio
P	Probability value
pg	Page
QoL	Quality of life

RCT	Randomised controlled trial
RMO	Registered Medical Officer
RR	Risk ratio
SABD	Short acting bronchodilator
SD	Standard deviation
TDF	Theoretical domains framework
TMO	Trainee Medical Officer
UK	United Kingdom
USA	United States of America
USD	United States Dollar
ZK	Zoe Kopsaftis
β2-agonist	Beta two agonist

Peer-reviewed journal publications

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1. **Kopsaftis ZA**, Royals K, Carson-Chahhoud KV. Barriers and facilitators to best practice care for people with chronic obstructive pulmonary disease: A qualitative study. Qualitative Health Research (IF 2.181; Submitted March 2019)

In Press (n= 2)

2. **Kopsaftis Z**, Carson-Chahhoud KV, Austin MA, Wood-Baker R, Smith BJ. Oxygen therapy in the pre-hospital setting for acute exacerbation of chronic obstructive pulmonary disease. Cochrane Database of Systematic Review (IF 6.754; Expected Publication March 2019)
3. Carson-Chahhoud KV, **Kopsaftis ZA**, Sharrad K, Esterman AJ. Evidence for smoking Quitlines. An evidence check rapid review brokered by the Sax Institute (IF N/A – policy document; Expected March 2019) (Appendix 1)

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4. **Kopsaftis Z**, Sulaiman NS, Mountain OD, Carson-Chahhoud KV, Phillips PA, Smith BJ. Short-acting bronchodilators for the management of acute exacerbations of chronic obstructive pulmonary disease in the hospital setting: Systematic review; BMC Systematic Reviews; 2018; 7:213 (p1-13) (IF 1.574)
5. **Kopsaftis Z**, Wood-Baker R, Poole P. Influenza vaccine for chronic obstructive pulmonary disease (COPD). Cochrane Database of Systematic Reviews; 2018, Issue 6 (p1-76); DOI: 10.1002/14651858.CD002733.pub3 (IF 6.754)

6. **Kopsaftis Z**, Carson KV, Van Agteren J, Smith BJ 'Cessation of smokers seeking treatment and advice from health care professionals in the hospital setting'; Australian and New Zealand School of Government funded a policy document to be published in the public policy journal *Evidence Base Mar 2018; Volume 2018; Issue 1; Pages 1-35 DOI 10.21307/eb-2018-001* (IF N/A – policy document)
7. **Kopsaftis Z**, Carson KV. Inhaled anticholinergics for chronic obstructive pulmonary disease in the elderly. *Gerontology and Geriatric Research* 2015; 4(6): e1000259 (IF N/A)

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1. **Kopsaftis ZA**, Royals KS, Smith BJ, Carson-Chahhoud KV. Exploring health professional experiences and perspectives of best practice care for people with chronic obstructive pulmonary disease. Accepted as poster discussion at the Thoracic Society of Australia and New Zealand conference, Gold Coast, Australia for the 2019 Annual Scientific Meeting
2. **Kopsaftis ZA**, Royals KS, Smith BJ, Carson-Chahhoud KV. A theory-based intervention for improved uptake and adherence to chronic obstructive pulmonary disease guidelines in the hospital setting: An intervention mapping approach. Accepted as oral presentation at the Thoracic Society of Australia and New Zealand conference, Gold Coast, Australia for the 2019 Annual Scientific Meeting

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3. **Kopsaftis Z**, Carson KV, Austin MA, Wood-Baker R, Smith BJ. Oxygen therapy in the pre-hospital setting for acute exacerbations of COPD: A Cochrane systematic review. Thoracic Society of Australia and New Zealand, Perth, March-April 2016 (***Award winning presentation – Best Oral Presentation in the Evidence Based Medicine Special Interest Group***)
4. **Kopsaftis Z**. Clinical practice guidelines in the digital health/ eHealth era. Virtually Healthy Colloquium, Adelaide, South Australia, September 2015
5. **Kopsaftis Z**, Sulaiman N, Carson K, Phillips P, Smith B. Short-acting bronchodilators for in-hospital management of acute exacerbations of COPD: Systematic Review. Basil Hetzel Institute Research Day, Adelaide, South Australia October 2015 (***Award winning presentation – Best Oral Presentation by a Junior Clinical Researcher***)

Poster conference presentations:

6. **Kopsaftis Z**, Sulaiman N, Carson K, Oliver M, Phillips P, Smith B. Short-acting bronchodilators for in-hospital management of acute exacerbations of COPD: Systematic Review. European Respiratory Journal 2018 52:PA774; DOI: 10.1183/13993003.congress-2018.PA774; 2018 European Respiratory Society Annual Congress, Paris, France
7. **Kopsaftis Z**, van Agteren J, Carson K, O'Loughlin T, Smith B. Smoking cessation in the hospital setting: a systematic review and meta-analysis. European Respiratory Journal 2017 50: PA1271; DOI: 10.1183/1393003.congress-2017.PA1421; 2017 European Respiratory Society Annual Congress, Milan, Italy

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8. Invited guest speaker, West Lakes Ladies Probus Club, July 2016

Co-authored conference abstract presentations:

9. Royals K, **Kopsaftis ZA**, Carson KV. Guideline use and best practice in COPD: A nursing perspective. Submitted to the Thoracic Society of Australia and New Zealand conference, Gold Coast, Australia for the 2019 Annual Scientific Meeting
10. Sulaiman NS, **Kopsaftis Z**, Carson KV, Phillips P, Smith BJ. The effectiveness of short-acting bronchodilators for the management of acute exacerbation of chronic obstructive pulmonary disease in the inpatient or hospital setting: A systematic review. Thoracic Society of Australia and New Zealand, Perth, March-April 2016
11. Truong B, Van Agteren J, **Kopsaftis Z**, Carson KV, Smith B. Risk factors for asthma hospitalisation: A systematic review. Australasian Asthma Conference, Adelaide, October 2017 (***Award winning presentation: Asthma Australia Excellence Award***)

12. King CM, Carson KV, Van Agteren J, **Kopsaftis ZA**, Smith BJ. A qualitative study using innovative technology via a smartphone application to provide demonstrative inhaler technique education for asthma patients. Thoracic Society of Australia and New Zealand, Canberra, March 2017

Awards

- 2017 Co-author on an abstract selected as recipient of the Asthma Australia Excellence Awards for the Australasian Asthma Conference Annual Scientific Meeting held in Adelaide, Australia for the oral presentation titled:

“Risk factors for asthma hospitalisation: A systematic review”

- 2016 Recipient of the Evidence Based Medicine Special Interest Group Best Oral Presentation for the Thoracic Society of Australia and New Zealand Annual Scientific Meeting held in Perth, Australia for the oral presentation titled:

“Oxygen therapy in the pre-hospital setting for acute exacerbations of COPD: A Cochrane systematic review”

- 2015 Recipient of the Best Oral Presentation by a Junior Clinical Researcher Award for the Basil Hetzel Institute Research Day held in Adelaide, Australia for the presentation titled:

“The effectiveness of short-acting bronchodilators for the management of acute exacerbation of chronic obstructive pulmonary disease in the inpatient or hospital setting: A systematic review.”

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- 2018 Carson-Chahhoud KV, Esterman AJ, **Kopsaftis ZA (CIC)**. Rapid review of evidence commissioned by the Sax Institute "Evidence for smoking Quitlines"; October 2018 – April 2019; **\$25,000.00**
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- 2016 **Kopsaftis ZA (CIA)**, Carson-Chahhoud KV, van Agteren J, Smith BJ. Policy document preparation commissioned by the Australian and New Zealand School of Government “Smoking cessation policies for hospitalised smokers”; 2016-2017; **\$10,000.00**
- 2016 **Kopsaftis Z**, Carson KV, Austin MA, Wood-Baker R, Smith BJ. Best Oral Presentation in the Evidence Based Medicine Special Interest Group “Oxygen therapy in the pre-hospital setting for acute exacerbations of COPD: A Cochrane systematic review”; **\$500**
- 2015 **Kopsaftis Z**, Sulaiman N, Carson K, Phillips P, Smith B. Best Oral Presentation by a Junior Clinical Researcher “Short-acting bronchodilators for in-hospital management of acute exacerbations of COPD: Systematic Review”; **\$1,000**
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Summary

Chronic obstructive pulmonary disease (COPD) is a highly prevalent condition characterised by progressive airflow limitation through the lungs. It is a significant socioeconomic burden and appropriate management of COPD has become a health priority, resulting in a breadth of innovation and published research. There are international guidelines that collate this evidence in order to steer clinical decision making. Guideline concordant care results in a reduced rate of COPD exacerbations, improving hospital utilisation and patient related outcomes. Despite this, uptake and adherence to guidelines remains variable in practice and interventions that address this are desirable. The research undertaken in this thesis aims to synthesise and consolidate evidence to inform best-practice management of COPD across key treatment areas. It further aims to identify barriers and facilitators to provision of best-practice care for people with COPD.

Synthesis and consolidation of key areas of the evidence base relating to COPD management occurred through two Cochrane reviews (Chapters 3 and 4), two systematic reviews (Chapters 5 and 6) and one literature review (Chapter 7). Though in general the evidence base underpinning these key areas of practice was found to be limited and somewhat out-dated some recommendations can be made from the findings. Inactivated vaccine reduces the number of COPD exacerbations and should be considered as part of everyday best-practice. The use of oxygen therapy for the pre-hospital management of acute exacerbations of COPD (AECOPD) is potentially dangerous when delivered at high flow, with a titrated approach associated with significantly reduced mortality. Routine use of short acting bronchodilators in the hospital setting to treat AECOPD should be initiated at a low dose (2.5mg) of salbutamol delivered via metered-dose inhaler to avoid increased risk of adverse events. Smoking cessation is essential to COPD management and available evidence suggests that interventions should be tailored to the individual and the setting within the hospital space. Finally, clinicians should seriously consider their decision-making around prescription of pharmacotherapy for exacerbations of COPD, particularly the potentially superfluous addition of muscarinic agents.

Through qualitative investigation (Chapter 8), several organisational and behavioural barriers to the provision of best-practice care for COPD by health

professionals were identified. In addition, potential facilitators were highlighted that may be used to inform future innovation strategy to improve translation of evidence into practice, including the use of smartphone technology.

The evidence produced in this thesis suggests a need for updated research specifically supporting the in-hospital management of people with an exacerbation of COPD. Furthermore, the findings presented in this thesis have provided an evidence base that has acted as the foundation for the next phase of research essential to improve provision of clinical care for people with COPD. The work has underpinned the development of a theory-based multi-component intervention (Appendices 2 and 3) and some of the clinical practice recommendations within it. Moreover, next steps are planned to assess the feasibility and evaluation of this intervention, with the view to conducting a full-scale evaluation in the future with a view to better support translation of evidence into practice.

Chapter 1. Introduction

Evolution from the first descriptions of “voluminous lungs” by a Swiss physician Théophile Bonet in 1679 [1] to what we know today as chronic obstructive pulmonary disease (COPD) has taken more than three centuries [2]. A British physician, Charles Badham, first identified chronic bronchitis as a disabling health condition associated with this lung condition in 1814 [1]. Seven years later in 1821, physician René Laënnec linked emphysema as yet another component of this same condition, with environmental factors as the principle cause, as tobacco smoking was not common place during this era [1]. However, it was not until 1959 that medical professionals attending the Ciba Guest Symposium defined the components that make up the COPD diagnosis as we know it today [1]. Despite our growing knowledge of COPD over this period, global efforts to prevent and manage this chronic, debilitating and costly condition remain an ongoing priority [3].

1.1 COPD

In 2012 38 million deaths worldwide were attributed to non-communicable diseases, of these almost 11% were the result of chronic respiratory illnesses such as COPD [4]. COPD is a preventable chronic condition, affecting approximately 10% of the global population and is indicated by progressive limitation of airflow through the lungs [5, 6]. This airflow reduction is only partially reversible and is primarily attributed to inflammation in response to inhalation of noxious particles and gases [6]. This chronic inflammatory response prompts both a narrowing of the small airways and emphysematous change [7].

The airflow limitation caused by narrowing of the small airways may be partially reversible. In response to an irritant the airways constrict further, pathological change progressively occurs including increased mucous production and plugging, as well as bronchial fibrosis [6, 8]. While some of this pathology may be improved using various management strategies, the destructive nature of the emphysematous change associated with COPD is irreversible [6, 7]. This change is characterised by destruction of the alveolar sacs, resulting in loss of elasticity and enlargement of the airspaces, ultimately leading to a reduction in surface area available for gas exchange, as well as gas trapping following hyperinflation [8, 9].

COPD phenotypes have been classified, providing a foundation for further research and more importantly, potential for individually tailored treatment [10, 11]. Established phenotypes of COPD are chronic bronchitis with or without emphysema and asthma [10]. The individuals with asthmatic-COPD are of particular interest as exacerbation frequency is increased in this group [12, 13]. It should be noted however, that during classification of these sub-groups of COPD there were a group of people with COPD who did not fit a defined phenotype [10, 11]. This is illustrative of the heterogeneity of COPD as a disease and the challenges facing health professionals in terms of diagnosis, classification and management.

Several risk factors have been identified for COPD, the most important of which is cigarette smoking [14, 15]. The association between cigarette smoke inhalation and decreasing forced expiratory flow in one second (FEV₁) has been long established. In their landmark study Fletcher and Peto [14] presented the results of an eight-year cohort study highlighting that lung function declines steadily with age; importantly, the study determined that smokers experienced a more rapid deterioration in FEV₁ (Figure 1). Though there were some limitations identified with this study, namely that the study consisted of males aged between 30 to 59 years only, the results have been widely accepted by the medical profession to apply more broadly. Furthermore, the link between cigarette smoking and COPD has been confirmed in subsequent investigations over the years in both men and women, across a wider age range, demonstrating increasing risk with increasing number of pack years (packs smoked per day multiplied by years of smoking) [5, 15, 16].

Exposure to noxious particles via means other than cigarette smoking, e.g. occupational exposure to dust, vapours, gas and fumes, is also a known risk factor, contributing to up to 31% of COPD [5, 17-19]. This has been noted in both men and women, regardless of smoking status, working in a range of professions including coal mining, textiles and farming [20-26]. In addition, COPD-related mortality risk increases by 2.5% with every year of exposure to diesel fumes [27]. Though not a great risk in the developed world, domestic exposure to noxious particles, such as biomass fuel generated through indoor cooking, also contribute to the burden of COPD [6, 28, 29]. The global risk is, therefore, substantial given that approximately three billion people use biomass and coal as their primary

energy source [30-32]. Furthermore, while conclusive data relating to the causative effects of air pollution on COPD are limited, the association between existing outdoor pollutants and progressions and exacerbations of existing COPD is well documented [31, 32]. Other identified risk factors for COPD include genetic predisposition (namely α_1 antitrypsin deficiency) recurrent respiratory infections, lower socioeconomic status, poorer nutrition and other comorbidities [6].

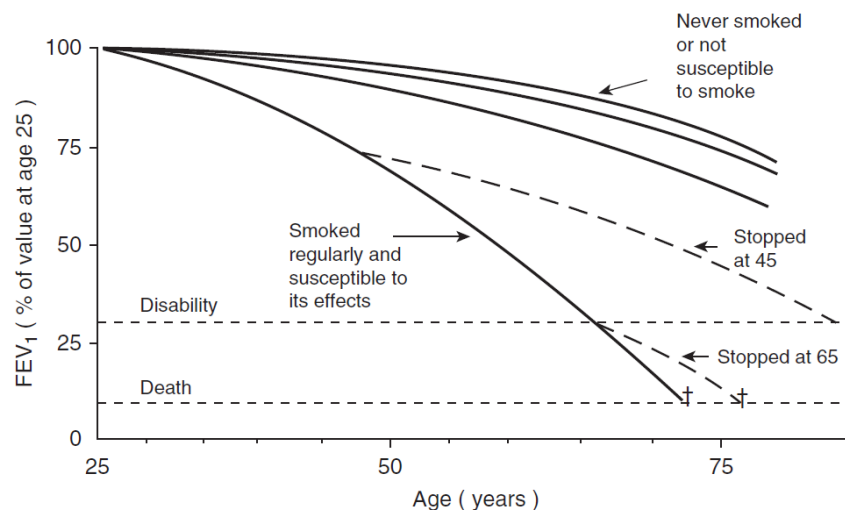


Figure 1: Fletcher-Peto diagram of FEV1 decline in men according to smoking habits. Reproduced by Vestbo and colleagues [33] with permission from original [14]. **Key:** † = Death.

People with COPD experience a number of symptoms and manifestations of the disease that negatively impact their quality of life. On any given day they may experience one or multiple symptoms including breathlessness, chronic cough, sputum production, wheezing, chest tightness, fatigue, anxiety, depression and weight loss [7, 11]. Acute exacerbations of COPD (AECOPD) are defined by acute increased inflammation of the airways, and a worsening in any one or more of the aforementioned symptoms [9, 34]. Exacerbations are thought to be triggered by a confluence of several factors including the individual, the environment and some presence of a respiratory virus and/or airway bacteria [35].

Of the potential triggers for AECOPD, viral respiratory infections generally result in more severe exacerbations with higher likelihood of hospital admission and prolonged recovery times [36-38]. There is some evidence that the presence of bacteria is associated with greater risk of exacerbation, however, the greatest risk may come from viral and bacterial coinfection, which has been shown to result in

more severe reduction in lung function and longer hospital length of stay [34, 39-41]. Finally, several studies have highlighted the increase in exacerbation and hospitalisation rates associated with greater levels of environmental pollution [42-46].

Exacerbation severity and frequency may increase with severity of the underlying COPD. Though variability remains in reported annual incidence of exacerbation in individuals with similar severity [17, 47]. A more reliable definition of exacerbation severity may be according to utilisation of health services. Increases in regular inhaled pharmacotherapies denote a mild exacerbation, requirement of antibiotic and steroid use indicate moderate severity while a severe exacerbation requires a hospital admission [34].

Estimates of mortality and morbidity due to COPD are confounded by inconsistent use of terminology and reporting, as well as the fact that it is commonly under-diagnosed and clinically overlooked [7, 48-51]. Despite the likelihood of underestimation, COPD is still widely acknowledged as a major leading cause of death, ranking third overall in the United States of America (USA) [52, 53]. Currently available studies indicate that morbidity increases with age and is likely to be impacted by the presence of other comorbid conditions including mental health disorders and cardiovascular disease (see section 1.1.1d), which may affect COPD management and contribute further to the individual's ill health [54-58]. In addition, the impact of COPD on Disability Adjusted Life Years (DALYs) lost has steadily increased in recent years climbing from eighth leading cause in 2005 to fifth by 2013 [59, 60].

Furthermore, the socioeconomic burden associated with COPD is significant worldwide. Direct healthcare costs associated with COPD are estimated to be 6% of total health budget in the European Union and amounting to \$32 billion in the USA, the lion's share of this expenditure is attributable to AECOPD and subsequent utilisation of health services [61, 62]. Primary care consultations for exacerbations of COPD exceed those by the general population with an average of approximately four visits per annum [63]. Impacts on the tertiary health system are also severe, with in excess of 0.9% of all hospital admissions and 2.4% of all acute medical admissions attributable to COPD in England [9]. Despite the significant burden placed on the hospital system, trends show a lack of

improvement for key performance indicators including admissions and length of stay, highlighting a need for appropriate and effective interventions to alleviate the strain [9].

In Australia, COPD is responsible for 1.3% of all hospital admissions and 4% of deaths in patients aged 55 years or older [64]. At a rate of 282.6 per 100,000 people, COPD is ranked second for avoidable hospital admissions nationwide, with the median length of stay being five to six days for people 55 years and older [65, 66]. Moreover, the rate of hospitalisations increase with age and given Australia's ageing population, with the number of older people projected to increase by approximately 10% by 2061 [64, 67], the socioeconomic burden of COPD is a long-term concern. The economic impact of this disease is significant, with estimated national expenditure for COPD in 2008/09 totalling \$929 million, 57% of which was attributable to inpatient costs [65]. Hence, addressing adequate and appropriate inpatient management of COPD to help reduce this burden is a priority.

1.1.1 Management of COPD:

Though not curable, COPD is a manageable condition and with an appropriate treatment plan, an opportunity to slow disease progression exists. Approaches can be largely separated into pharmacological and non-pharmacological categories. These are often combined to create an individualised and multifaceted approach to management of an individual's COPD.

1.1.1a Smoking Cessation:

Approximately half of all smokers develop some airway limitation, with 15-20% becoming clinically significant [14]. Among susceptible individuals there is a strong association between the amount of tobacco smoked and the rate of decline in FEV₁ [14]. For people diagnosed with COPD, smoking cessation is the most important intervention to preserve remaining lung function by decreasing the rate of decline and delaying the onset of disability.

Although tobacco prevalence has remained relatively stable in recent years, promotion of smoking cessation programs, such as the National Tobacco Strategy 2012-2018 [68] have seen a 10% reduction in the proportion of adults who smoke daily from 1995 to 2018 [69]. A comprehensive review of smoking cessation

programs in patients with respiratory diseases saw an integration of public policy, information dissemination programs and health education through the media and schools as key components to a successful tobacco control strategy [68]. These smoking cessation programs have proven to be effective regardless of gender, race and ethnic groups [70]. While relapse is common, further use of pharmacotherapies and behavioural techniques can significantly increase the rate of successful quit attempts [71-78]. Therefore, continued efforts in smoking cessation remain a high priority in various COPD management guidelines.

Pharmacotherapies for nicotine dependence have proven efficacy and are recommended for almost all nicotine dependent smokers attempting to quit [71, 79]. All forms of nicotine replacement therapy (NRT) have proven to be 1.6 times more effective in smoking cessation efforts at six-month follow-up when compared to no intervention [80]. They are offered in a range of forms (such as transdermal patch, gum, inhaler, lozenge, mouth spray and oral strip) to suit patient preferences, needs and tolerance. Combining two forms of NRT (patch plus oral form) is superior to one form alone [80].

Varenicline tartrate, developed as a nicotinic acetylcholine receptor partial agonist, is a prescription medication used to reduce both withdrawal symptoms and cravings for cigarettes and other nicotine-containing products [81]. Numerous trials have assessed its efficacy and found it to be significantly more effective than placebo for smoking abstinence [82, 83].

Depression is a common comorbidity in people with COPD [84-88] and can make smoking cessation efforts difficult if not well controlled [89, 90]. Antidepressants can be prescribed for smoking cessation. A Cochrane systematic review [91] has shown both nortriptyline and bupropion hydrochloride to be effective in assisting with long-term smoking cessation efforts, although may have contraindications and side effects. Overall evidence suggests that combination NRT (patch plus oral form) and varenicline (used as monotherapy), when used together, are the most effective form of pharmacological treatment [7, 9]. Despite the high incidence of hospitalisation associated with AECOPD and the typically prolonged length of stay, which presents an opportunistic teachable moment, evidence-based cessation strategies are lacking provision in practice.

1.1.1b Pharmacological approaches:

Pharmacological interventions are the lynch pin of current COPD treatment and are primarily comprised of short and long acting inhaled therapies. These inhaled therapies are typically categorised into either β 2-agonists or muscarinic agents. Though they have a different mechanism of action both work to encourage dilation of the airways, which is critical for patients with COPD who experience varying levels of dyspnoea from a stable to exacerbated state. Short acting bronchodilator agents are colloquially referred to as 'reliever' medications and are prescribed for that purpose rather than prolonged regular use [9]. Well conducted systematic reviews have identified that use of a short acting β 2-agonist produces a significant bronchodilator effect demonstrated on spirometry testing compared to placebo (weighted mean difference 140 ml (95% CI 40 to 250) for FEV₁) and that co-intervention with a muscarinic agent (e.g. ipratropium bromide) has an additive effect (weighted mean difference = 30 ml (95% CI 0 to 60) for FEV₁) [92, 93]. However, multiple studies highlight the associated increased risk of cardiovascular adverse events with this treatment, the number needed to harm estimated to be 40 (95% CI 18 to 185) per annum [94-96]. Though there is a good body of evidence to support their efficacy in creating a bronchodilator effect in people with stable COPD, there is a dearth of evidence to support the appropriate administration of these medications in the hospital setting where they are freely and frequently administered to relieve exacerbation induced breathlessness. Given the potential for cardiovascular adverse events, investigation into the optimal inpatient treatment regime is desirable to ensure any benefit surpasses risk.

Complementing 'reliever' medications are 'preventers', or long acting bronchodilators. These are also comprised of both β 2-agonist and muscarinic agents but with a longer duration of action (12 to 24 hours) [9]. In response to the need to reduce COPD burden on society, there has been an influx of new inhalers in recent years that has created more options than ever before for clinicians treating COPD. Recent meta-analyses of long acting muscarinic agents determined that there were no discernible differences between different devices for FEV₁, breathless and quality of life measures [9, 97, 98]. A further meta-analysis demonstrated superiority of long acting muscarinic agents over long acting β 2-agonists in reducing exacerbation rates (RR 0.88, 95% CI 0.84 to 0.93) and AECOPD-related hospitalisations (RR 0.78, 95% CI 0.69 to 0.87) [99].

Combination long acting β_2 /muscarinic agents are also available for COPD management. This combination therapy has been found to provide superior clinical efficacy compared with monotherapy for important outcome measures including FEV₁ and quality of life, with no increased risk of adverse events [100]. Further innovation in the field of COPD management has led to development of a combination long acting β_2 /muscarinic agent (formoterol fumarate/ glycopyrronium bromide) inhaler which also contains a corticosteroid (betamethasone dipropionate), so addressing the airway inflammation present in COPD as well as bronchoconstriction. In a recently published study this combination inhaler was effective in reducing rate of exacerbations (rate ratio 0.77, 95% CI 0.65-0.92) compared to a double agent inhaler [101]. Though this inhaler is likely a beneficial option for people with severe COPD, it is not yet available in Australia, and is perhaps a good example of external factors that may impede provision of best-practice by clinicians.

1.1.1c Non-pharmacological approaches:

Although the current medical model heavily favours prescription of pharmacotherapy for COPD treatment, there are several non-pharmacological approaches that have been demonstrated to improve clinical outcomes. Given the prominence of inhaled therapy in the COPD landscape, correct inhaler technique is imperative to ensure optimal use and dose delivery [102]. However, a recent systematic review identified that correct technique was only exhibited 31% of the time, a trend that has not improved in 40 years [103]. Furthermore, errors in inhaler technique are associated with greater exacerbations. Nevertheless it is an aspect of best-practice care that is often overlooked by clinicians in practice. This is despite the development of freely available educational videos endorsed by the Lung Foundation of Australia and evidence that intervention by health professionals can improve medication adherence [9, 102, 104-106].

Regular exercise, though a challenge for many people with COPD owing to the associated exertional breathlessness, is recommended as it demonstrably reduces risk of all-cause, cardiovascular and respiratory mortality [89, 107-110]. Furthermore, enrolment in pulmonary rehabilitation programs are recommended for people with COPD and those in a post AECOPD state, as it confers a multitude of benefits including reduced rate of exacerbation improved symptoms and health related quality of life, as well as, improved anxiety and depression, peripheral

muscle function and exercise capacity [89, 107, 109, 111-115]. Despite the strength of evidence for this recommendation, available literature suggests only 13% of eligible people with COPD are referred [116].

Other beneficial non-pharmacological approaches to COPD management include: airway clearance techniques, provision of psychosocial support and appropriate nutrition [117-122]. Notwithstanding the breadth of effective non-pharmacological approaches to COPD management, reality is that they are often underprovided in practice while pharmacological interventions are relatively well prescribed [116]. Future interventions to improve best-practice management of COPD should emphasise and facilitate increased use of non-pharmacological management options.

1.1.1d Management of comorbidities:

An often overlooked but critical element of best-practice care for COPD includes identification and management of comorbidities [123]. COPD is associated with high prevalence of medically important comorbidities including cardiovascular disease, asthma, stroke, diabetes, anxiety and depression, poly-pharmacy, osteoporosis, metabolic disease and mobility issues [61, 124-127]. Comorbid respiratory and psychiatric disorders are associated with two or more exacerbations per year [128]. Hence, it is important to consider each individual patient and their relative comorbidities at the forefront of planning for COPD management to reduce dangerous pharmacological interactions and other potential factors that may interfere with successful management [7, 9].

Evidently there is a breadth of options, pharmacological and non-pharmacological, available for consideration when approaching the management of people with COPD. The evidence base underpinning these many varied options has been collated into lengthy documents called best-practice guidelines in order to provide a basis for quality clinical decision making.

1.1.2 Best-Practice Guidelines for COPD:

As research and innovation over a number of decades has focussed on developing, refining and evaluating pharmacological and non-pharmacological strategies toward respiratory disease treatment and management there has been an influx of publications in the area. These studies form part of over 2,055

publications estimated to be indexed online each and every day by databases such as MEDLINE [129], while the number of new trials registered has increased exponentially in the past 15 years [130]. Compounding this are reservations that the rapidly proliferating literature may be prone to multiple biases both methodologically within single studies and as a collective evidence base (i.e. publication bias). Convergence of these circumstances leaves health professionals increasingly inundated with masses of information with unclear clinical benefit and application. Furthermore, ever increasing financial restrictions in health have resulted in an increased desire for evidence based health care decisions and policy-making [131-134]. Hence, systematically assembled and critically appraised syntheses of available evidence have become a cornerstone of knowledge translation and evidence based medicine [135, 136]. Evidence of this trend in health service decision-making, is the growing respect and interest in high quality systematic reviews, the gold standard of which are those following methodology of the Cochrane Collaboration [137, 138].

The typically narrow focus of a systematic review and strict inclusion criteria, however, means that in order to treat one patient a clinician may need to draw on the findings of multiple systematic reviews, while missing potentially clinically useful information omitted due to the stringent methodology [17]. This is why the presence and use of clinical practice guidelines (CPGs) is ever more important. The Institute of Medicine defines them as follows:

“Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.” [135]

A CPG can be identified as high quality if it is a regularly updated systematic review of existing literature assembled through a rigorous and transparent methodological process by a multidisciplinary panel of experts and stakeholders. It needs to provide balanced recommendations for disease management, taking into account relevant benefits versus risks according to the quality of underpinning evidence [135]. Numerous high quality CPGs for the management of COPD have been developed and refined over the years [7, 9, 139]. These lengthy documents cover best-practice management from appropriate diagnosis and

assessment through to palliative care considerations (see section 1.1.1). The guidelines not only present recommendations to improve patient related outcomes but a series of systematic reviews undertaken by Purdy *et.al.*, has identified that by ensuring clinicians adopt evidence-based practices in clinical decision making for COPD, improvements in quality of life and a reduction in the need for hospital admissions can be obtained [140]. As an example, Table 1 outlines several level I and II evidence recommendations provided in the Thoracic Society of Australia and New Zealand COPD-X guideline, which could translate to a substantial reduction in hospital utilisation if adhered to in practice [9]. According to the National Health and Medical Research Council (NHMRC) level I evidence constitutes a systematic review of all relevant randomised controlled trials (RCTs), whilst level II is evidence obtained from at least one methodologically robust RCT [141].

Table 1: Level I and II evidence COPD-X recommendations for reducing hospitalisation due to AECOPD.

Intervention	Demonstrated impact	Effect estimate	COPD-X reference
Level I			
LAMAs	“...LAMAs had reduced exacerbation rates ...and exacerbation-related hospitalisations ... compared to LABAs” [99] NB: most participants in this analysis had <u>Tiotropium</u> as their LAMA	22% improvement (RR 0.78, 95% CI 0.69 to 0.87)	Optimise function (O) 1.2.1 pg. 37
Tiotropium	“... tiotropium reduced the odds of a COPD exacerbation ... and related hospitalisations compared to placebo or ipratropium.” [142]	36% improvement (OR 0.64, 95% CI 0.51 to 0.82 NNT 30, 95% CI 22 to 61)	Prevent deterioration (P) 5.1 pg. 100
	“... tiotropium was more effective in preventing COPD exacerbations leading to hospitalisation [compared to a range of other LABAs]” [143]	14% improvement (OR 0.86, 95% CI 0.79 to 0.93)	P5.2 pg. 100
Acclidinium	“...Acclidinium resulted in marginal improvements in quality of life and FEV ₁ , and reduced the number of patients with exacerbations requiring hospitalisation ” [144]	NNT 77 , 95% CI 51 to 233	O1.2.1 pg. 37
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” [145]	52% improvement (OR 0.48, 95% CI 0.35 to 0.67 NNT 9)	Manage eXacerbations (X) 2.2.2 pg. 129
Non-invasive ventilation	“The use of NIV reduces hospital length of stay. ” [146]	MD -3.39 days , 95% CI -5.93 to -0.85	X3.2 pg. 134
Hospital at	“... compared to standard care, participants allocated to	24% improvement	X1 pg. 126

home	hospital in the home were significantly less likely to be readmitted to hospital within the next 1 to 6 months.” [147]	(RR 0.76, 95% CI 0.59 to 0.99)	
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... ” [148]	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 Pg. 109
Pulmonary rehabilitation	“Pulmonary rehabilitation also reduced hospital readmissions. ”[149]	56% improvement OR 0.44, 95% CI 0.21 to 0.91	X3.6 pg. 136
Intervention	Demonstrated impact	Effect estimate	COPD-X reference
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).” [150]	34% improvement (RR 0.66, 95% CI 0.56 to 0.78)	O4.2 pg. 50
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. ” [117]	MD - 0.75 days , 95% CI - 1.38 to -0.11	X3.4 pg. 135
Discharge bundles	“... the use of COPD discharge bundles reduced hospital readmissions ... ” [151]	20% improvement (RR 0.80, 95% CI 0.65 to 0.99)	X3.7 pg. 138
Supported discharge	“...has been shown to reduce re-admissions for COPD exacerbations compared to usual care ...” [152]	45% improvement (HR 0.55, 95% CI 0.35 to	X3.8 pg. 138

programs & medication adherence	“Adherence to inhaled medications regimes is associated with reduced risk of death and admissions to hospital due to exacerbations in COPD...” [153]	0.88) 44% improvement (RR 0.56, 95% CI 0.48 to 0.65)	O pg.33

Key: LAMA=long acting muscarinic agent; LABA=long acting β 2 agonist; RR=risk ratio; 95% CI=95% confidence interval; OR=odds ratio; NNT=number needed to treat; COPD=chronic obstructive pulmonary disease; FEV₁=forced expiratory volume in one second; MD=mean difference; QoL = quality of life; ICS = inhaled corticosteroids; NIV = Non-invasive ventilation.

Pharmacological approaches	Acute management approaches	Pre-discharge considerations

The evidence base, with potential to reduce mortality and optimise COPD management, is consistently developing and high quality national and international CPGs [7, 9, 139] have been developed to assist facilitation of integration this knowledge into practice. However, studies highlight that uptake and adherence by clinicians is variable in practice, such that up to 40% of patients with COPD do not receive guideline concordant care [116, 154-157].

1.1.3 Translating COPD evidence into practice:

Each year the Australian Government, businesses and not-for-profit organisations invest around \$30 billion on research and development [158]. Yet the majority of research outcomes and interventions remain inaccessible to the people they were intended to help [159]. The mean time to translate just 14% of clinical research into practice is estimated at 17 years when supported by substantial additional costs [160, 161]. Of this translated research, there is a long history of studies suggesting that 30-40% of patients do not receive care according to current scientific evidence [116, 154-157, 162, 163], while 20% or more of the care provided is not needed or potentially harmful to patients [156, 163].

Evidence-based practice is the systematic consolidation of relevant up-to-date evidence and translation of this content for clinical use, with consideration of patient values and preferences [132]. The intention of this process is to optimise clinical decision making and subsequently improve patient care [164]. To date, efforts to implement best-practice medical care by doctors have several known barriers, including perceived lack of time, lack of knowledge or resources [164, 165], belief that application of research findings conflict with needs of the individual patient [166], lack of awareness of the evidence base, lack of peer/colleague support [167] and a desire to maintain the status quo of everyday practice with a lack of motivation to change [6, 168].

Attempts to address these barriers have focussed on passive forms of health professional education through traditional models such as lectures [169], conferences and use of printed materials [170]. These approaches have been generally unsuccessful in modifying practice [168]. As such, the scientific and medical community have called for multi-faceted solutions tailored to address

specific barriers by using creative strategies [168] that inspire curiosity to create engagement [171] and are more appropriate in a digital information age [169].

1.2 Technology to bridge the evidence practice gap for COPD management

The information technology boom in recent years has infiltrated all aspects of daily life and its ready availability makes it a potentially cost effective means of improving efficiency, safety and health professional and patient satisfaction [172-175]. As a result there has been a great interest in developing ways to implement and adopt information technology in health service organisations, through smartphone and clinical decision support technology [176-180].

1.2.1 Use of smartphone technology for COPD management:

Smartphones have become the most popular and widespread type of mobile technology device [181, 182]. Over half of adults claim ownership of one and with the increasing market competition and prices become more affordable it is highly likely that these figures will continue to rise [181-184]. Though this is an emerging area in health research there is some evidence that smartphone technology is a viable way to deliver health interventions to a range of demographics and age groups [181, 185-187]. To date, most studies focus on use of smartphones to bridge the knowledge translation gap for patients in order to assist with improved self-management [182, 183, 186]. However, there is a paucity of evidence around the use of smartphones to facilitate similar interventions for health professionals. Future studies may capitalise on the popularity and convenience of this technology as an intervention to improve care.

1.2.2 Use of clinical decision support technology for COPD management:

Technological applications and solutions have begun to increasingly permeate healthcare organisations, gathering momentum as popular innovations with the potential to reduce errors and improve delivery of quality care at low cost [188, 189]. Specifically, electronic medical records (EMRs) are becoming increasingly popular in both acute and community settings, not only for their ability to improve communication and documentation between clinicians regarding patient care, but also for their ability to facilitate the ordering of appropriate medications and tests [189]. The latter feature has been noted to reduce prescriber error and reduce medication related adverse events by as much as 55% generally and significantly

decrease prescription errors by up to 40% in the AECOPD context specifically [188-191]. There is also some non-randomised data that indicates physician use of order set functionality to guide management of AECOPD in the hospital setting translates to modest improvement in length of stay, though this effect did not extend to readmissions [190, 191]. Despite the great potential for quality improvement with use of an EMR in clinical practice, barriers to implementation exist. The EMR functionality typically extends well beyond clinical decision support, with its purpose extending to areas including administration and medical imaging. This can place a strain on optimal system functionality causing user dissatisfaction [192]. The National Health Service in the UK provided a real-world view of EMR rollout challenges, with only 3% of target hospitals meeting their target deadline, resulting in costly timeline pushbacks lasting up to two years [193].

Much like the evidence base for smartphone technology, research into the effectiveness of clinical decision support technology in improving best-practice care for COPD is limited owing to its relative infancy. However, a systematic review into its application to chronic disease management revealed promising, though conflicting results, indicating that use of this technology facilitated improvement in care processes and improved patient related outcomes [194]. Future research may consider the use of an EMR or clinical decision support tool to facilitated improved knowledge translation, taking advantage of its ability to seamlessly integrate with clinicians' daily workflow [195].

1.3 Summary

COPD presents a costly burden to society and as such optimal management is a high priority [4, 66]. Over the years, many pharmacological and non-pharmacological approaches to management have been developed and the rapidly growing evidence base to support their use in practice contributes to the information overload facing health professionals daily. Best-practice guidelines have been developed to provide a high quality synthesis of the literature in order to assist clinicians with this and support them to underpin their practice with evidence [7, 11, 139]. Furthermore, guideline concordant care results in reduced exacerbations of COPD and subsequent hospital utilisation [140]. However,

uptake and adherence to these guidelines in practice is variable and interventions which can address this problem are desirable [116].

The research presented in this thesis aims to update and fill gaps in the literature relating to key areas of COPD management in the hospital setting and identify perceived barriers and facilitators to provision of best-practice by health professionals. This thesis will then discuss how the results of this research have informed the development of an evidence-based intervention to improve guideline adherence in practice.

Chapter 2. Overview of aims and methods

For the majority of publications/manuscripts included in this thesis a detailed description of the aims and methodology is reported within the manuscript itself (*Chapters 4-8*). Information pertaining to Human Research Ethics Committee (HREC) approvals for this thesis is provided in Section 2.2 for *Chapter 9* and the intervention development described in *Chapter 10*.

2.1 Overview of aims

A summary of the aims/hypotheses for each manuscript presented in this thesis are below.

Influenza vaccine for COPD (*Chapter 4*)

The aim of this Cochrane systematic meta-analysis is to evaluate the safety and efficacy of influenza vaccinations to prevent exacerbations of COPD and to summarise the available evidence for clinical guidelines.

Oxygen therapy in the pre-hospital setting for exacerbations of COPD (*Chapter 5*)

The aim of this Cochrane systematic review is to evaluate the effectiveness of supplying oxygen therapy during transportation to hospital via ambulance and other pre-hospital settings to examine the impact on severity of COPD exacerbations during hospitalisation.

Short-acting bronchodilators for the management of acute exacerbations of COPD in the hospital setting (*Chapter 6*)

The aim of this systematic review is to examine the safety and efficacy of short-acting bronchodilators for the management of acute exacerbations of COPD within the inpatient setting.

Smoking cessation policies for hospitalised smokers (*Chapter 7*)

The aim of this commissioned policy document is to summarise available evidence to support smoking cessation among patients admitted to hospital, for use by policy makers and health professionals.

Inhaled anticholinergics for COPD in the elderly (*Chapter 8*)

The aim of this invited review was to synthesise available evidence surrounding the use of inhaled anticholinergics for the management of elderly patients with COPD.

Barriers and facilitators to best practice care for people with COPD: A qualitative study (*Chapter 9*)

The aim of this qualitative investigation is to identify barriers and facilitators to current COPD management and to identify gaps in current clinical practice to provide recommendations for future evaluation and research.

2.2 Details relating to ethics approvals relating to this thesis

Ethics approval for the qualitative study presented in Chapter 9 was obtained from the Central Adelaide Local Health Network (CALHN) HREC on the 28th of June 2018 (reference number: HREC/18/CALHN/150).

The Intervention Mapping process to guide the development of resources informed by the evidence produced in this thesis was approved by the HREC of The Queen Elizabeth Hospital/ Lyell McEwan Hospital/ Modbury Hospital (now known as CALHN HREC). Approval was granted on the 2nd of January 2018 (reference number: HREC/17/TQEH/259).

Chapter 3.

Influenza vaccine for chronic obstructive pulmonary disease

(Systematic review and meta-analysis)

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Statement of authorship for jointly authored papers within the thesis

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Influenza vaccine for chronic obstructive pulmonary disease

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Author contributions:

By signing the Statement of Authorship, each author certifies their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of principal author (candidate)	Zoe Kopsaftis		
Contribution to the paper	Updated the Cochrane protocol, screened the literature search based on titles and abstracts, performed second full text screening to identify studies for inclusion, extracted study data for characteristics, risk of bias and results, analysed the data including meta-analysis and narrative synthesis, drafted manuscript and sent to co-authors for input, made changes based on co-author, peer review and editorial feedback and approved final version.		
Signature		Date	22/02/2019
Name of co-author	Richard Wood-Baker		
Contribution to the paper	Analysed the data, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions, approved final version and supervised the process.		
Signature		Date	1 st March 2019

Name of co-author	Philippa Poole		
Contribution to the paper	Original reviewer of the previous publication of this Cochrane review. Analysed the data, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions, approved final version and supervised the process.		
Signature		Date	4 th Feb 2019

Influenza vaccinations are currently recommended in the care of people with COPD. However, these recommendations are based largely on evidence from observational studies with very few randomised controlled trials reported. Appraisal of the Cochrane library, one of the highest ranked journals in evidence based medicine research (ranked 11 out of 151 journals in the medicine, general and internal category), identified a review published in the year 2000 (almost two decades old and in need of an update based on the latest evidence).

The Cochrane Database of Systematic Reviews is frequently used to underpin policy, practice and provide recommendations for future evaluations and research based on a methodologically rigorous systematic appraisal of the available published and unpublished evidence. Cochrane practices not only ensure that a broad cross-section of resources are searched to identify relevant studies for inclusion, it also safeguards the quality of evidence with risk of bias evaluations alongside each study, to identify any possible issues with interpretation of results. Therefore, to systematically consolidate evidence to underpin a best-practice clinical resource, it was necessary to perform a Cochrane review to establish an evidence base of current interventions globally and to determine what has been effective, ineffective and build recommendations based on this available data.

Eleven randomised controlled trials were identified on a global scale as meeting all of the eligibility criteria for this meta-analysis, though only six included people with COPD and all were more than a decade old. Based on available evidence, inactivated vaccine reduced exacerbations in people with COPD. The size of effect was similar to that seen in large observational studies and was due to a reduction in exacerbations occurring three or more weeks after vaccination due to influenza. A mild increase in transient adverse effects was observed, however, no evidence of an increase in early exacerbations were identified.



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Influenza vaccine for chronic obstructive pulmonary disease (COPD) (Review)

Kopsaftis Z, Wood-Baker R, Poole P

Kopsaftis Z, Wood-Baker R, Poole P.

Influenza vaccine for chronic obstructive pulmonary disease (COPD).

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[Intervention Review]

Influenza vaccine for chronic obstructive pulmonary disease (COPD)

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ABSTRACT

Background

Influenza vaccinations are currently recommended in the care of people with COPD, but these recommendations are based largely on evidence from observational studies, with very few randomised controlled trials (RCTs) reported. Influenza infection causes excess morbidity and mortality in people with COPD, but there is also the potential for influenza vaccination to cause adverse effects, or not to be cost effective.

Objectives

To determine whether influenza vaccination in people with COPD reduces respiratory illness, reduces mortality, is associated with excess adverse events, and is cost effective.

Search methods

We searched the Cochrane Airways Trials Register, two clinical trials registries, and reference lists of articles. A number of drug companies we contacted also provided references. The latest search was carried out in December 2017.

Selection criteria

RCTs that compared live or inactivated virus vaccines with placebo, either alone or with another vaccine, in people with COPD.

Data collection and analysis

Two review authors independently extracted data. All entries were double-checked. We contacted study authors and drug companies for missing information. We used standard methods expected by Cochrane.

Main results

We included 11 RCTs with 6750 participants, but only six of these included people with COPD (2469 participants). The others were conducted on elderly and high-risk individuals, some of whom had chronic lung disease. Interventions compared with placebo were inactivated virus injections and live attenuated intranasal virus vaccines. Some studies compared intra-muscular inactivated vaccine and intranasal live attenuated vaccine with intra-muscular inactivated vaccine and intranasal placebo. Studies were conducted in the UK, USA and Thailand.

Inactivated vaccine reduced the total number of exacerbations per vaccinated participant compared with those who received placebo (mean difference (MD) -0.37, 95% confidence interval (CI) -0.64 to -0.11; $P = 0.006$; two RCTs, 180 participants; low quality evidence). This was due to the reduction in 'late' exacerbations, occurring after three or four weeks (MD -0.39, 95% CI -0.61 to -0.18; $P = 0.0004$; two RCTs, 180 participants; low quality evidence). Both in people with COPD, and in older people (only a minority of whom had COPD), there were significantly more local adverse reactions in people who had received the vaccine, but the effects were generally mild and transient.

There was no evidence of an effect of intranasal live attenuated virus when this was added to inactivated intramuscular vaccination.

Two studies evaluating mortality for influenza vaccine versus placebo were too small to have detected any effect on mortality. However, a large study ($N=2215$) noted that there was no difference in mortality when adding live attenuated virus to inactivated virus vaccination,

Authors' conclusions

It appeared, from the limited number of RCTs we were able to include, all of which were more than a decade old, that inactivated vaccine reduced exacerbations in people with COPD. The size of effect was similar to that seen in large observational studies, and was due to a reduction in exacerbations occurring three or more weeks after vaccination, and due to influenza. There was a mild increase in transient local adverse effects with vaccination, but no evidence of an increase in early exacerbations. Addition of live attenuated virus to the inactivated vaccine was not shown to confer additional benefit.

PLAIN LANGUAGE SUMMARY

Influenza vaccine for people with chronic obstructive pulmonary disease (COPD)

Question

Do influenza vaccines reduce episodes of respiratory illness or death in people with chronic obstructive pulmonary disease (COPD)?

Background

COPD is an umbrella term used to describe progressive lung diseases, including emphysema, chronic bronchitis, and refractory (non-reversible) asthma. The disease is characterized by increasing breathlessness. Despite the almost universal recommendation that people with COPD should receive an annual influenza vaccination, very few randomised controlled trials (studies in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention) have evaluated the effect of this treatment. Influenza vaccines may be produced with an inactivated virus (small particles of the virus wall) or live attenuated virus (reduced power but still alive).

To try to answer our question, we conducted a detailed search for studies from around the world that investigated the use of influenza vaccines for people with COPD.

Study characteristics

We included six studies with 2469 participants with COPD, and a further five studies with 4281 older or high risk participants, a proportion of whom had chronic lung disease.

Key results

We found some moderate-quality evidence that inactivated influenza vaccine did decrease 'flare ups' of COPD, especially those that are related to the influenza virus itself. The inactivated influenza virus vaccine was given as an injection in the muscle, and was associated with an increase in local side effects (such as pain) at the site of injection, which were short-lived. The inactivated virus vaccine did not cause influenza, or any significant worsening of COPD. Adding a live attenuated virus to the inactivated virus did not add any further protection for the participants.

Quality of the evidence

The evidence was of moderate quality. There have been no new trials since 2004. We conducted the last literature search in December 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Influenza vaccine compared to placebo for chronic obstructive pulmonary disease (COPD)						
Patient or population: chronic obstructive pulmonary disease (COPD) Setting: community Intervention: inactivated influenza vaccine Comparison: placebo						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Influenza vaccine				
Total exacerbations per participant	The mean number of total exacerbations per participant ranged across placebo groups from 0.83 to 1.35	MD 0.37 lower (0.64 lower to 0.11 lower)	-	180 (2 RCTs)	⊕⊕○○ Low ^a	Despite the effect size, this is based on a very small number of trials and participants. However there was good agreement between these two studies (low I ²). One study was not conducted in an epidemic year. We extrapolated some data. Ideally more trials would be done to refine these effect sizes
Early exacerbations per participant	The mean number of early exacerbations per participant ranged across placebo groups from 0.14 to 0.34	MD 0.01 higher (0.11 lower to 0.13 higher)	-	180 (2 RCTs)	⊕⊕○○ Low ^a	See above

Late exacerbations per participant	The mean number of late exacerbations per participant ranged across placebo groups from 0.48 to 1.21	MD 0.39 lower (0.61 lower to 0.18 lower)	-	180 (2 RCTs)	⊕⊕○○ Low ^a	See above
Days disability from respiratory illness	not reported					
Hospital admissions	76 per 1000	26 per 1000 (7 to 93)	OR 0.33 (0.09 to 1.24)	180 (2 RCTs)	⊕⊕○○ Low ^{a,b}	
Mortality	76 per 1000	67 per 1000 (23 to 182)	OR 0.87 (0.28 to 2.70)	180 (2 RCTs)	⊕⊕○○ Low ^{a,b}	
Local effects at injection site	63 per 1000	274 per 1000 (106 to 546)	OR 5.57 (1.75 to 17.71)	125 (1 RCT)	⊕⊕○○ Low ^a	Single study on participants who all had COPD (Wongsurakiat 2004a), but very similar findings in studies with a mixed population (Cate 1977; Govaert 1994)

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

^a Small number of studies which are over ten years old limit our confidence in the generalisability of these findings to currently available vaccines (downgraded once for indirectness).

^b Studies too small and events too infrequent to detect a consistent effect (downgraded once for imprecision)

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) occurs predominantly in older people who have smoked, and is characterised by progressive airflow obstruction that is largely irreversible. As the disease progresses, exacerbations may occur several times per year, and may require hospital admission. These exacerbations can take several weeks to resolve, during which time considerable morbidity may occur and result in significant health care costs. Infection with influenza is an important cause of excess mortality and morbidity in people with COPD (Rothbart 1995). It may affect the progression of the disease (Centanni 1997), and frequency of exacerbations (Sethi 2002). People with COPD are at an increased risk for respiratory illness-related hospitalisation during influenza outbreaks, irrespective of age and degree of morbidity (Monto 1987).

Description of the intervention

Annual influenza vaccination is almost universally recommended in COPD guidelines (ATS 1995; ATS 2004; BTS 1997; GOLD 2018; NICE 2010; Siafakas 1995; Yang 2017). The largest body of evidence to support this recommendation comes from observational studies in the older population. In a large, serial cohort study of nearly 150,000 older people, those who had been vaccinated had a reduction of about 32% in the rates of hospitalisation for all respiratory conditions, and a reduction of approximately 50% in all-cause mortality over their untreated counterparts (Nichol 1998). In people with chronic lung disease, those who were vaccinated had a 52% reduction in hospitalisations and a 70% reduction in death rate during influenza seasons (Nichol 1999). A meta-analysis of 20 cohort studies of influenza vaccination in older people showed a 56% reduction in respiratory illness, a 53% reduction in pneumonia, a 50% reduction in hospitalisation, and a 68% reduction in deaths from all causes during influenza outbreaks (Gross 1995). The benefit was seen especially in epidemic years, when the vaccine strain was identical or similar to the epidemic strain (Gross 1995). Most studies suggest that vaccination is very cost effective. For example, Nichol and colleagues estimated that vaccination was associated with a reduction in health care costs of about USD 171 per year per high risk person vaccinated (Nichol 1998).

How the intervention might work

The effectiveness of the vaccine depends on the immunocompetence of the vaccine recipient and the degree of similarity between virus strains in the vaccine and those in circulation (ACIP 1999). Most vaccine programmes use an inactivated virus vaccine, which

contains three virus strains (usually 2 type A and 1 type B), representing the influenza viruses likely to circulate in the upcoming winter. The vaccine is made from highly purified, egg-grown viruses that have been inactivated. These vaccines may be whole virus, sub virion, or purified-surface-antigen preparations. The mechanism of protection by the vaccine is thought to occur via circulating antibodies to HA (Hemagglutinin) and NA (Neuramidase), acting against severe infection of the lower respiratory tract. Stimulation of cytotoxic T-cell responses may also be important (Patriarca 1994). In general, older people have lower phagocytic function, and mount less of an immune response to vaccination than younger people (Treanor 1992). To improve vaccine efficacy, live attenuated viruses have been trialled. Levels of secretory anti-HAs, immunoglobulins (Igs) and anti-influenza A virus cytotoxic T-cell responses were better in people with COPD after immunisation with monovalent live attenuated vaccine than with inactivated influenza A virus vaccines (Gorse 1991; Gorse 1995; Gorse 1996). Some investigators have co-administered more than one type of vaccine, such as cold attenuated virus with inactivated virus vaccine, in an attempt to increase vaccine efficacy in people with COPD (Gorse 1997).

Why it is important to do this review

Despite guideline recommendations, vaccination of older people (the age group that includes most people with COPD) is not universal. In the USA in 1997, only 65.5% of older people were vaccinated in the previous year (BRFSS 1998). Yet, the only absolute contraindication to vaccination is chicken egg allergy. Other reasons for not vaccinating include uncertainty about the degree and longevity of protection in the older population and concern about adverse effects (Patriarca 1994). People with COPD, and their doctors, often express concern that vaccination precipitates exacerbations, despite the fact that it is not possible to contract influenza from inactivated virus. Adverse effects usually manifest within 24 hours of vaccination, and can be local or systemic. Several studies have shown that mild local side effects, at the site of injection, are more common in those who were vaccinated, than in those given placebo (Govaert 1994; Nichol 1995). Systemic reactions include myalgia, fatigue, headache, and low-grade fever. These are more common in females, and after the administration of whole-virus than sub virion vaccines. Higher doses and levels of pre-existing antibody also increase the likelihood of these reactions (Cate 1977). The most feared complication of influenza vaccination is Guillain-Barre Syndrome (GBS). However, this is extremely rare (approximately 1/1,000,000), and the benefits of the vaccine are thought to far out-weigh the risks of developing vaccine-associated GBS (ACIP 1999).

This systematic review evaluated the evidence from RCTs that had studied the effect of influenza vaccination in people with COPD. The review was originally published in 2000 (Poole 2000), and updated in 2006 (Poole 2006).

OBJECTIVES

To determine whether influenza vaccination in people with COPD:

1. Reduces respiratory illness;
2. Reduces mortality;
3. Is associated with excess adverse events; and
4. Is cost effective.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCT).

Types of participants

We included studies of adults with COPD, as defined by the American Thoracic Society (ATS 1995), or European Respiratory Society (Siafakas 1995). We also included studies with participants who were defined as having chronic bronchitis.

Types of interventions

We included studies randomising people to receive at least one annual influenza vaccination. Influenza vaccination may have been one of the following types: live attenuated whole virus, inactivated, or a split-virus type vaccine, and may have been administered by either intramuscular injection or intranasal spray.

Types of outcome measures

We classified outcomes as early or late. 'Early' referred to the early post vaccination period, when immunity may not yet have developed, but adverse effects may have occurred

Primary outcomes

1. Exacerbations of COPD, defined as an increase in breathlessness, volume or purulence of sputum, or a combination. This was assessed in terms of both total numbers of exacerbations and participants with one or more exacerbations in the study period.
2. Days of disability from respiratory illness, defined as days in bed, days off work, or days when the person was unable to undertake normal activities
3. Hospital admissions

4. Mortality in the year following vaccination (All cause and respiratory-related)

Secondary outcomes

1. Change in lung function from baseline, at the end of the study period
2. Adverse effects: acute
3. Acute respiratory illnesses subsequently proven to be influenza-related
4. Cost effectiveness

Studies would be excluded if they:

1. Did not report outcomes of interest for this review
2. Were not placebo controlled

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The most recent search was conducted in December 2017. The Cochrane Airways Trials Register contains studies identified from several sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);
2. Weekly searches of MEDLINE Ovid SP;
3. Weekly searches of Embase Ovid SP;
4. Monthly searches of PsycINFO Ovid SP;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in [Appendix 1](#). See [Appendix 2](#) for search terms used to identify studies for this review.

Searching other resources

We searched for additional articles of interest in the bibliographic lists from all full-text papers we retrieved. In 2006, we searched bibliographies of large reviews of influenza vaccination trials (Galasso 1977; Gross 1995), and recommendations of Advisory Councils (ACIP 1999; BRFSS 1998).

To locate other published or unpublished RCT data in 2006, we contacted pharmaceutical companies that had been involved in the conduct of vaccine trials, the manufacture of vaccines, or both.

We contacted the following companies: Smith Kline Beecham, Glaxo-Wellcome, Merck Sharp and Dohme, Astra, Parke Davis, Wyeth, Pasteur Merieux, and Commonwealth Serum Laboratories. In 2006, we also wrote to authors who had published extensively in the field to ask if they were aware of any further RCTs, published or unpublished.

For the review update (December 2017), we searched clinical trials registries (ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform) for current, recently completed, and ongoing studies.

Data collection and analysis

Selection of studies

For the original review, three review authors (PJP, RWB, EC) independently screened the titles and abstracts for potentially eligible studies and then retrieved the full texts to further screen for inclusion. For the updates this was done by two review authors (PJP and ZK). We resolved disagreement through discussion.

Data extraction and management

Review authors agreed the format of data extraction sheets. Two review authors independently extracted data. One review author entered the data onto the data extraction sheets, and then into Review Manager 4. A second review author double-checked each entry. For versions of this review published after the 2006 update, we used Review Manager 5 (RevMan 2014).

Assessment of risk of bias in included studies

Two review authors (PJP, ZK) independently assessed the risk of bias for all included studies, using the criteria outlined in the *Cochrane Handbook of Systematic Reviews of interventions* (Higgins 2011). We resolved disagreements through discussion. We assessed the risk of bias according to the following items:

- Random sequence generation;
- Allocation concealment;
- Blinding;
- Incomplete outcome data
- Selective outcome reporting;
- Other potential bias.

We judged each potential source of bias as high, low or unclear risk of bias. We summarised our judgements of the risk of bias across different studies for each of the items listed.

Measures of treatment effect

We analysed continuous data as mean differences (MD) with 95% confidence intervals (CI) and dichotomous data as odds ratios

(OR) with 95% CI or Peto odds ratios (Peto) with 95% CIs where pooling of odds ratios, or approximation to the odds ratio (i.e. for rare events) was required and appropriate i.e. intervention and control groups have similar numbers and number of events were rare (Higgins 2011).

Unit of analysis issues

The participant was the unit of analysis.

Dealing with missing data

Where there were insufficient data in the paper, we requested further data by writing to the author or pharmaceutical company sponsoring the study.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots and calculation of the I^2 value; which was interpreted broadly as follows:

- 0 to 40%: may represent negligible/low heterogeneity
- 30 to 60%: moderate heterogeneity
- 50 to 90%: substantial heterogeneity
- 75 to 100%: considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

We had planned to assess publication bias using a funnel plot, if there were a sufficient number of studies in a forest plot (more than 10).

Data synthesis

We used a fixed-effect model and performed a sensitivity analysis with a random-effects model.

We anticipated that the follow-up period would be 12 months. Because of the small number of studies involved in this review, we did not annualise the event rate. If further data become available, it may be necessary to annualise the event rate, particularly if follow-up periods vary.

Subgroup analysis and investigation of heterogeneity

In the case of significant heterogeneity, we had planned to run a sensitivity analysis based on risk of bias. If any heterogeneity could not be explained in terms of risk of bias, we planned the following sub-group analyses:

1. Type of control group
2. Vaccine type
3. Severity of COPD (by baseline lung function)
4. Setting of study
5. Match between strain of vaccine and infecting strains
6. Age of participants

'Summary of findings' tables

We created a 'Summary of findings' table using the GRADEPro software ([GRADEpro GDT 2015](#)). We included all primary outcomes and adverse events. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it related to the studies that contributed data for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We justified all decisions to downgrade the quality of studies using footnotes.

RESULTS

Description of studies

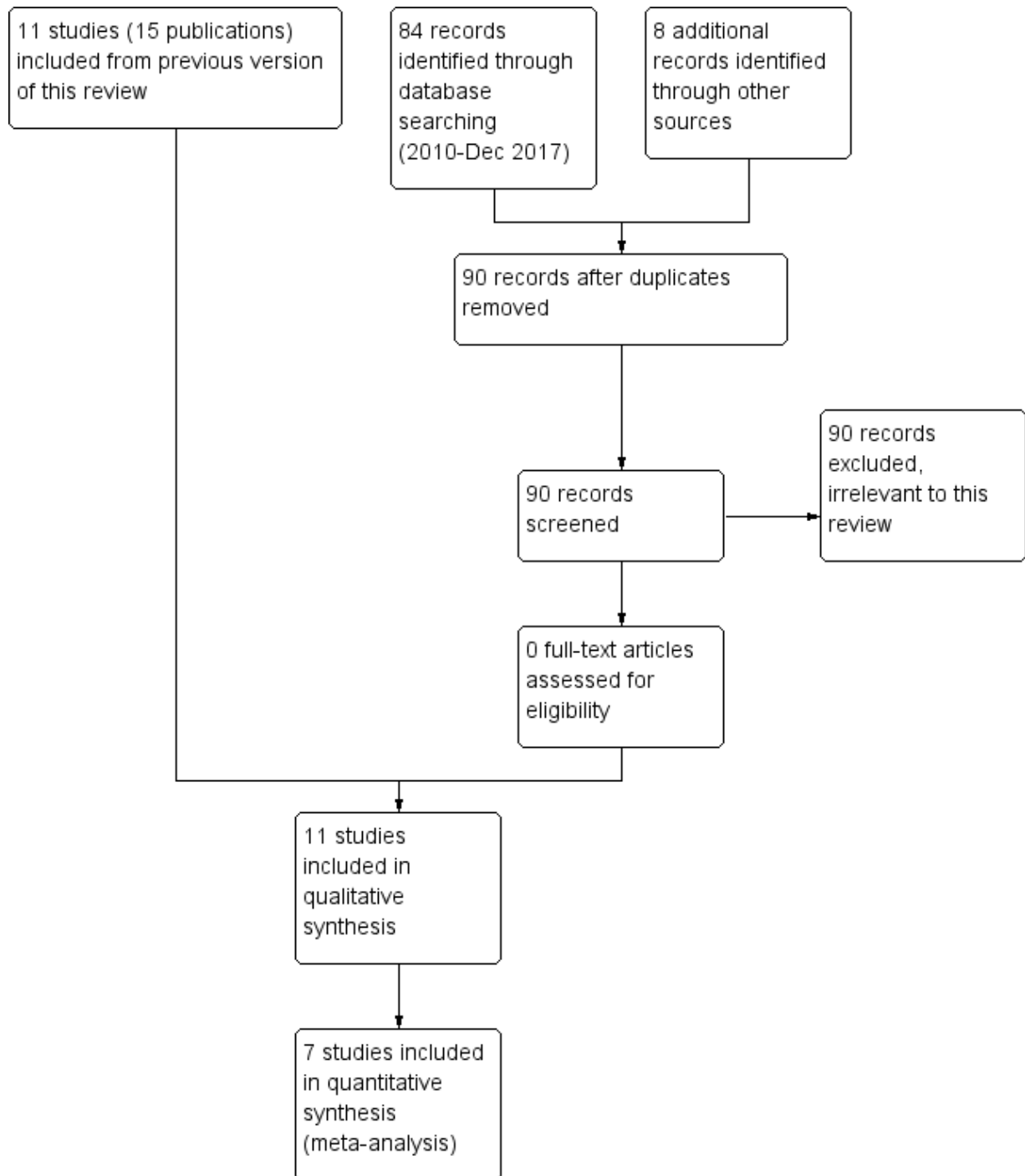
Results of the search

For the original review, we screened 105 abstracts of papers from the initial searches. After excluding those that were clearly ineligible, we obtained full texts for 25. An additional 40 articles were identified from bibliographies and references provided by pharmaceutical companies. Commonwealth Serum Laboratories provided another 70 references from an independent search. We obtained full-text articles when the title and abstract indicated the study was possibly eligible. We reviewed a total of 70 full texts for possible inclusion.

The 2003 search yielded four new abstracts, including two reports of the same eligible study ([Gorse 2003](#); [Neuzil 2003](#)). The 2004 search yielded a further five abstracts, including two reports of the same eligible study ([Wongsurakiat 2003](#); [Wongsurakiat 2004a](#)). Dr Wongsurakiat identified a further study, published after the 2006 search ([Wongsurakiat 2004b](#)).

We did not identify any new eligible studies from searches conducted in December 2017 (see [Figure 1](#) and 'Characteristics of excluded studies' table for further detail).

Figure 1. Study flow diagram for 2018 update



We included 11 studies (reported in 16 publications) in this review, with 6750 participants. We wrote, requesting more information, on six of them (Cate 1977; Gorse 1995; Govaert 1994/Govaert 1994a; Treanor 1992; Treanor 1994; Wongsurakiat 2004a). Dr Treanor and Dr Cate kindly supplied individual participant data. We received a reply from Dr Gorse but he was unable to supply us with further data. Dr Wongsurakiat kindly provided useful further information.

Included studies

Eleven studies met the entry criteria (see 'Characteristics of included studies' table); all were RCTs, using a parallel group design. All studies were double-blind and placebo-controlled, except for Gorse 1995 and Gorse 1997. These two studies were single-blind and compared intra-muscular inactivated vaccine and intranasal live attenuated vaccine with intra-muscular inactivated vaccine and intranasal placebo. Because these studies assessed the additional benefit of a second vaccine, we assessed them as a separate comparison in this review.

Population

Six of the 11 trials in this review studied participants with COPD or chronic bronchitis alone (Fell 1977; Gorse 1997; Gorse 2003; Howells 1961; MRC 1980; Wongsurakiat 2004a). These studies ranged in size from 29 participants in Gorse 1997, to 2215 in Gorse 2003, and included a total of 2469 participants. The other five trials were conducted in older or chronically ill people, or both, a proportion of whom had chronic lung disease. In these studies, the percentage of people with chronic lung diseases varied from 32% in Gorse 1995, to 5% in Cate 1977. From these authors, we sought individual participant data for the subgroup with chronic lung disease, in particular COPD. Where possible, data from the lung disease subgroup are included, although in none of these studies was it possible to ascertain whether this lung disease subgroup had COPD. The studies that included a minority of people with chronic lung disease are described in the discussion section for comparison with the six studies carried out exclusively in people with COPD.

The following descriptions refer only to the six studies specifically investigating influenza vaccination in COPD or chronic bronchitis alone:

Timing: three studies were conducted during winter months (Fell 1977; Gorse 2003; Howells 1961).

Setting: Fell 1977 was in a group practice, and four were in hospital outpatient clinics (Gorse 1997; Gorse 2003; Howells 1961; Wongsurakiat 2004a).

Duration: length of trials varied from as little as three weeks with MRC 1980, to one year (Wongsurakiat 2004a).

Inclusion and exclusion criteria: Howells 1961, MRC 1980, and Fell 1977 studied people with chronic bronchitis. Gorse 1997, Gorse 2003, and Wongsurakiat 2004a specifically studied people with pre-existing COPD, categorised by FEV₁/FVC ratio less than 70% (forced expiratory volume in the first second/Forced vital capacity). Exclusion criteria were varied. They were explicit in Gorse 1997, Gorse 2003, Wongsurakiat 2004a, and MRC 1980, limited in Howells 1961 to Grade 4 bronchitis, and were not reported at all in Fell 1977.

Participant characteristics: the mean age was 67.3 years in the five studies that reported it (Fell 1977; Gorse 1997; Gorse 2003; Howells 1961; Wongsurakiat 2004a). The percentage of males ranged from 64% in Fell 1977 to 100% (Gorse 1997). The latter was a study in US veterans.

Comorbidities: 31% of the treatment group in Gorse 1997 had underlying liver disease. Both treatment and control groups in this study had similar proportions of other underlying diseases. 30% of the treatment group of Fell 1977 was on digoxin, and 8% had coexistent asthma and chronic bronchitis. In Gorse 2003, 95% had comorbidities, and in Wongsurakiat 2004a, this level was 33%.

Smoking history: 97% of the participants of Gorse 1997 had a smoking history, 93% in Fell 1977, 95% in Gorse 2003, and 96% in Wongsurakiat 2004a.

Lung function: the mean peak flow was 280 L/min from the two studies that reported these measurements. Wongsurakiat 2004a stratified the participants in the study by baseline FEV₁. Thirty-six per cent of people had an FEV₁ ≥ 70% predicted, 26% an FEV₁ of 50% to 69%, and 38% an FEV₁ < 50%. The mean baseline FEV₁ in Gorse 2003 was 1.38 L (43.5% predicted).

The treatment and control samples were generally well matched, except in Fell 1977, where baseline adverse symptoms were higher in the vaccinated group. This particular study was unusual in that it used the early post vaccination symptoms as the baseline for assessing late post vaccination symptoms. In this study, despite randomisation, there was a significant difference between treatment and control in baseline symptom scores, serum antibody levels, and comorbidities. No details of baseline characteristics were provided by one study (MRC 1980).

Intervention

Vaccination type: two studies used inactivated virus (Howells 1961; Wongsurakiat 2004a). Four studies assessed the effects of live attenuated intranasal virus vaccines (Fell 1977; Gorse 1997; Gorse 2003; MRC 1980), with Gorse 1997 and Gorse 2003 assessing the add-on benefit of live intranasal virus, while both treatment and control groups received inactivated virus vaccine intramuscularly. We examined these studies separately in the analysis.

Match between vaccine and influenza strains: [Fell 1977](#) reported that their study was carried out in a non-epidemic year. [Wongsurakiat 2004a](#) reported their study was carried out in a non-epidemic year; however, there was a good match between the influenza that did occur and the serotypes in the vaccine. [Gorse 2003](#) reported a regional outbreak in the study area, with a virus antigenically similar to a vaccine strain. The other studies did not report the match.

Outcome measures

Clinical outcomes that could be evaluated included: exacerbations ([Fell 1977](#); [Gorse 1997](#); [Gorse 2003](#); [Howells 1961](#); [Wongsurakiat 2004a](#)), hospitalisations, lung function, adverse effects, and mortality. An assessment of serological outcomes alone was not the purpose of this review. Outcomes were defined as 'early' and 'late' to try and address whether vaccination led to an increase in exacerbations before immunity had developed. We had planned to define 'early' as one to two weeks after vaccination, but [Howells 1961](#) used a period of three weeks, and [Wongsurakiat 2004a](#), four weeks. [Wongsurakiat 2004a](#) recorded all acute respiratory infections (ARIs; total of 269 events), which were then subdivided by presentation into common cold (85 events), influenza-like illnesses (20 events), acute exacerbations (161 events), and pneumonia (three events). Thus, the commonest presentation was 'acute

exacerbation' (60% of events). He also conducted an economic evaluation ([Wongsurakiat 2003](#)). [Gorse 2003a](#) assessed health status by the chronic lung disease index (CLDI), reported by vaccination status.

Dropouts: there was a range of 0% to 19% of participant withdrawals. There were none reported in [Gorse 1997](#). In the [MRC 1980](#) multi-centre study, 16 participants from one centre had no baseline data and 15 had incomplete records. In [Gorse 2003](#) (the largest study with 2215 participants), 9% dropped out. In [Wongsurakiat 2004a](#), three out of 125 participants dropped out.

Excluded studies

The main reasons for study exclusion were a lack of randomisation, and absence of primary outcome data ([Gorse 1988](#); [Gorse 1996](#); [Lama 1998](#)). We excluded another two studies because they lacked a placebo control ([Ambrosch 1979](#); [MRC 1959](#)). See 'Characteristics of excluded studies' table for full details.

Risk of bias in included studies

See [Figure 2](#) for a summary of the 'Risk of bias' assessments. We judged many domains as unclear risk of bias, due to lack of detail present in the publications. This is unsurprising, considering all included trials were published in 2004 or earlier, when standards and guidelines for reporting were less stringent.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cate 1977	?	?	?	?	?	?	?
Fell 1977	?	?	+	+	+	?	?
Gorse 1995	?	?	?	-	?	?	?
Gorse 1997	?	?	?	?	+	?	?
Gorse 2003	+	?	?	?	?	?	?
Govaert 1994	+	+	+	+	+	?	?
Howells 1961	?	+	+	+	+	?	?
MRC 1980	?	?	?	?	-	?	?
Treanor 1992	?	?	?	?	+	?	?
Treanor 1994	?	?	?	?	+	?	?
Wongsurakiat 2004a	+	+	+	?	+	?	?

Allocation

We judged three trials ([Gorse 2003](#); [Govaert 1994](#); [Wongsurakiat 2004a](#)) at low risk of bias for random sequence generation, but the remaining eight studies reported insufficient information to permit a judgement. We judged three trials ([Govaert 1994](#); [Howells 1961](#); [Wongsurakiat 2004a](#)) to be at low risk of bias for concealment of the allocation sequence, while the remaining eight were unclear.

Blinding

We judged four trials to be at low risk for performance bias ([Fell 1977](#); [Govaert 1994](#); [Howells 1961](#); [Wongsurakiat 2004a](#)) and three at low risk of detection bias ([Fell 1977](#); [Govaert 1994](#); [Howells 1961](#)) as they described suitably identical placebos, however, the remaining studies were unclear; this was due either to not describing the nature of the placebo, the nurse delivering the intervention not being blinded, or a lack of detail about blinding procedures.

One trial did not blind the outcome assessor and consequently, we marked it as high risk of bias ([Gorse 1995](#)). We judged three as low risk because they used blinded outcome assessors, but seven studies didn't describe this in sufficient detail to permit a judgement other than unclear.

Incomplete outcome data

We judged one study to be at high risk of attrition bias owing to the fact that 11 of the vaccinated participants were excluded from the study from a single centre ([MRC 1980](#)). Seven studies were judged to be at low risk ([Fell 1977](#); [Gorse 1997](#); [Govaert 1994](#); [Howells 1961](#); [Treanor 1992](#); [Treanor 1994](#); [Wongsurakiat 2004a](#)), and three were at unclear risk ([Cate 1977](#); [Gorse 1995](#); [Gorse 2003](#)).

Selective reporting

All studies were reported in insufficient detail to permit a decision.

Other potential sources of bias

None noted.

Effects of interventions

See: [Summary of findings for the main comparison](#) Influenza vaccine compared to placebo for chronic obstructive pulmonary disease (COPD)

Influenza vaccination versus placebo

Results that follow relate to the six trials in people with COPD, chronic bronchitis, or both.

Primary outcome

Exacerbations of COPD

Two studies in 180 participants with COPD, chronic bronchitis, or both (both used inactivated virus vaccination) reported continuous data for exacerbation rates ([Howells 1961](#); [Wongsurakiat 2004a](#)). Vaccination significantly reduced the number of exacerbations per participant during the follow-up period (MD -0.37 exacerbations, 95% CI -0.64 to -0.11; $P = 0.006$; two RCTs, 180 participants; [Analysis 1.1](#)).

We determined the number of early or late exacerbations per participant by further interpretation of the data. For the placebo group of [Howells 1961](#), 20 participants experienced 24 exacerbations. Since there were eight participants experiencing early exacerbations, there would have been at least eight early exacerbations. Similarly, since there were 12 participants experiencing late exacerbations, there would have been at least 12 late exacerbations. Thus the assumption was made that in order to make up the total of 24 exacerbations, there were two more early and two more late exacerbations. In support of this conclusion is the statement in the paper that similar numbers of early exacerbations were recorded in both placebo and vaccinated groups. Sensitivity analysis using 12 early and 12 late exacerbations showed no difference in the significance of our results. [Wongsurakiat 2004a](#) provided the number of early and late exacerbations without a spread. As the number of early exacerbations was small, it was assumed that these occurred in separate participants, and we calculated the SD accordingly. We allocated the SD of the 'total exacerbations' per participant provided by the author to the 'late exacerbations'.

While there was no statistically significant effect of vaccination on early exacerbation rates (MD 0.01, 95% CI -0.11 to 0.13; $P = 0.87$; two RCTs, 180 participants; [Analysis 1.2](#)), inactivated influenza vaccination significantly reduced late exacerbation rates (MD -0.39, 95% CI -0.61 to -0.18; $P < 0.001$; two RCTs, 180 participants; [Analysis 1.3](#)).

[Wongsurakiat 2004a](#) reported no clear difference in the overall incidence or severity of acute respiratory infections (ARIs) between the vaccination and placebo groups.

Participants with at least one exacerbation or acute respiratory illness in the study period

Three studies, with 444 participants, contributed to this outcome (Fell 1977; Howells 1961; Wongsurakiat 2004a). There was no significant difference between vaccination and placebo-treated participants with respect to the number of participants having at least one exacerbation or acute respiratory illness (Peto 0.81, 95% CI 0.44 to 1.48; $P = 0.49$; three RCTs, 444 participants; Analysis 1.4). However, there was significant heterogeneity in this result ($P = 0.001$), so it must be treated with caution. A sensitivity analysis by vaccine type showed that if only the two studies that used inactivated virus vaccine were included, this heterogeneity was removed, with a reduction in the number of participants with at least one exacerbation or acute respiratory illness in the study period with vaccination (OR 0.42, 95% CI 0.21 to 0.85; $P = 0.02$; two RCTs, 180 participants). Results from Howells 1961 and Wongsurakiat 2004a showed no significant difference in the number of individual participants with early exacerbations (Peto 1.08, 95% CI 0.52 to 2.26; $P = 0.84$; two RCTs, 180 participants; Analysis 1.5), but Howells 1961 did show a significant reduction in the number of participants with late exacerbations (Peto 0.13, 95% CI 0.04 to 0.45; $P = 0.002$; one RCT, 55 participants; Analysis 1.6). In Wongsurakiat 2004a, nine of 76 exacerbations in the vaccination group were early; while 10 of 85 exacerbations in the placebo group were early. We assumed that they each occurred in a different participant. Clearly, over the course of the study, there were some participants who had more than one exacerbation; the number of individual participants in each group who had late exacerbations was not reported.

Days of disability from respiratory illness

Not reported.

Hospital admissions

Two studies, with 180 participants, reported data on this outcome (Howells 1961; Wongsurakiat 2004a). There was no significant effect of vaccination over placebo on hospitalisation (Peto 0.33, 95% CI 0.09 to 1.24; $P = 0.52$; two RCTs, 180 participants; Analysis 1.7). In Howells 1961 there were no hospitalised participants in the treatment group, and only two in the control group. Wongsurakiat 2004a reported the number of hospitalisations for influenza-related respiratory infections only. There were two in the vaccine group and five in the placebo group. They reported no clear difference in the severity of acute respiratory infections between groups, including no clear difference in the chance of being hospitalised ($P = 0.2$ by log rank test). None of the vaccinated participants required mechanical ventilation for acute respiratory infection, whereas five in the placebo group did.

Mortality

Two studies, with 180 participants, reported all-cause mortality; there was a total of 13 deaths (Howells 1961; Wongsurakiat

2004a). There was no significant difference between vaccine and placebo-treated groups (Peto 0.87, 95% CI 0.28 to 2.70; $P = 0.81$; two RCTs, 180 participants; Analysis 1.8). One control participant died during an acute exacerbation (Howells 1961). In Wongsurakiat 2004a, 12 of 125 participants died (eight of which were unrelated to acute respiratory infection); of those that were ARI related there was no demonstrable difference between vaccination and control (OR 0.33, 95% CI 0.03 to 3.24; Analysis 1.9).

Secondary outcomes

Lung function

One small study (55 participants) reported FEV₁ changes from baseline (MRC 1980). There was no significant difference between the groups' overall change in FEV₁ (MD -0.02, 95% CI -0.12 to 0.08; Analysis 1.10), nor in their change in early FEV₁ (MD -0.01, 95% CI -0.09 to 0.07; Analysis 1.11) but there was insufficient evidence to prove no difference in treatments. Wongsurakiat 2004b reported no clear difference in lung function between groups at one and four weeks after vaccination.

Adverse effects and acute respiratory illness subsequently proven to be influenza-related

Wongsurakiat 2004b evaluated local and systemic symptoms in the weeks following vaccination. There was no significant difference in the incidence of systemic adverse effects between the treated and placebo groups (OR 0.74, 95% CI 0.31 to 1.74; Analysis 1.12). The only significant difference observed was in the local reaction at the injection site; seen in 27% of vaccinees and 6% of the placebo group (OR 5.57, 95% CI 1.75 to 17.71; Analysis 1.13).

Fell 1977 (44 participants) reported early (within two weeks of vaccination) upper respiratory tract symptoms. One vaccinated participant also developed pleuritic pain. There was no statistically significant difference between vaccinated and control participants in terms of breathlessness or tightness (Peto 1.28, 95% CI 0.38 to 4.31; $P = 0.696$; Analysis 1.14; Analysis 1.15). The occurrence of a wheeze within the first two weeks was greater in vaccinated participants (Peto 3.57, 95% CI 1.10 to 11.56; $P = 0.034$; Analysis 1.16). No statistically significant difference between groups was noted for cough (Peto 4.09, 95% CI 0.74 to 22.49; $P = 0.106$; Analysis 1.17).

Two studies assessed the clinical presentations to see if they were related to influenza virus infection (Howells 1961; Wongsurakiat 2004a). Howells 1961 used the hemagglutination inhibition (HAI) test, and Wongsurakiat 2004a used both serology and virology swabs. Overall, inactivated influenza vaccination resulted in a marked decrease in influenza-related respiratory infections (OR 0.19, 95% CI 0.07 to 0.48; $P < 0.001$; two RCTs, 180 participants; Analysis 1.18). The effect was similar whether participants had

mild, moderate, or severe COPD, or chronic bronchitis (test for heterogeneity $P = 0.73$). Influenza accounted for 8% (13/161) of the acute exacerbations in the [Wongsurakiat 2004a](#) study. Further, the study demonstrated that there was no significant difference in early ARI (OR 0.72, 95% CI 0.34 to 1.50; [Analysis 1.19](#)).

In terms of sputum production no significant difference was noted between the vaccination group and control (Peto 2.03, 95% CI 0.48 to 8.66; $P = 0.338$; [Analysis 1.20](#)). Breathlessness was recorded significantly less often ($P < 0.05$) in the 5 of 21 participants who had a serological response to vaccination than in the placebo group.

The [Treanor 1994](#) paper reports that 12% of the older people vaccinated with live attenuated virus reported systemic symptoms of malaise and myalgias, as did 10% of inactivated virus vaccinees. The placebo group reported none. Twenty-six per cent of those who received the live virus reported lower respiratory tract symptoms of hoarseness and non-productive cough, as did 13% of those who received the inactivated virus, and 9% of those who received placebo. Twenty-nine per cent of those who received live virus reported upper respiratory tract symptoms of sneezy, runny, or stuffy nose or sore throat, as did 37% of those who received the inactivated virus, and 18% of those who received placebo. Six per cent of those who received the live virus experienced fever, as did 2.5% of those who received the inactivated virus. None of the placebo group reported any febrile illness. In the subgroup of participants with chronic lung disease in this study, of the 20 participants who received some form of influenza vaccination, 11 reported a total of 20 adverse effects, while of the two participants who received the placebo, one participant reported two adverse effects.

The [Govaert 1994](#) paper reports 25% of high risk vaccinees experienced one or more adverse reactions, compared to 16% of those who received placebo, however, effects, if any, appeared to have been mild and transitory. Eleven per cent of all vaccinees experienced systemic effects, as did 9.4% of the placebo recipients. When a multiple regression analysis that looked at the effect of lung disease on systemic adverse reactions was performed, the difference between vaccinees and the placebo group was statistically significant (OR 1.95, 95% CI 1.24 to 3.07). Local effects were experienced by 17.5% of all vaccinees in this study, but in only 7.3% of the placebo group ($P < 0.001$). This study also showed that differences between the treatment groups for adverse effects reduced with age.

The [Cate 1977](#) paper reports 7.8% of those who received inactivated virus reported mild systemic reactions, and 4.9% reported moderate to severe ones. The control group who received saline placebo reported similar numbers of mild systemic reactions, but no moderate to severe ones. Most systemic reactions resolved within two days of vaccination. In the vaccinated group, 18.5% of participants experienced erythema (local redness) with or without induration (hardening) at the injection site, compared to none in the control group.

Cost effectiveness

Wongsurakiat calculated the incremental cost effectiveness ratios of inactivated virus vaccination by applying the direct medical costs from a Thai health provider perspective to the results obtained in the RCT ([Wongsurakiat 2004a](#)). There were two types of cost: cost of treatment as an outpatient, and cost of hospitalisation. More than 90% of the costs of influenza-related acute respiratory illness (ARI) were costs of hospitalisation. In people with moderate or severe COPD, more than 90% of the hospital costs were due to costs of treating those who required mechanical ventilation. The costs were based on 1997 prices using Thai Bhat (THB), with vaccination costing 248.40 THB. In the paper the author concluded that cost savings would be 629,538 THB for every 100 people with mild COPD vaccinated, 184 THB for every 100 with moderate COPD, and 680,647 THB for those with severe COPD, i.e. vaccination was very cost effective, but more so in those with more severe COPD.

Live attenuated intranasal vaccine plus inactivated intramuscular vaccine versus placebo intranasal or inactivated intramuscular vaccine

Four studies (2817 participants) evaluated the effect of adding live attenuated virus to inactivated virus vaccination ([Gorse 2003](#); [Gorse 1995](#); [Gorse 1997](#); [Treanor 1992](#)). The [Gorse 1997](#) and [Gorse 2003](#) studies were specifically conducted on people with COPD, but the others were carried out in older people, only a minority of whom had lung disease. For simplicity, 'treatment' refers to the live intranasal plus inactivated group, and 'control' to the placebo intranasal plus inactivated vaccine group. Only the [Gorse 1997](#) and [Gorse 2003](#) studies provided data in a form that could be used in analyses.

Primary outcomes

Exacerbations of COPD

There were no significant differences in the total number of exacerbations per participant between the two groups (MD 0.01, 95% CI -0.35 to 0.37; $P = 0.96$; two RCTs; 1137 participants; [Analysis 2.1](#)). In the former, exacerbations were defined as the occurrence of increased cough, shortness of breath, sputum production, or a combination. There was no clear difference in either the early exacerbation rate per participant (MD -0.21, 95% CI -0.55 to 0.13; $P = 0.23$; one RCT, 29 participants; [Analysis 2.2](#)), or late exacerbations (MD -0.23, 95% CI -0.08 to 0.54, $P = 0.14$; one RCT, 29 participants; [Analysis 2.3](#)) between groups. In the latter, participants were asked to report any febrile influenza-like illness (ILI). This was then investigated by serology, swabs, or both to determine if it was influenza-related.

There was no clear difference in the number of participants who reported improvements in their exacerbations (Peto 1.48, CI 0.30

to 7.42; $P = 0.63$; one RCT, 29 participants; [Analysis 2.4](#)); this finding was consistent when broken down into early improvements (Peto 1.65, 95% CI 0.16 to 17.49; one RCT, 29 participants; [Analysis 2.5](#)), and late improvements (Peto 1.26, 95% CI 0.19 to 8.43; one RCT, 29 participants; [Analysis 2.6](#)).

In the Gorse 2003a paper, a univariate and stepwise multivariate logistic regression analysis of associations was performed, with at least a 15% improvement or worsening in health status, as measured by the chronic lung disease symptom index. This was a secondary study outcome. Analysis showed that 217 (21%) in the group that received inactivated vaccine plus intranasal vaccine had at least a 15% improvement at the end of the study over pre-vaccine status, compared with 163 (16%) in the control group that had received inactivated virus vaccine alone (OR 1.39, CI 1.10 to 1.74).

Days of disability from respiratory illness

Not reported

Hospital admissions

Not reported

Mortality

In the [Gorse 2003](#) paper, the largest study with 2215 participants, there were 64 deaths (3%); there was no difference between intervention and control groups for this outcome (OR 1.14, 95% CI 0.69 to 1.87; one RCT, 215 participants; [Analysis 2.7](#)). Of the 64 participants who died, five participants in the treatment group and two in the placebo group had influenza-like illnesses, four of which were laboratory-documented.

Secondary outcomes

Lung function

There was no consistent effect on early changes in lung function in [Gorse 1997](#) either in terms of percent predicted FEV₁ (MD 2.90; 95% CI -14.14 to 19.94; one RCT, 20 participants; [Analysis 2.8](#)) or FEV₁/FVC ratio (MD -0.90; 95% CI -12.02 to 10.22; one RCT, 29 participants; [Analysis 2.9](#)). The results from [Gorse 2003](#) suggested significant effect on lung function in favour of the active virus group (MD -0.05; 95% CI -0.10 to 0.00, one RCT, 2215 participants; [Analysis 2.10](#)), however, there was a significant difference between the two study groups at baseline reported in the paper, with the active group being lower, and improving more. The investigators reported that they did not believe this to be clinically important. The lung functions of the two groups at the end of the study were similar. [Gorse 1997](#) reported that more participants in the active virus group experienced a one category improvement in

lung function compared to control, however, this was found to be non-significant (Peto 4.00; 95% CI 0.68 to 23.60; one RCT, 29 participants; [Analysis 2.11](#)). The investigators also reported that a small number of participants in the active virus group experienced a one-category decrease in lung function, however, once again this was found to be non-significant (Peto 7.04; 95% CI 0.66 to 74.68; one RCT, 29 participants; [Analysis 2.12](#)). [Gorse 2003](#) measured FEV₁ at the end of the study period and found that there was no evidence of an effect on lung function for those receiving the active virus compared to control (MD -0.05; 95% CI -0.16 to 0.06; one RCT, 382 participants; [Analysis 2.13](#)).

The [Treanor 1994](#) paper reported no significant differences in lung function between groups. From data supplied by the author, for the subgroup with underlying chronic lung disease, those who were vaccinated had a mean decrease in FEV₁ from 1.8 litres to 1.6 litres, whereas for the one placebo recipient for whom lung function was recorded, there was a small increase in FEV₁.

Adverse effects

There were no significant differences in the reports of new upper respiratory tract symptoms between the groups in the [Gorse 1997](#) study (Peto 1.89, 95% CI 0.45 to 8.04; $P = 0.39$; one RCT, 29 participants; [Analysis 2.14](#)).

There were no statistically significant differences between treatment and control for any adverse effects in the early period (Peto 0.86, 95% CI 0.63 to 1.17; $P = 0.34$; two RCTs, 2244 participants; [Analysis 2.15](#)). When evaluating the results of [Gorse 2003](#) alone, the number of days participants displayed early signs and symptoms favoured control (MD 0.40; 95% CI 0.19 to 0.61; one RCT, 2215 participants; [Analysis 2.16](#)). Furthermore, analysis of the number of participants with early adverse events, divided in to sub-groups by type, showed no evidence of an effect between intervention or control for any single adverse effect; however, the pooled effect was significantly in favour of the active virus group (OR 0.49; 95% CI 0.26 to 0.92; $P = 0.027$; one RCT, 2215 participants; [Analysis 2.17](#)).

There was some evidence of an effect for adverse effects in the late period following vaccination, favouring the control group (Peto 2.33, 95% CI 1.22 to 4.46; $P = 0.011$; two RCTs, 2244 participants; [Analysis 2.18](#)). [Gorse 2003](#) stated in their paper that the proportion of participants with adverse effects at least possibly related to immunisation, did not differ between groups. There were, however, significantly fewer participants with early signs and symptoms in the group receiving inactivated virus vaccine only, as well as a smaller number of participants with late adverse effects. In this group, there was a total number of 99 events in 88 individuals (7.9% of total).

From one RCT ([Gorse 2003](#)) there was no evidence of an effect between active virus and control for the outcome of influenza-related ARI (OR 0.84; 95% CI 0.57 to 1.24; one RCT, 2215 participants; [Analysis 2.19](#)). Further, data from the same study demon-

strated no statistical difference in the number of participants with at least one influenza-like illness between groups (OR 1.07; 95% CI 0.86 to 1.33; one RCT, 2215 participants; [Analysis 2.20](#)).

In [Treanor 1992](#) (523 participants), which was a study with a lung disease subgroup, 24% of the treatment group experienced respiratory illnesses compared to 28% of the control group. In the treatment group, 12% of participants experienced an influenza-like illness, compared to 16% of the control group. In the control group, there were two cases of laboratory-documented influenza A infection, which resulted in hospitalisation. One death due to influenza virus A infection occurred in the control group, compared to none in the treatment group. This study also showed that 10.1% of the treatment group experienced early adverse reactions, compared to 8.3% of the control group. In the treatment group, 3.9% of participants reported early systemic effects consisting of headache, myalgias, malaise, or fatigue, compared to 5.0% of the control group. Of the control group, 1.1% reported fever, and 2.7% of them reported respiratory symptoms consisting of rhinitis or pharyngitis. However, 2.2% of the treatment group reported fever, and 6.7% reported respiratory symptoms. Five per cent of the live virus vaccinees experienced sore arms, compared to 18% of the inactivated virus vaccinees. None of the placebo group reported sore arms. The tendency for inactivated virus to cause local side effects to a greater extent than live virus was statistically significant in this study ($P = 0.02$).

In the [Gorse 1995](#) paper it was reported that 12% of all participants experienced transient, mild pain at the site of local intramuscular injection.

Acute respiratory illness subsequently proven to be influenza-related

Not reported

Cost effectiveness

Not reported

DISCUSSION

Summary of main results

This systematic review evaluated the few RCTs that have reported on the effects of influenza vaccination in people with COPD. Despite iterative and exhaustive searches, we only identified 11 studies that met our inclusion criteria, with only six of these having been performed solely on 2562 people with COPD or chronic bronchitis. The entry criteria for these studies were variously reported, but where reported, they showed that the majority of participants had a smoking history and airway obstruction. The earlier studies

enrolled younger participants than the more recent studies. The other studies in the review included older participants, those with chronic illnesses, or both, of whom a subset had chronic lung disease.

Influenza vaccination versus placebo

There was no evidence of any significant effect on hospitalisation, mortality rates, lung function decline, or exercise tolerance between the vaccine and placebo groups. For the infrequent outcomes of hospitalisation and mortality, the studies were probably too small to detect any difference. One participant in the control group in [Gorse 2003](#) developed Guillain-Barré syndrome, although further details of severity and outcome were not provided. Thus, this review showed no evidence of an increase in Guillain-Barré syndrome with vaccination.

We did not intend to evaluate serological outcomes, such as a significant rise in antibody titre in this review. However, some authors looked at outcomes in the subgroup with a serological response to vaccination. The limited data from these comparisons was consistent with that of the clinical outcomes alone. It also suggested that if people seroconverted, they had fewer adverse effects.

[Neuzil 2003](#) and [Wongsurakiat 2004a](#) studied the clinical presentation of symptomatic laboratory-documented influenza (LDI). Using stepwise logistic regression, [Neuzil 2003](#) found that during an influenza outbreak period, only fever and myalgia were associated with LDI. Together, they had a positive predictive value of 41%. In [Wongsurakiat 2004a](#), the most specific presentation of LDI was 'influenza-like illness' (namely generalised aches, fever and headache, with or without respiratory tract symptoms). However, LDI occurred in only 10% of participants, indicating a low positive predictive value of this symptom complex for LDI. The conclusion was that it was difficult to diagnose influenza infection clinically, with certainty, in people with COPD.

The one cost-effectiveness analysis that was conducted, based on an RCT, suggested that inactivated virus vaccination was highly cost-effective in people with COPD, particularly those with severe airways obstruction. This analysis took into account direct health care costs only, and not indirect costs, or any future health care costs that might be incurred by people with COPD living longer. It was conducted in a non-epidemic year, and therefore, underestimated the benefits that would be gained in an epidemic year.

Influenza vaccinations were generally well tolerated. There was a significant increase in local effects ranging from pain at the site of injection, to erythema, with or without induration, but all effects appeared to be mild and transitory. These findings were consistent with results from [Nichol 1994](#), a large, well conducted randomised placebo-controlled trial of influenza vaccination in healthy adults, in which they observed no significant side effects of vaccination, except for arm soreness (63.8% of vaccinees compared to 24.1% placebo; $P = 0.001$).

One of the main barriers to increasing vaccination rates in people with COPD is the concern of patients and their health professionals that vaccination may increase early exacerbations, before immunity has developed. The evidence in this review showed that inactivated virus vaccination did not have a significant impact, on either the total number of early exacerbations, or on the number of people with COPD who had early exacerbations or early acute respiratory illnesses.

Live attenuated intranasal plus inactivated intramuscular versus placebo intranasal plus inactivated intramuscular vaccination

Because of the risk of influenza and the lesser immunogenicity of vaccines in the elderly (including people with COPD), there is interest in the extra protection afforded by the addition of live attenuated virus to inactivated virus vaccination. This approach to clinical trial design has the advantage that high-risk groups are not denied vaccination, but larger numbers of participants are needed if the study is to have sufficient power to detect an effect. The studies in this review showed that there was no greater protective effect of live plus inactivated vaccine over inactivated vaccine alone in any of the clinical outcomes of interest. On the other hand, there may be a slight increase in adverse effects with the combination, although this was seen only in [Gorse 2003](#), and the investigators did not regard it as significant.

Overall completeness and applicability of evidence

Recent literature searches indicated that new RCTs for influenza vaccine in COPD have stagnated, with no studies meeting our inclusion criteria since 2006. This is perhaps a reflection of consistent recommendations in major clinical guidelines for COPD management over the last decade, based on existing observational studies and limited placebo controlled RCTs. The most recent updated search for this review returned a number of studies investigating immunostimulants for COPD management, and while outside the scope of this review, may present an adjunct to disease management, by preventing respiratory tract infection and subsequent COPD exacerbations ([Collet 1997](#)).

Quality of the evidence

The main issue was that there were few RCTs of influenza vaccinations in COPD, and data were generally not reported in the same way. Where data were combined, confidence intervals were wide, making it difficult to determine whether 'no evidence of effect' actually meant 'evidence of no effect', or an effect was missed. However, the studies that were found were of satisfactory methodological quality, with almost all low or unclear risk of bias assessments in all domains. The effects observed in RCTs were internally

consistent, biologically plausible, and supported by observational studies. Furthermore, results from the two main studies had little heterogeneity between them.

Potential biases in the review process

We performed the review in accordance with a pre-published protocol to reduce biases. However, we did make some post hoc changes, See [Differences between protocol and review](#).

Agreements and disagreements with other studies or reviews

In the original Cochrane Review in 2000, we wrote "the strong recommendations in current guidelines make it ethically difficult now to conduct large, randomised, placebo-controlled trials of influenza vaccination, even though it would appear desirable to do so". Interestingly, and without our knowledge, such a trial had been conducted but not reported at the time ([Wongsurakiat 2004a](#)). The authors believed the study to be justified on the grounds that prior to 1997, influenza vaccine had been unavailable in Thailand. This study of inactivated influenza vaccination tracked 125 participants over one year following vaccination, with only three dropouts. An analysis with the results from [Howells 1961](#), another carefully conducted RCT, showed that inactivated influenza vaccine significantly reduced COPD exacerbations with an effectiveness $((1-RR) \times 100\%)$ of over 60%. Moreover, inactivated influenza vaccination had an effectiveness of over 80% in reducing influenza-related acute respiratory illness (ARI).

The effectiveness of vaccination was confined to late exacerbations, i.e. those occurring more than three to four weeks after inactivated virus vaccination. The investigators chose to study this time period specifically, in order to allow time for immunity to develop. The authors of [Wongsurakiat 2004a](#) and others made the point that the effectiveness of the vaccine in reducing exacerbations depended on how much influenza-related ARI was present during the study period, i.e. whether there was an epidemic or not. [Fell 1977](#) and [Wongsurakiat 2004a](#) were conducted in non-epidemic years, whereas [Howells 1961](#) was undertaken in an epidemic year. Influenza virus caused 8% of the 'acute exacerbation' and 10% of the 'influenza-like illness' presentations in [Wongsurakiat 2004a](#), but was responsible for 37% of the acute exacerbations in [Howells 1961](#).

To further emphasise this point, the findings of [Howells 1961](#) and [Wongsurakiat 2004a](#) were both consistent with [Govaert 1994a](#), a large ($N = 1906$), high quality RCT conducted in older people, 9% of whom had chronic lung disease. It assessed the effect of inactivated influenza virus vaccination on the development of influenza or influenza-like illnesses. When such illnesses were diagnosed by clinical assessment, the relative risk for influenza-related illness was 0.53 (95% CI 0.39 to 0.73). When the diagnosis was

made using the International Classification of Health Problems in Primary Care (ICHPPC-2-Defined), the relative risk was 0.83 (95% CI 0.65 to 1.05). However, post hoc analysis showed that during an epidemic, the relative risk for influenza-related illness diagnosed by clinical assessment was 0.41 (95% CI 0.28 to 0.61), and by ICHPPC-2-Defined criteria was 0.74 (95% CI 0.24 to 1.00). This study also demonstrated an overall halving of influenza risk by vaccination. Results for subgroups of those participants at high risk (including those with lung conditions) and those over the age of 70 years were not statistically significant, but the numbers in each group were small. In [Treanor 1994](#), a study of older people who were in institutions where laboratory-documented outbreaks of influenza A occurred, only 8% of the treatment group, compared to 20% of the control group, had respiratory illnesses. Similarly, only 4% of the treatment group, compared to 11% of the control group, experienced an influenza-like illness. Inactivated influenza vaccination is likely to have an even greater effect in epidemic years than seen in this review.

Even though the number of RCTs (and participants) was relatively small, the effectiveness of influenza vaccination seen in this review was consistent with that seen in large observational studies. In one of these, involving 1900 older people with chronic lung disease, those who were vaccinated had a halving of the risk of hospitalisation for pneumonia, and a 70% reduction in the risk of death during influenza seasons ([Nichol 1999](#)). A meta-analysis of 20 cohort studies of influenza vaccination in the older population showed a 56% reduction in respiratory illnesses and a 50% reduction in hospitalisation ([Gross 1995](#)). Most of these studies had been conducted in epidemic years.

AUTHORS' CONCLUSIONS

Implications for practice

There was RCT-based evidence that inactivated influenza vaccination had a clinically important and significant effect on influenza-related exacerbations, and probably an effect on the total of exacerbations in people with COPD. This effect is likely to be greater in epidemic years when the proportion of exacerbations due to influenza would be higher. The sizes of the effect were similar to those seen in cohort studies, and there was no evidence that inactivated virus vaccination caused exacerbations. The addition of intranasal live attenuated virus did not confer any added benefit.

While influenza vaccine was associated with significant reductions in exacerbation rates compared with placebo, it was associated with local adverse effects.

To reduce exacerbations in COPD overall would require a combination of approaches, including vaccination, as only a small percentage were caused by the influenza virus. In people with COPD,

symptomatic influenza infections were difficult to diagnose clinically, with any certainty.

Implications for research

The evidence of effectiveness of influenza from observational studies has been viewed by many as sufficient for the strong recommendations in COPD guidelines. These studies may be biased, as there are potentially many differences between those who volunteer to be vaccinated and those who do not. Only some of the biases can be controlled for. These strong recommendations are now supported by some good quality RCT data. It is ethically difficult to conduct further large, randomised, placebo-controlled trials of influenza vaccination, even though it would appear desirable to do so. Any planned study would need to be large, since the incidence of influenza is low (particularly in non-epidemic years) and vaccine efficacy is less than 100% in older people. The effectiveness of influenza vaccination is best determined during epidemic years, with a good match between vaccine and circulating strains, yet this is not known until the influenza season starts, by which time trials have started. For studies conducted during non-epidemic times, results from participants who seroconvert may be used as a surrogate to determine the effectiveness of immunisation, however, clinical outcomes need to be reported, particularly if cost-effectiveness is to be studied.

There are still insufficient data from large enough RCTs to determine the effect of vaccination on rarer events in the trial period, such as hospitalisation or mortality. Measures of health status should be built into clinical studies of COPD as a matter of course.

Public health and policy approaches to increasing vaccine uptake need studying and incorporation into a systematic review, as do public health and other approaches to reducing the impact of influenza outbreaks. Studies should continue to look at ways to improve the effectiveness of vaccines, or combinations of vaccines. This might include adding new vaccine types, while administering the recommended inactivated virus vaccine, or conducting short term placebo-controlled studies, at the end of which all placebo recipients are vaccinated.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Cate 1977

Methods	Duration: about 7 months Withdrawals: 8 volunteers were lost but none had experienced vaccination-related complications Follow-up schedule: adverse reactions recorded on days 1 and 2 post vaccination. HAI antibody titres at 4 weeks compared after re-vaccinations for a subgroup 5 months later	
Participants	Setting: June to Nov 1976, Texas Medical Centre, USA Number: 413; 8 withdrawals; 348 in combined vaccine groups Characteristics: all participants were ambulatory and either older (> 50 years) or high-risk adults. The average age was 64.3 (SD 7.3) years with 60.7% female participants. About 5% had lung disease, most of which was COPD. 35% were considered high-risk, due to cardiovascular complications, chronic and underlying disease Baseline characteristics: no details Comorbidities: no details Diagnostic criteria: over the age of 50 years, or adults with a chronic disorder that placed them at high risk for serious complications of influenza infection Exclusion criteria: no details	
Interventions	Vaccination type: inactivated, bivalent influenza virus vaccine (A/New Jersey/76 and A/Victoria/75) in 200/200 or 400/400 CCA units, 0.5 mL dosage intramuscularly Vaccines were either subvirion or whole Control: saline placebo, intramuscular, 0.5 mL dosage	
Outcomes	Early: days 1 and 2 post vaccination. Adverse effects were recorded as symptom scores, including systemic and local reactions. Serology; HAI antibody titres were performed at 4 weeks Late: HAI antibody titres performed again after revaccination in a subgroup, about 5 months later	
Notes	Not specifically people with COPD	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quasi-randomised
Allocation concealment (selection bias)	Unclear risk	Vaccines and placebo provided in randomly arranged coded sets of 10 dose vials, with a rotating sequence of administration

Cate 1977 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo controlled, but did not state if placebo identical-looking
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make determination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Eight volunteers lost to follow-up reported as "none known to have had any unexpected complication from the vaccination." Further details were not provided
Selective reporting (reporting bias)	Unclear risk	No trial registry record available
Other bias	Unclear risk	Used volunteers and provided reimbursement to participants. None noted

Fell 1977

Methods	Duration: 20 weeks Withdrawals: 1 (vaccinated participant developed pleuritic pain on day 14 of baseline) Follow-up schedule: during exacerbations
Participants	Setting: Nov 1975, group practice; Deddington, Oxfordshire, UK (non-epidemic conditions) Number: 45 enrolled; 22 in vaccinated group, 23 in control. 1 vaccinated participant withdrew during baseline Characteristics: 28 men (64%) and the average age was 59.43 years Baseline characteristics: The average age of the vaccinated group was 61 years and 58 years in the control group. The proportion of men in the vaccinated group was 57% but 70% in the control. Smoking histories were similar Randomisation was unsuccessful in a number of areas; symptom scores of first 2 weeks after vaccination were used. The vaccinated group had greater symptom reports (not statistically significant) and lower mean PEFR. 19% of the vaccinated group had histories of asthma and 30% were on digoxin at entry, while none in the control had either. Over 60% of the vaccinated group had circulating HAI antibody against the Wellcome Research Laboratories (WRL) 105 strain before vaccination while less than 35% of the control did Comorbidities: past history of asthma in 19% and use of digoxin in 30 % of vaccinated Diagnostic criteria: chronic bronchitis; 3 months productive cough annually for 3 years, MRC questionnaire completed. Severity of COPD unclear Exclusion criteria: none described
Interventions	Vaccination type: live attenuated, WRL-105 (A/Finland/4/74-H3N2, A/Okuda/57-H2N2), intranasal, 0.5 mL carrier, 0.25 per nostril Control: placebo, freeze-dried excipients of vaccine, indistinguishable by appearance or

	reconstitution
Outcomes	Early: adverse effects in Weeks 1 and 2 recorded by guided participant self-assessment, hospitalisation Late: respiratory scores of adverse reactions greater than baseline, antibody responses to vaccination
Notes	Prescribed use of live vaccination but was a small study, conducted in a non- epidemic setting

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation reported, however, no details regarding methods of randomisation reported
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled. "The freeze-dried excipients of the vaccine were used as placebo, which was indistinguishable from vaccine in appearance or reconstitution characteristics."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants completed self-assessments but were blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported exclusion of one participant from analyses
Selective reporting (reporting bias)	Unclear risk	No trial registry record available
Other bias	Unclear risk	Insufficient information to make determination

Gorse 1995

Methods	Duration: 4 weeks Withdrawals: no details Follow-up schedule: days 1 to 7 with immunological assays conducted on days 14 and 28
Participants	Setting: 1993 to 1994; Jefferson Barracks Division Nursing home, St Louis VA Medical Centre and at St Louis Altemheim nursing home, USA Number: 50; 25 in each of treatment and control groups Characteristics: older adults, chronically ill nursing home residents, 86% male, average

	age 74.95 years Baseline characteristics: generally comparable with average age in the treatment group being 74.3 (SE 1.6) years and 75.6 (SE 1.9) years in the control. 28% of the treatment group had lung conditions and 36% of the control. Levels of other Comorbidities, WBC counts, cholesterol, and pre-vaccination serum HAI antibodies were similar Comorbidities: heart 64%, lung 32%, neurologic 84%, diabetes mellitus 40%, GI 30%, renal 24%, tobacco use 70%, alcohol use 62% Diagnostic criteria: older adults > 60 years, (32% with lung disease) Exclusion criteria: 1. history of hypersensitivity to influenza virus vaccines and eggs, 2. receipt of influenza vaccination less than 6 months prior to study, 3. incompetence to give written informed consent, 4. current administration of any antineoplastic chemotherapy, 5. hematologic malignancy not in remission, 6. blood haemoglobin levels less than 11 g/dL	
Interventions	Vaccination type: 1. Bivalent live attenuated influenza A virus vaccine (CAV) derived from cold-adapted influenza A/Ann Arbor/6/60 (H2N2) and A/Kawasaki/9/86 (H1N1) and A/Beijing/353/89 (H3N2). Intranasal; 0.5 mL dose 2. Trivalent inactivated subvirion influenza virus vaccine (TVV). The first 26 received A/Texas/36/91 (H1N1), A/Beijing/353/89 (H3N2), B/Panama/45/90. The next 26 received A/Texaz/36/91 (H1N1), A/Beijing/32/92 (H3N2), and B/Panama/45/90 Intramuscular Control: 1. Saline placebo intranasal 2. Trivalent inactivated influenza virus vaccines (TVV), Intramuscular, identical to vaccinated group	
Outcomes	Early: adverse effects; mild upper respiratory symptoms, transient mild pain, malaise, febrile illness. Serology; virus titres determined and levels of anti-influenza A virus cytotoxic activity Late: serology, some adverse effects	
Notes	Not specifically COPD participants. There is a possible advantage of administering live attenuated with inactivated virus because in frail older people who have decreased immune responsiveness due to underlying disease, there is evidence of increased memory of anti-influenza A virus cytotoxic T cell (CTL) activity	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Of each consecutive pair enrolled, one was assigned to intervention and one to control
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination

Gorse 1995 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled. Same delivery method with participants and laboratory personnel blinded. See below - study nurse was unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	The nurse administering the immunisation was unblinded. This study nurse also “examined the vaccine injection site and evaluated the subjects for clinical signs and symptoms of influenza virus infection on 4 of the first 7 days, and 2 and 4 weeks after vaccination.”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported that three participants could not be evaluated, but no further explanation given
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Gorse 1997

Methods	Randomisation: no details Allocation concealment: participants and study personnel were blinded but not the study nurse administering vaccines Outcome assessment was conducted under blind conditions. Duration: unclear, more than 28 days Withdrawals: none reported Follow-up schedule: clinical evaluation 3 times between each of days 1 to 5, 7 to 10, 21 to 28 after immunisation
Participants	Setting: 1994 to 1995 Outpatient clinics of St Louis Department of Veterans Affairs Medical Centre, USA Number: 29; 16 in CAV/TVV group and 13 in TVV/placebo group Characteristics: the average age was 65.2 (SD 2.1) years. All male volunteers. Demographic characteristics and mean pre-vaccination clinical lab tests were comparable; mean total WBC was 7710 (SD 298) cells/microL. Mean lymphocytes were 22.7% (SD 1.4) of total WBC. Mean serum albumin was 4.3 (SD 0.07) g/dL. Mean total cholesterol was 222.8 (SD 12.4) mg/dL Baseline characteristics: demographics and lab results largely comparable. Proportions of participants with underlying medical illnesses comparable with the exception of higher proportion of liver disease in CAV/TVV group Comorbidities: 32% of CAV/TVV participants had underlying liver disease. Overall, other diseases were comparable; 21% renal, 66% heart disease, 38% neurologic, 21% diabetes mellitus. 97% of the participants reported having smoked tobacco products in

	the past. 90% reported having consumed alcohol in the past Diagnostic criteria: COPD with severe obstruction to airflow on average and FEV₁/FVC% < 70%. Medical history consisting of respiratory symptoms, physical examination and clinical lab tests were used Exclusion criteria: 1. History of hypersensitivity to influenza virus and eggs 2. Receipt of influenza vaccine < 6 months prior to enrolment 3. Incompetence to give written informed consent 4. Co-administration of immunosuppressive medication 5. Hematologic malignancy not in remission 6. Blood Hb concentration < 11g/dL	
Interventions	Vaccination type: 1. Bivalent live attenuated influenza virus vaccine (CAV) derived from cold-adapted influenza A/Ann Arbor/6/60 (H2N2) and A/Kawasaki/9/86 (H1N1) and A/Beijing/353/89 (H3N2). Intranasal with 0.4 mL in each naris 2. Trivalent inactivated subvirion influenza virus vaccine (TVV) - A/Texas/36/91 (H1N1), A/Shandong/9/93 (H3N2), B/Panama/4/90. Intramuscular, 15 µg of HA from each of 3 strains per 0.5 mL dose Control: 1. Saline placebo intranasal 2. TVV, intramuscular, identical to vaccinated group	
Outcomes	Early: all measured 7 to 10 days after immunisation. Clinical status; pulmonary function using basic spirometry, measuring FEV₁, FVC and FEV₁/FVC %. Adverse symptoms such as cough, nasal congestion, runny nose, etc. Serology; levels of anti-HA immunoglobulins in nasal washings Late: spirometry was repeated for those who reported changes in obstruction to airflow or respiratory symptoms at 7 to 10 days. Serology; cellular immune testing of in vitro levels of interleukins 2 and 4	
Notes	To calculate standard deviations from continuous data, we assumed that only 1 exacerbation was experienced by each participant	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation reported, however, no details regarding methods of randomisation reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled. Same delivery method with participants and laboratory personnel blinded. Study nurse was unblinded

Gorse 1997 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The nurse administering the immunisation was unblinded. Unclear who did the follow-up checks on the days following vaccination
Incomplete outcome data (attrition bias) All outcomes	Low risk	All vaccinated participants were evaluated and reported in the study results
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Gorse 2003

Methods	Duration: six + months Protocol: spirometry performed to check eligibility, then IM and intranasal vaccine given. Participants kept diary card for 7 days. Follow-up visit 3-4 weeks after vaccination, and antibody determination. Thereafter 2 weekly phone calls, and final follow-up visit at 6 months. Participants reported if developed respiratory illness. Dropouts: 90 in intervention (8.1%), 110 in control (9.9%). 64 deaths
Participants	Setting: Winter; USA; 1998 to 1999; people with COPD meeting spirometric criteria for COPD from 20 VA Medical Centre sites Exclusion: allergic to vaccine components, received influenza vaccine less than six months previously, immunocompromised, cystic fibrosis, febrile illness 72 hours prior or exacerbation of COPD within 3 weeks prior, or history of Guillain-Barré syndrome Number: 2215; 1107 in intervention and 1108 in control group Age: 50 or over. Mean age 67.8 years, 98.2% male, 83.5% white, 95% had smoking history, 95% had comorbidity, mean FEV ₁ 1.34 L, 42.6% predicted, FEV ₁ /FVC 0.53
Interventions	Trivalent inactivated influenza virus vaccine (TVV) -A/Beijing/262/95-like (H1N1), A/Sydney/5/97-like (H3N2), B/Beijing/184/93; intramuscular into deltoid; 0.5 mL dose. Same lot in all participants On same day, participants also received either: Intervention: Trivalent, types A and B, live cold adapted influenza virus vaccine (CAIV-T) corresponding to the strains in the TVV, 0.25 mL per nostril, or Control: intranasal saline as a large particle aerosol
Outcomes	Primary outcome: - Added efficacy of CAIV-T as assessed by laboratory-documented influenza-caused illness (LDI). LDI defined as sudden onset of respiratory illness with one or both of (1) influenza A or B culture positivity from nasal or oropharyngeal swabs, (2) four-fold increase in antibody titre for influenza A or B Secondary outcomes: - efficacy of CAIV-T on influenza-like illness (ILI) on influenza-like illness (ILI). ILI was defined as one of two definitions (I) febrile, 100 F° and influenza virus in the

Gorse 2003 (Continued)

	locality and 3/10 criteria met, or (ii) influenza virus not present in locality and 4/10 criteria met• Illness severity was documented• Lung function• VAS of overall sense of health Adverse reactions: early reactions monitored for 7 days using diary Additional outcome of chronic lung disease severity index (CLDSI) was reported in Gorse 2003a.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment 1:1, stratified by site
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, all participants received intramuscular vaccination; however, the method of intranasal delivery of intervention versus control was different
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make determination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make determination
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Govaert 1994

Methods	Duration: 5 months Withdrawals: 47 incomplete questionnaires, none due to influenza-related morbidity or mortality Follow-up schedule: clinical assessments, questionnaire completed at 4, 10 and 23 weeks, serological tests at week 3 and 5 months
Participants	Setting: Winter 1991-92, 15 General Practices in Southern Netherlands Number: 1838; 927 vaccinated and 911 in the control Characteristics: Mean age 67 (SD5.6), 4 morbidity categories; heart, lung (9%), diabetes mellitus, and

	others, or healthy. 54% female Baseline characteristics: similar ages, sex ratios, risk status, previous vaccination rates. 13.5% heart, 11.3% lung, 2.3% diabetes mellitus in the vaccine group and 13.6% heart, 10.4% lung, 2.2% diabetes mellitus in the control. 54.7% female in the vaccine group compared to 50.7% in the control Comorbidities: cardiological, pulmonary, and other metabolic Diagnostic criteria: over 60 years of age, with conditions, if present, that were not severe enough to necessitate mandatory vaccination; not specifically COPD Influenza diagnosed serologically, by a physician or by International Classification of Health Problems in Primary Care 2nd Edition (ICHPPC-2) defined criteria Exclusion criteria: 1. Less than 60 years of age 2. High risk groups 3. Those in old people's or nursing homes Other reasons for non-participation included inability to consent and fear of injections
Interventions	Vaccination type: Purified, split virion vaccine (A/Singapore/6/86 (H1N1), A/Beijing/353/89 (H3N2), B/Panama/45/90, B/Beijing/1/87) Control: physiological saline placebo
Outcomes	Early: none Late: mortality, exacerbation rates in the form of occurrence of influenza or influenza-like illnesses, HAI antibody titres; adverse reactions assessed at week 4; local, systemic, subgroup analysis
Notes	A subsequent report, Govaert 1994a was a sub-study of this trial reported the adverse reactions;

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation schedule used with 4 strata according to each morbidity category
Allocation concealment (selection bias)	Low risk	At the vaccination session, the participant revealed a previously allocated study number to the vaccination team, which enabled allocation of the participant to the next consecutive number in the appropriate stratum
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled using a 'visually' identical syringe

Govaert 1994 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers blinded to vaccination status analysed questionnaires completed by the participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate reporting of participants lost to follow-up. One death reported in the control group. Authors noted that participants with incomplete data were retained in the analyses where possible
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Howells 1961

Methods	Duration: about 4 months Withdrawals: 1 (control group participant died during an acute exacerbation) Follow-up schedule: initially at week 2, then every 4 weeks by both observers
Participants	Setting: Winter 1960, NW Wolverhampton, UK Number: 55 enrolled; 26 in vaccinated group, 29 in control Characteristics: 37 men (67%) of average age 52.78 years (SD 12.51); overall average peak expiratory flow (PEF) was 270.09 L/min (SD 111.88). The overall maximum breathing capacity was 64.33 L/min (SD 30.59) Baseline characteristics: The average age of the vaccinated group was 54.08 years (SD 14) and the control was 51.62 years (SD 11.12). 58% of the vaccinated group was male and 76% of the control. The vaccinated participants had an average duration of symptoms of around 17 years, while the control had around 20 years. The average PEF for the vaccinated group was 266.35 L/min (SD 101.12) and 273.45 L/min (SD 120.29) for the control. This difference could be attributed to 2 people with asthma who had relatively higher peak flows. The average maximum breathing capacity for the vaccinated group was 62.81 L/min (SD 28.66) and 65.75 L/min (SD 32.75) for the control. Comparable antibody levels to influenza viruses in all participants Comorbidities: 7% of control were asthmatics Diagnostic criteria: chronic bronchitis; "a minimum of 3 years' history of cough with phlegm on most days for at least 3 months of the year...". Participants were assessed to enable placement into Grades 1, 2 or 3 with increasing severity Exclusion criteria: people with Grade 4 bronchitis and TB
Interventions	Vaccination type: Flubron (A.A2 Asian-Formosa 7000, B England 5000), intramuscular Control: physiological saline solution

Outcomes	Early: exacerbations in weeks 1 to 3 recorded by clinical examination and measurement of PEF. Bacteriological and complement fixation results for cause of exacerbations Late: hospitalisation, mortality, as well as all early outcomes	
Notes	We made an assumption for the number of early and late exacerbations per participant for the placebo group. We knew the total number of exacerbations was 24 experienced by 20 participants out of 29. Thus, there would have been at least 8 early and 10 late exacerbations, according to the numbers of participants experiencing exacerbations in the placebo group. We added 2 exacerbations to each group to make up the total of 24. We felt justified in doing so because the study stated that similar numbers of early exacerbations were recorded in both groups, which was the case using our assumption	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make determination
Allocation concealment (selection bias)	Low risk	A key was provided by the statistical advisor to the nursing staff administering injections
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; a nurse uninvolved in the conduct of the research study administered the vaccination
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No details of outcome assessment blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants described and accounted for in results. One death occurred in the control group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

MRC 1980

Methods	Duration: unclear; more than 3 weeks Withdrawals: 16 participants from the Sheffield centre had no baseline recordings. 15 participants failed to complete all records (reasons not discussed) Follow-up schedule: no details
Participants	Setting: no details Number: 86 to begin with, but 16 had no baseline data and 15 had incomplete records. Thus, only 55 included in final analysis, with 36 in the vaccinated group and 19 in the control Characteristics: age range of 28 to 78 years Baseline characteristics: none recorded Comorbidities: no details Diagnostic criteria: chronic bronchitis (MRC definition) and airways obstruction with an FEV ₁ > 1 L Exclusion criteria: cardiac disease symptoms and steroid treatment
Interventions	Vaccination type: live attenuated, RIT 4050 (H2N3) vaccine virus; having surface antigens of the A/Victoria/75 virus in a lyophilised preparation; intranasal; 0.5 mL volume Control: placebo preparation without virus
Outcomes	Early: 7 days post vaccination. Upper and lower respiratory symptoms, systemic symptoms Spirometry: MEFV curves used to determine V50, V75, EVC, PEFr, FEV ₁ Late: day 21; all self-assessments, spirometry of early outcomes, and serology; HAI tests
Notes	Standard errors of serologically negative and positive participants were averaged to calculate a standard deviation for all vaccinees according to the formula: SD = SE * square root of N.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make determination
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make determination
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make determination
Incomplete outcome data (attrition bias) All outcomes	High risk	Eleven participants were vaccinated but excluded from the analyses; these originated

MRC 1980 (Continued)

		from one study site
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Treanor 1992

Methods	Duration: 3 years Withdrawals: 8; 7 from intranasal group; deaths due to unrelated causes, discharges from institutions Follow-up schedule: days 1 to 3 after each vaccination for adverse reactions and nasal sheddings; then daily staff nursing reports were used
Participants	Setting: 1987-90, 3 large nursing homes in Rochester, NY, USA; St Ann's Home, St John's Home and Monroe Community Hospital Number: 523; 345 participant years in the intranasal group and 346 participant years in the control Characteristics: older adults; Mean age of 84.2 years. 32% had cardiac or pulmonary conditions; 75% female Baseline characteristics: Relatively well matched for disabilities, age, sex ratios. Mean age in the vaccine group was 84.1 years with 26% of participants randomised to this group suffering either a cardiac or pulmonary condition; 4% of the vaccine group had both a cardiac and pulmonary condition. Mean age in the placebo group was 83.8 years with 23% of participants in this group suffering either a cardiac or pulmonary condition; 2% of participants in this group had both a cardiac and pulmonary condition Comorbidities: only details of cardiovascular and pulmonary complications Diagnostic criteria: none; all residents at these institutions were invited Exclusion criteria: 1. Acutely ill at time of enrolment 2. On current immunosuppressant therapy 3. Egg product allergy 4. Refusal of inactivated influenza vaccination
Interventions	Vaccination type: 1. Live attenuated, cold-adapted, monovalent influenza virus vaccination (A/Bethesda/1/85 (H3N2), A/Los Angeles/2 /87 (H3N2), A/Ann Arbor/6/60) intranasally in 0.5 mL doses 2. Inactivated, trivalent, subvirion influenza vaccine containing 9 different HAs intramuscular in 0.5 mL doses Control: 1. Intranasal placebo of sterile veal infusion broth 2. Trivalent inactivated subvirion influenza vaccine identical to treatment group

Treanor 1992 (Continued)

Outcomes	Early: days 1 to 3 post vaccination; adverse effects Late: years 1, 2, 3: serum antibody responses measured and occurrence of respiratory and flu-like illnesses were measured to evaluate the efficacy of adding live intranasal vaccination to the inactivated type	
Notes	Not specifically people with COPD	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details on randomisation sequence provided. Re-randomisation occurred every year
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient detail provided, although it is stated that this study was double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	A low number of dropouts reported per year, evenly across groups. Independent analysis each study year
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

Treanor 1994

Methods	Duration: at least 4 weeks Withdrawals: no details Follow-up schedule: early symptoms at days 3 to 4, serologic testing at 4 weeks post vaccination
Participants	Setting: outpatient clinics of Strong Memorial Hospital; Rochester, NY and a private practice, USA Number: 81; 34 in the live attenuated vaccination group, 30 in the inactivated vaccination group and 11 in the control Characteristics: older adults (> 65 years) and chronically ill, 65% female

	Baseline characteristics: distributions of chronic conditions, smokers and mean ages were roughly similar. 18% of the live vaccinated group had chronic lung disorders, and had a mean age of 68.9 years Comorbidities: chronic cardiac, pulmonary, endocrine, hematologic conditions, 25% smokers Diagnostic criteria: ambulatory adults over 65 years, or with at least 1 high risk condition Exclusion criteria: no details
Interventions	Vaccination type: 1. Cold-adapted, Live attenuated re-assortant influenza B virus vaccine (B/Ann Arbor/1/86 or B/Yamagata/16/88), intranasally in 0.5 mL doses with intramuscular placebo 2. Parenteral, trivalent, inactivated influenza vaccination (B/Ann Arbor/86 and B/Yamagata/88) intramuscularly, in 0.5 mL doses with intranasal placebo Control: placebo; intramuscular saline and intranasal veal infusion broth
Outcomes	Early: 3 to 4 days post vaccination; pulse oximetry, spirometry, virus cultures and HAI tests; symptoms for 7 days (upper and lower respiratory tract symptoms, systemic) Late: serology repeated at week 4, hospitalisations
Notes	Cold adapted, live attenuated influenza B vaccines are safe but not as immunogenic as inactivated ones in chronically ill or older people. There were no significant differences between the groups in outcomes of spirometry and adverse effects. Author provided individual participant data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No further details other than 'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make determination
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This study was double-blind, however, methods were not described in any more detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data or withdrawals reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination

Treanor 1994 (Continued)

Other bias	Unclear risk	Insufficient information to make determination

Wongsurakiat 2004a

Methods	Duration: 1 year. Withdrawals: 3 dropouts (1 vaccine, 2 control). Deaths 8 (5 vaccine, 3 control) all died from causes not related to acute respiratory infection Follow-up schedule: reviewed monthly. Bloods taken at week 0, week 4, and 6 and 12 months; participants reported acute respiratory infections, and had extra visit for full assessment, including the taking of acute and convalescent serum 4 to 6 weeks later. If respiratory infection presented for less than 6 days, swabs taken	
Participants	Setting: 1997-8. Thailand, university hospital, COPD outpatient clinic; non-influenza epidemic years in Thailand Number: 132 consecutive outpatients. 7 excluded as couldn't attend, making 125 in total, 62 in vaccine group and 63 in control group Inclusion: clinical COPD (COPD not defined although managed according to Thai guidelines), FEV ₁ < 70% and < 15% increase after bronchodilator Exclusions: egg allergy, immunocompromised, immunosuppressive drugs (except corticosteroids), or if comorbidities expected to reduce survival to < 1 year Characteristics: mean age 68.3 years, 94% male, 96% smoking history, 37% FEV ₁ < 50%, 44% FEV ₁ > 70%, 33% with comorbidities	
Interventions	Vaccination type: purified trivalent split-virus vaccine A/Texas/36/91 (H1N1), ANan-chang/933/95 (H3N2), B/Harbin/07/94. 0.5 mL on Day 1 and a second dose at 4 weeks; two-dose schedule given as first time that influenza vaccine available in Thailand Control was 0.5 mL of Vitamin B1	
Outcomes	Acute respiratory infections, antibody responses to vaccination and to acute respiratory infections (by HAI test), allowing classification of whether the infection was influenza-related Clinical classification of ARI into common cold, acute exacerbation, influenza-like illness, or pneumonia. Severity recorded; hospitalisation, ventilation, and stratified by COPD severity Adverse effects recorded carefully for 4 weeks after vaccination	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants stratified based on disease severity and numbered consecutively. These numerical identifiers had been previously randomised to either intervention or placebo

Allocation concealment (selection bias)	Low risk	A nurse not involved in participant care determined which numerical identifier was allocated to intervention or placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo controlled. Both vaccine and placebo were same volume and quantity, administered to all participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make determination
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study clearly outlines exclusions and dropouts; dropouts were very similar for both groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make determination
Other bias	Unclear risk	Insufficient information to make determination

ARI: acute respiratory infection; CAIV-T: live cold adapted influenza virus vaccine; CAV: live attenuated influenza A virus vaccine derived from cold-adapted influenza; CCA: chicken cell agglutinating; CLDSI: chronic lung disease severity index; COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in one second; FVC: force vital capacity; HAI: hemagglutination inhibition; ICHPPC-2: International Classification of Health Problems in Primary Care; ILI: influenza-like illness; IM: intramuscular; LDI: laboratory-documented influenza; MD: mean difference; MEFV: maximum expiratory flow - volume curve; MRC: Medical Research Council; PEF: peak expiratory flow rate; SD: standard deviation; TB: tuberculosis; TVV: trivalent inactivated influenza virus vaccine; USA: United States of America; UK: United Kingdom; VAS: visual analogue scale; V50: air flow rate at 50% vital capacity; V75: air flow rate at 75% vital capacity; WBC: white blood cells.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ambrosch 1979	Not placebo controlled and not COPD specific
Centanni 1997	Add-on benefit of bacterial immunostimulant is being assessed
Dorrell 1997	Not RCT, people with obstructive airways disease are only a small subgroup
Gorse 1986	Live and inactivated virus vaccines used without placebo as a control, not randomised
Gorse 1988	Serological results only; no primary outcomes suitable for this review

(Continued)

Gorse 1991	No randomisation of people with COPD.
Gorse 1996	Serological outcomes only, no primary outcomes suitable for this review
Howells 1975	No randomisation of older participants with lung disease
Keitel 1993	Healthy adults susceptible to virus vaccine were used
Lama 1998	Serological outcomes only; no primary outcomes suitable for this review, unclear if this is an RCT from the abstract. We were unable to retrieve the full paper
Margolis 1990	Randomised survey with a lung disease component but not placebo controlled
MRC 1959	3 inactivated vaccines used without placebo as a control
MRC 1984	Not randomised for people with COPD.
Paul 1988	Not RCT
Portari 1998	Not RCT, serological outcomes only; no primary outcomes suitable for this review
Powers 1991	Healthy older adults used
Prevost 1975	Not RCT
Saah 1986	Retrospective cohort study , not COPD
Treanor 1998	Older and high risk participants but no details of COPD or any other lung disease
Winson 1977	No randomisation of chronic bronchitis

DATA AND ANALYSES

Comparison 1. Inactivated influenza vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total exacerbations per participant	2	180	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.64, -0.11]
2 Early exacerbations per participant	2	180	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.11, 0.13]
3 Late exacerbations per participant	2	180	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.61, -0.18]
4 Participants with at least one exacerbation or acute respiratory illness	3	222	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.44, 1.48]
4.1 Clinical exacerbations	2	97	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.48, 2.33]
4.2 Any acute respiratory illness	1	125	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.22, 1.42]
5 Participants with early exacerbations	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.52, 2.26]
6 Participants with late exacerbations	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7 Hospital admissions	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.09, 1.24]
7.1 Clinical exacerbations	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.39]
7.2 Influenza-related exacerbations	1	125	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.09, 1.89]
8 Mortality (all cause)	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.28, 2.70]
9 Mortality (acute respiratory illness-related)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Overall change in lung function (FEV ₁ , L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Change in early lung function (FEV ₁ , L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Systemic adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Local effects at injection site	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14 Participants with early breathlessness	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
15 Participants with early tightness	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
16 Participants with early wheeze	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
17 Participants with early cough	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
18 Acute respiratory illness subsequently documented as influenza-related	2	180	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.07, 0.48]
18.1 FEV ₁ ≥ 70% predicted	1	45	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 1.11]
18.2 Participants with chronic bronchitis	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 0.96]
18.3 FEV ₁ < 50% predicted	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.99]

18.4 FEV ₁ 50% to 69% predicted	1	33	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.07, 2.98]
19 Early acute respiratory illness (ARI)	1	250	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.34, 1.50]
19.1 ARI within 1 week of vaccination	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.24, 4.26]
19.2 ARI between 1 and 4 weeks after vaccination	1	125	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.27, 1.50]
20 Participants with early sputum production	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Comparison 2. Inactivated + live virus versus inactivated virus + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total exacerbations per participant	2	1137	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.35, 0.37]
2 Early exacerbations per participant	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Late exacerbations per participant	1	29	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.08, 0.54]
4 Participants with improvement in exacerbations	1	29	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.30, 7.42]
5 Participants with early improvements	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
6 Participants with late improvements	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7 Mortality	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Early changes in lung function (% predicted FEV ₁)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Early changes in lung function (FEV ₁ /FVC %)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Post immunisation lung function (FEV ₁)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Participants with increased lung function (1 category)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
12 Participants with decreased lung function	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
13 FEV ₁ at end of study	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Participants with adverse effects (new upper respiratory tract symptoms)	1	29	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.89 [0.45, 8.04]
15 Participants with early adverse effects	2	2244	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.63, 1.17]
16 Number of days with early symptoms and signs	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

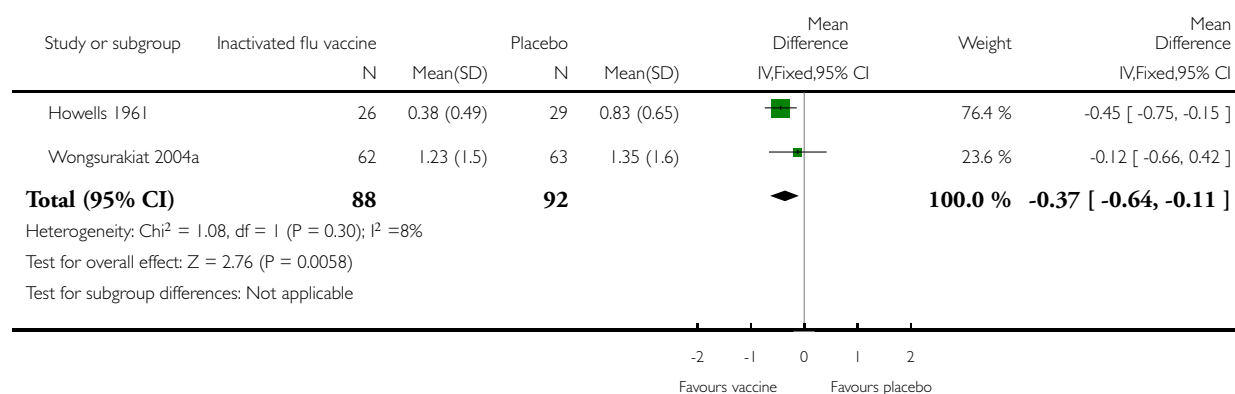
17 Number of participants with early adverse effects (by type)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 COPD	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.30, 1.48]
17.2 Dyspnoea	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.60, 5.41]
17.3 Pharyngitis	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.35, 2.86]
17.4 Flu syndrome	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.20, 1.91]
17.5 Rhinitis	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.42, 5.34]
17.6 Bronchitis	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.50, 8.05]
17.7 Increased cough	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.14, 2.51]
17.8 Myalgia	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.51 [0.49, 12.96]
17.9 Increased sputum	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.17, 3.36]
17.10 Pneumonia	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.37, 10.97]
17.11 Asthenia	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.37, 10.97]
17.12 Guillain-Barré syndrome	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.19]
17.13 Other	1	2215	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.26, 0.92]
18 Participants with late adverse effects	2	2244	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.33 [1.22, 4.46]
19 Acute respiratory illness subsequently documented as influenza-related	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
20 Participants with at least one influenza-like illness	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 1 Total exacerbations per participant.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 1 Total exacerbations per participant

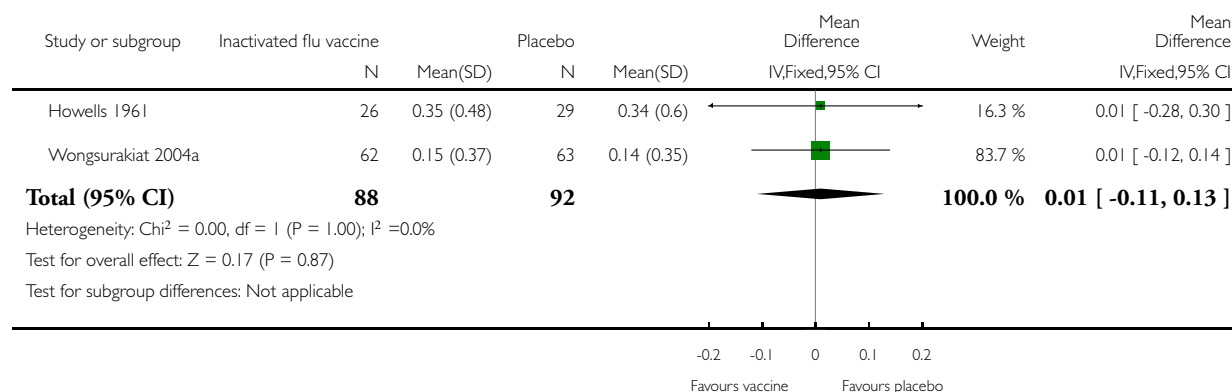


Analysis 1.2. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 2 Early exacerbations per participant.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 2 Early exacerbations per participant

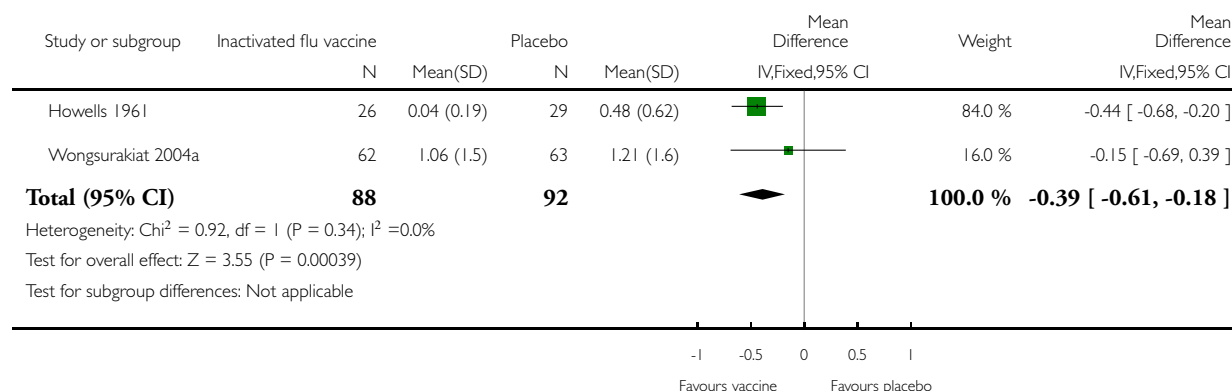


Analysis 1.3. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 3 Late exacerbations per participant.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 3 Late exacerbations per participant

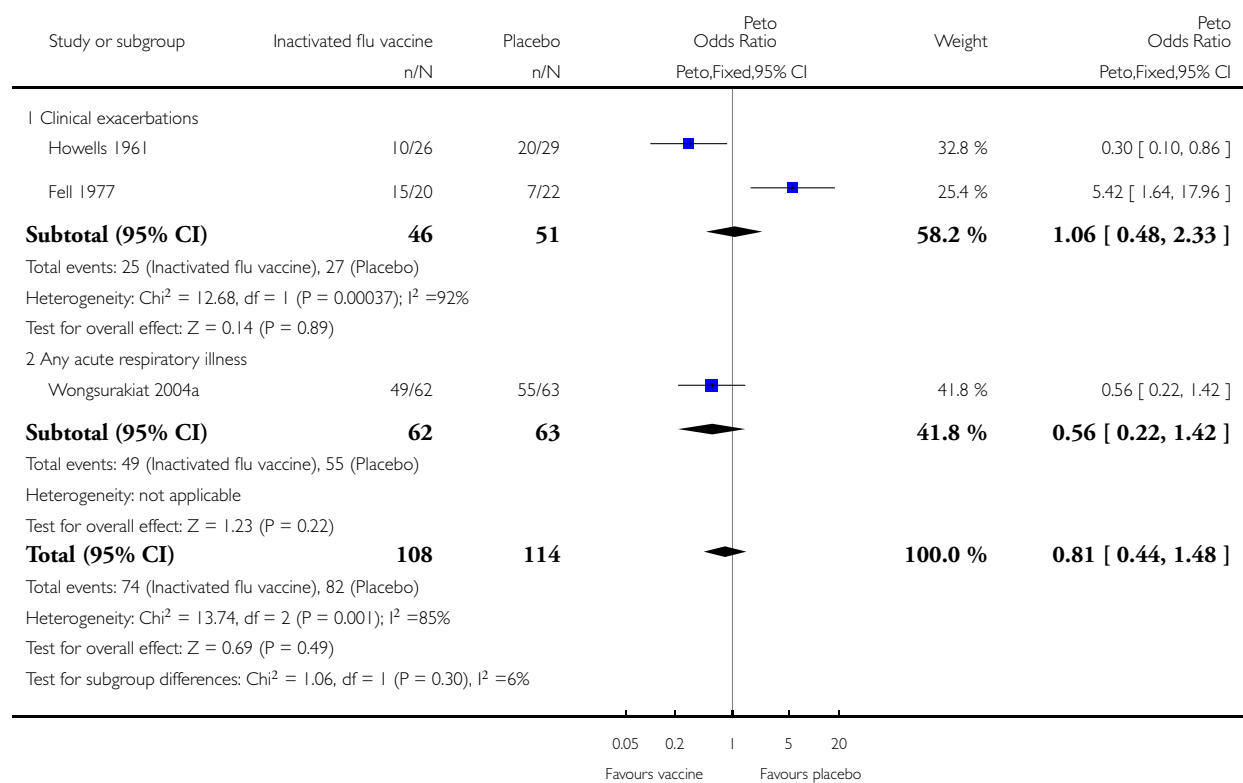


Analysis 1.4. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 4 Participants with at least one exacerbation or acute respiratory illness.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 4 Participants with at least one exacerbation or acute respiratory illness

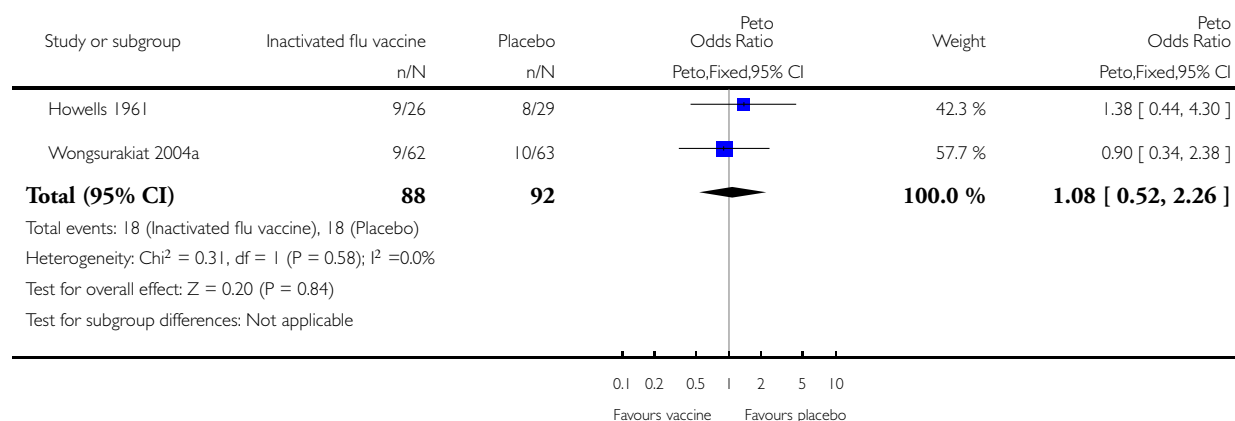


Analysis 1.5. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 5 Participants with early exacerbations.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 5 Participants with early exacerbations

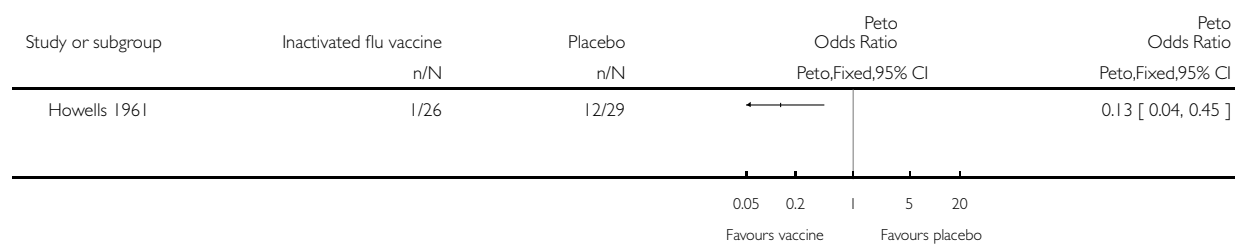


Analysis 1.6. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 6 Participants with late exacerbations.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 6 Participants with late exacerbations

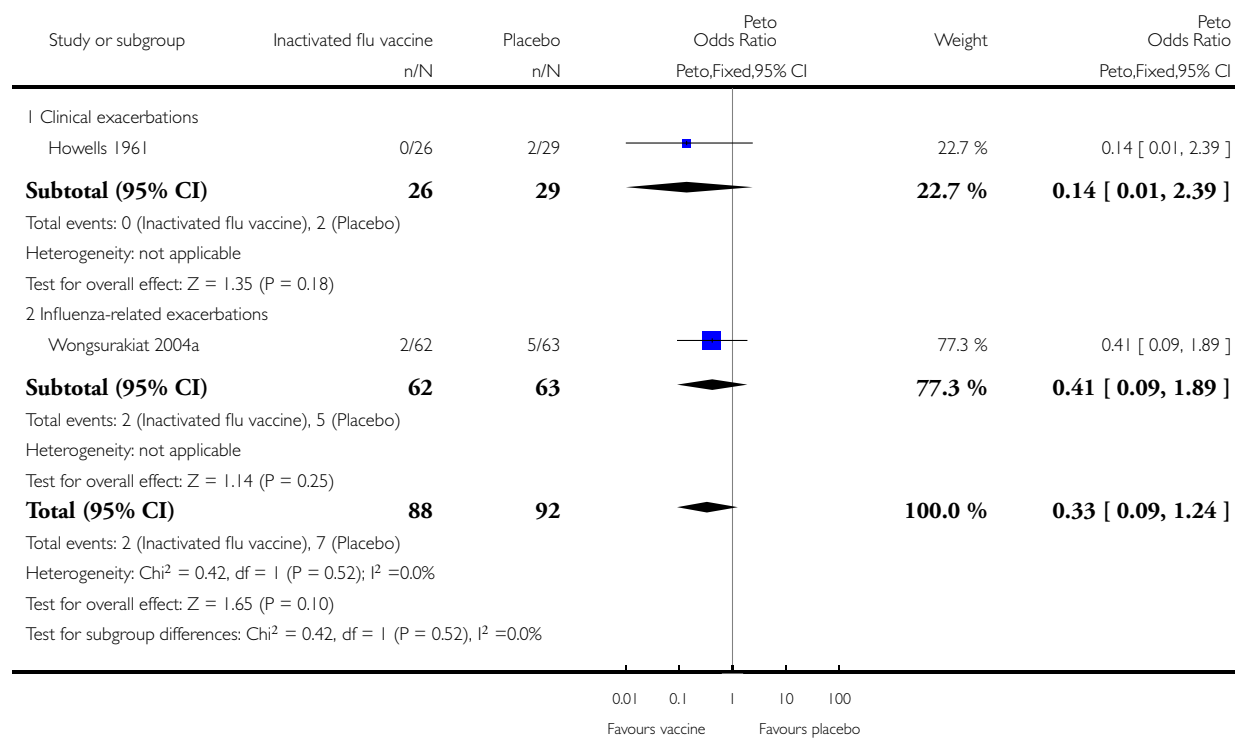


Analysis 1.7. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 7 Hospital admissions.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 7 Hospital admissions

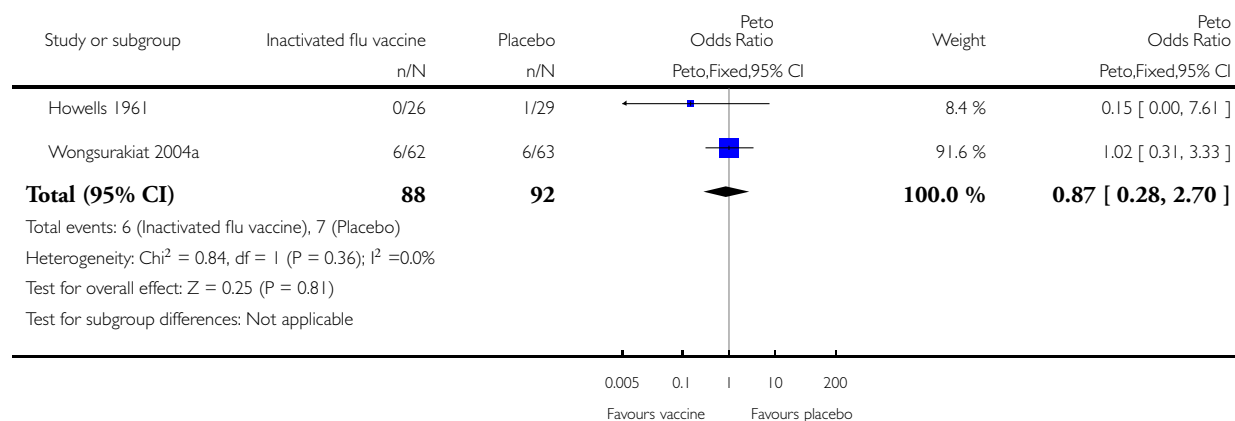


Analysis 1.8. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 8 Mortality (all cause).

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 8 Mortality (all cause)

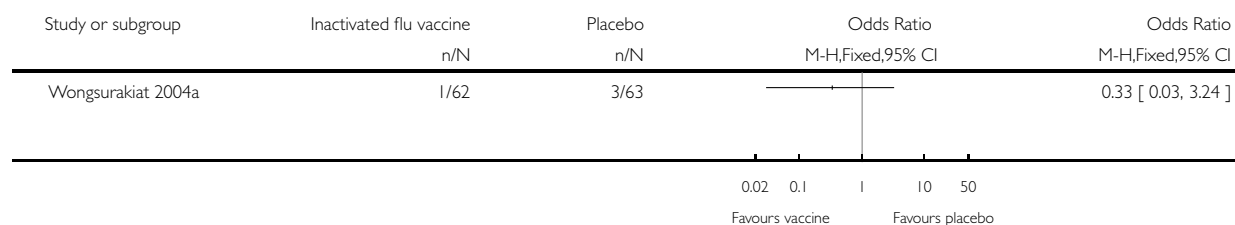


Analysis 1.9. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 9 Mortality (acute respiratory illness-related).

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 9 Mortality (acute respiratory illness-related)

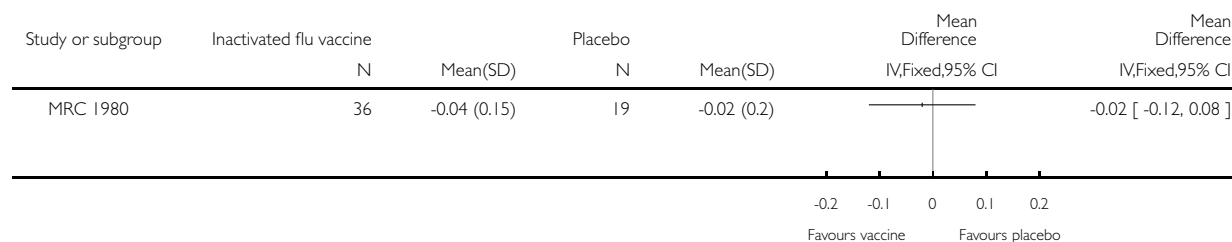


Analysis 1.10. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 10 Overall change in lung function (FEV₁, L).

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 10 Overall change in lung function (FEV₁, L)

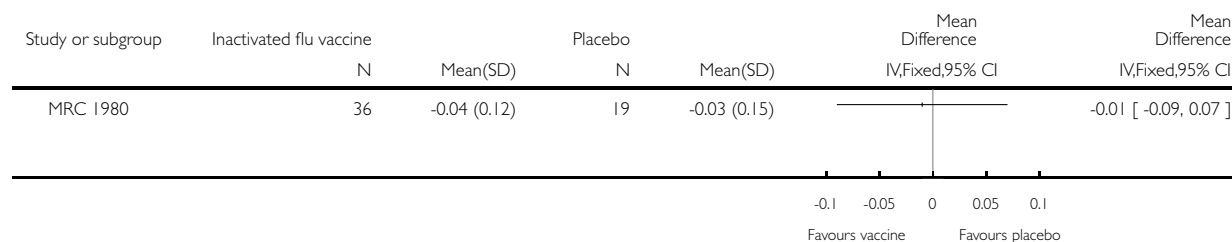


Analysis 1.11. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 11 Change in early lung function (FEV₁, L).

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 11 Change in early lung function (FEV₁, L)

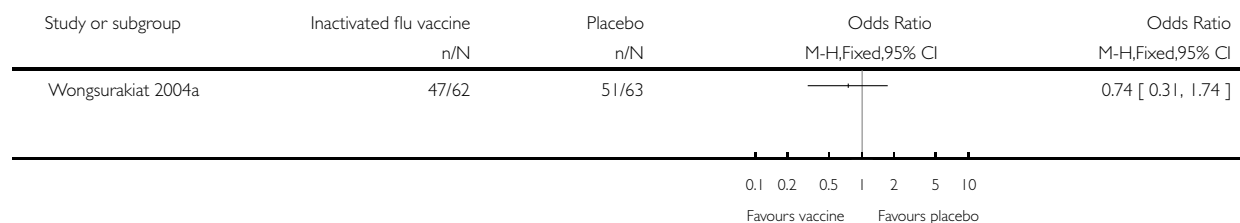


Analysis 1.12. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 12 Systemic adverse effects.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 12 Systemic adverse effects

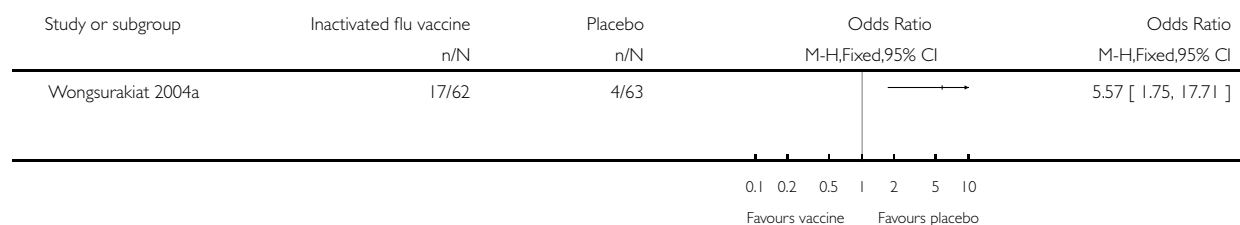


Analysis 1.13. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 13 Local effects at injection site.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 13 Local effects at injection site

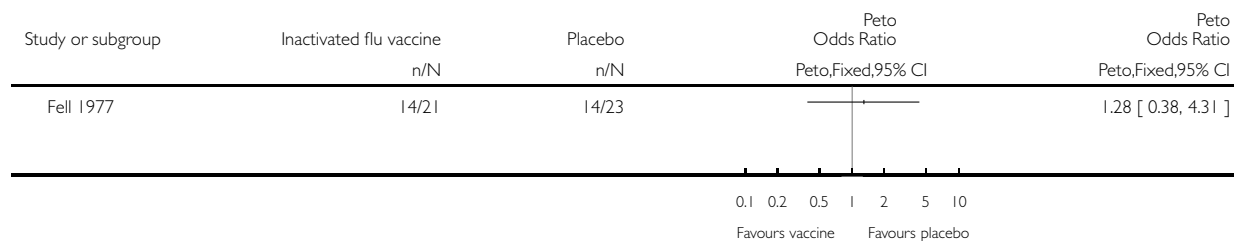


Analysis 1.14. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 14 Participants with early breathlessness.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 14 Participants with early breathlessness

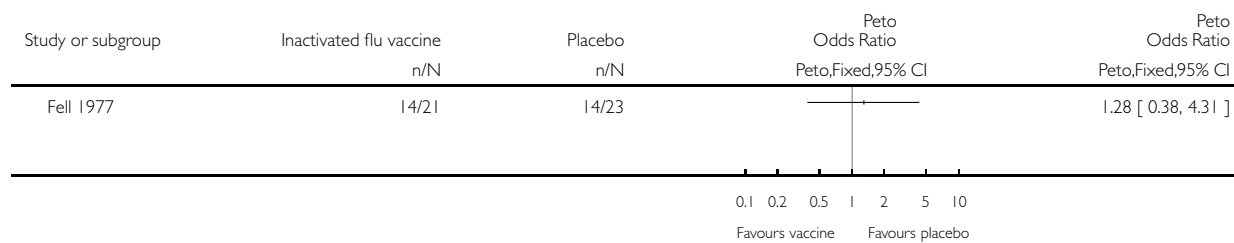


Analysis 1.15. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 15 Participants with early tightness.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 15 Participants with early tightness

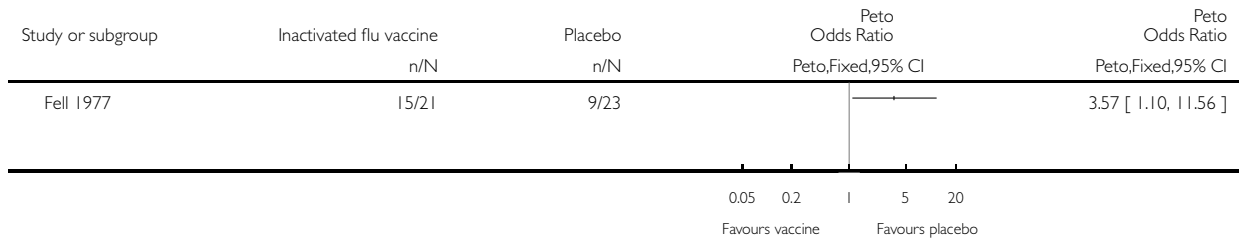


Analysis 1.16. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 16 Participants with early wheeze.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 16 Participants with early wheeze

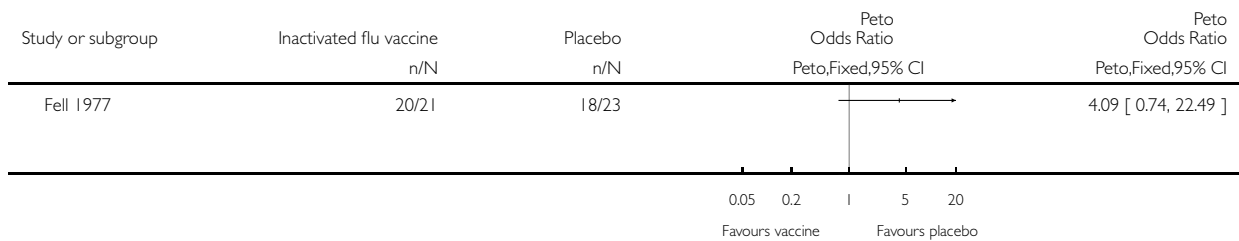


Analysis 1.17. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 17 Participants with early cough.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 17 Participants with early cough

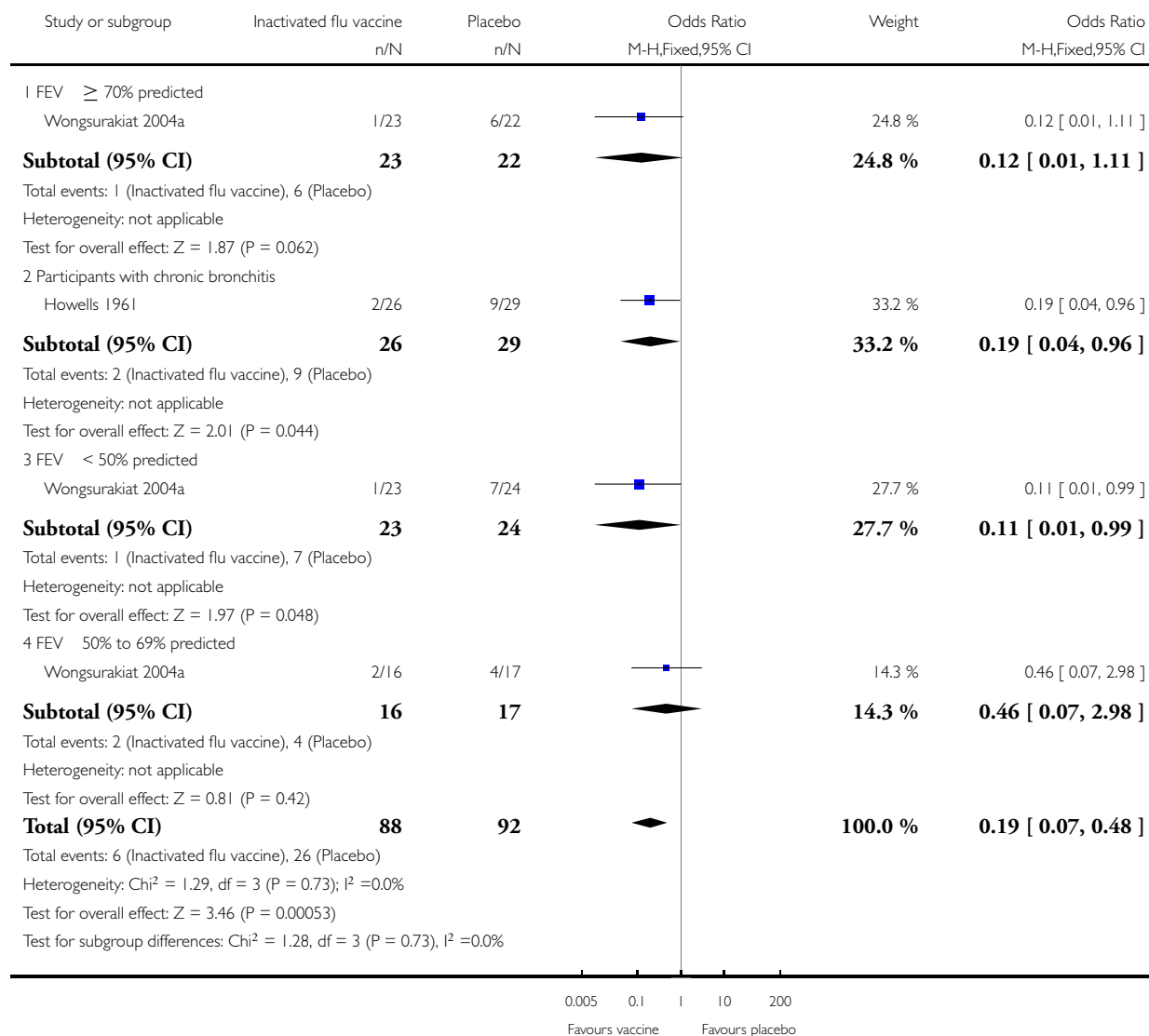


Analysis 1.18. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 18 Acute respiratory illness subsequently documented as influenza-related.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 18 Acute respiratory illness subsequently documented as influenza-related

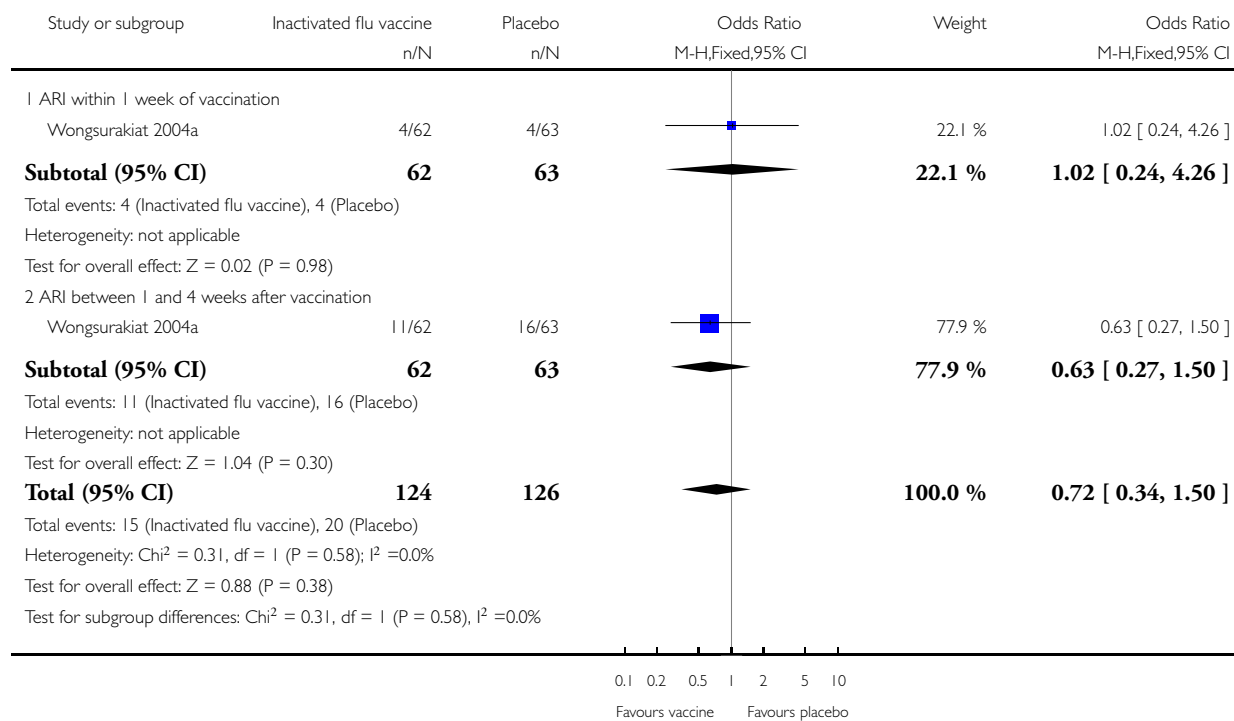


Analysis 1.19. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 19 Early acute respiratory illness (ARI).

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 19 Early acute respiratory illness (ARI)

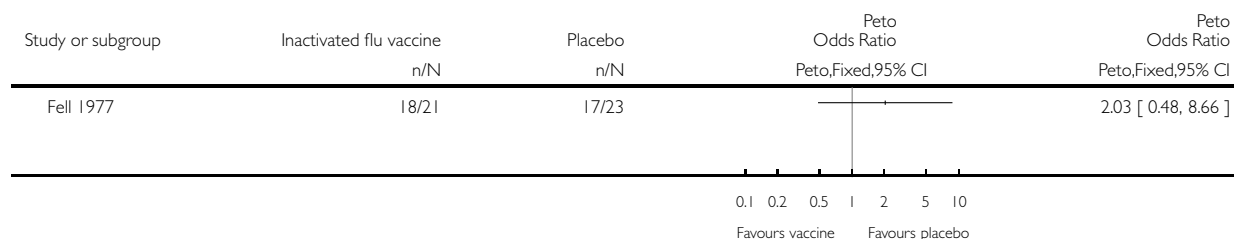


Analysis 1.20. Comparison 1 Inactivated influenza vaccine versus placebo, Outcome 20 Participants with early sputum production.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 1 Inactivated influenza vaccine versus placebo

Outcome: 20 Participants with early sputum production

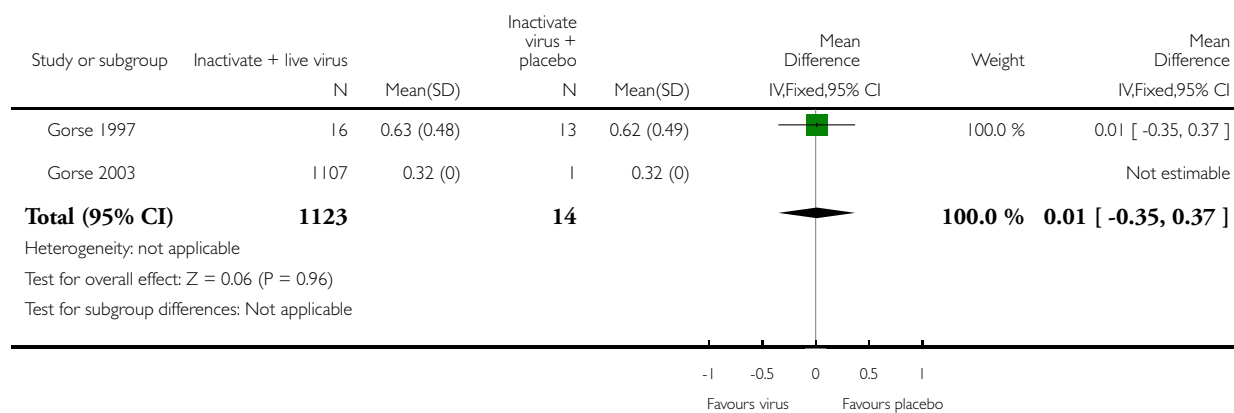


Analysis 2.1. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 1 Total exacerbations per participant.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 1 Total exacerbations per participant

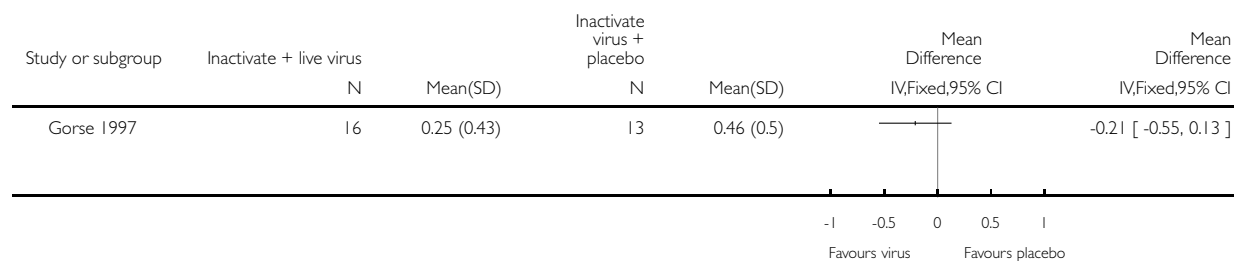


Analysis 2.2. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 2 Early exacerbations per participant.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 2 Early exacerbations per participant

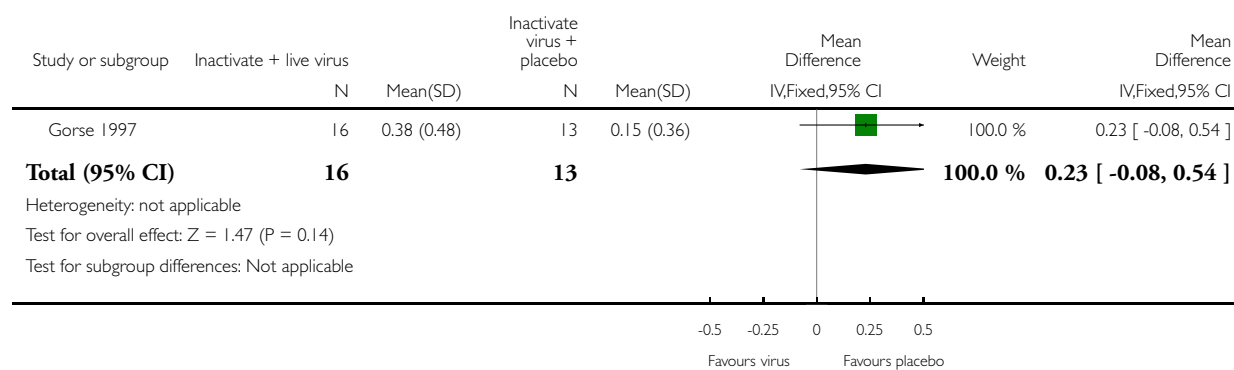


Analysis 2.3. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 3 Late exacerbations per participant.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 3 Late exacerbations per participant

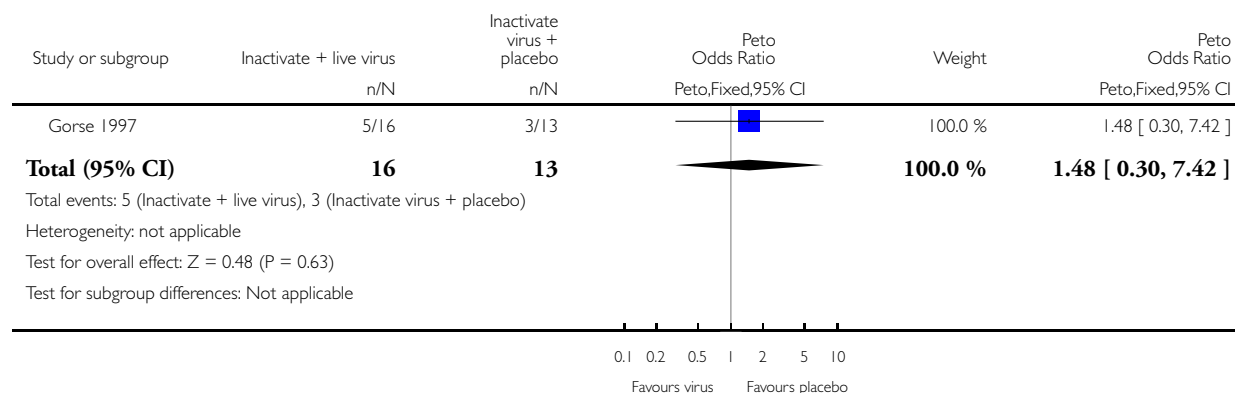


Analysis 2.4. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 4 Participants with improvement in exacerbations.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 4 Participants with improvement in exacerbations

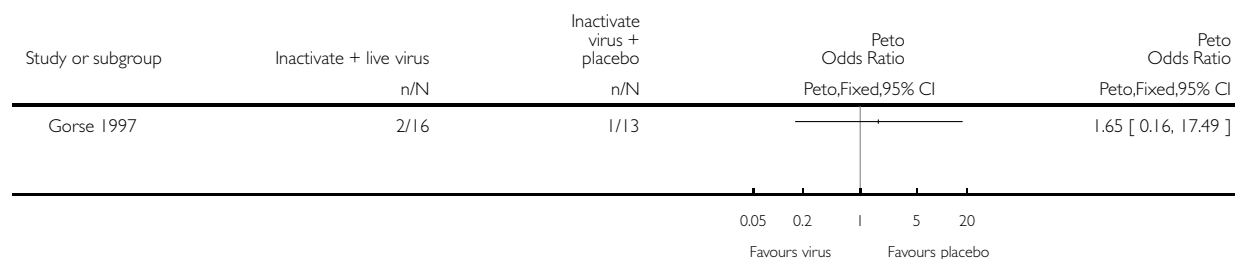


Analysis 2.5. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 5 Participants with early improvements.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 5 Participants with early improvements

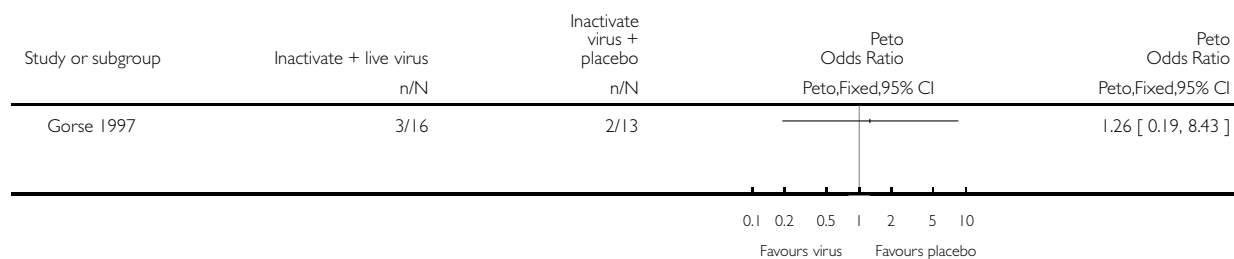


Analysis 2.6. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 6 Participants with late improvements.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 6 Participants with late improvements

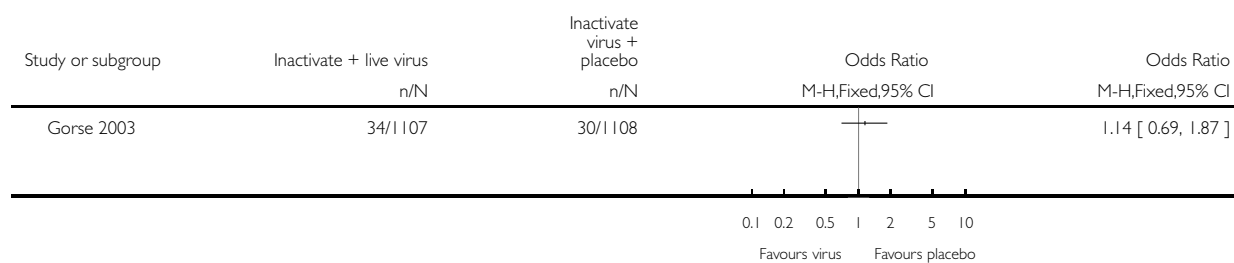


Analysis 2.7. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 7 Mortality.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 7 Mortality

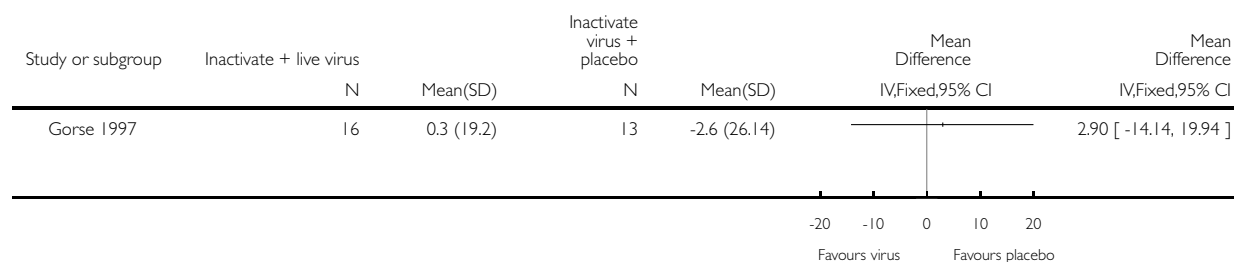


Analysis 2.8. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 8 Early changes in lung function (% predicted FEV₁).

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 8 Early changes in lung function (% predicted FEV₁)



Analysis 2.9. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 9 Early changes in lung function (FEV₁/FVC %).

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 9 Early changes in lung function (FEV₁/FVC %)

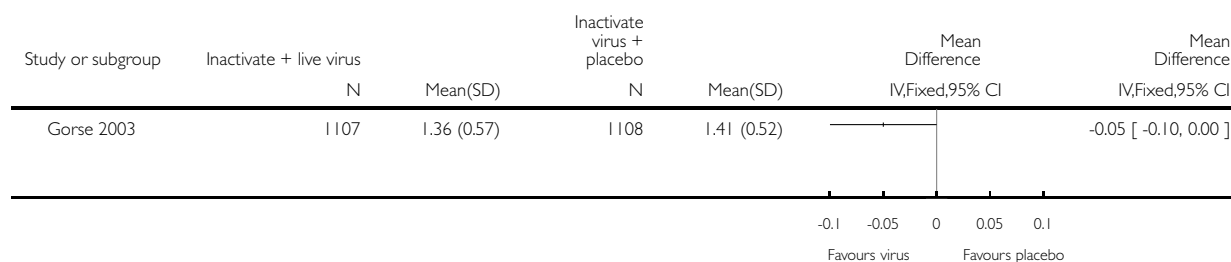


Analysis 2.10. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 10 Post immunisation lung function (FEV₁)

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 10 Post immunisation lung function (FEV₁)

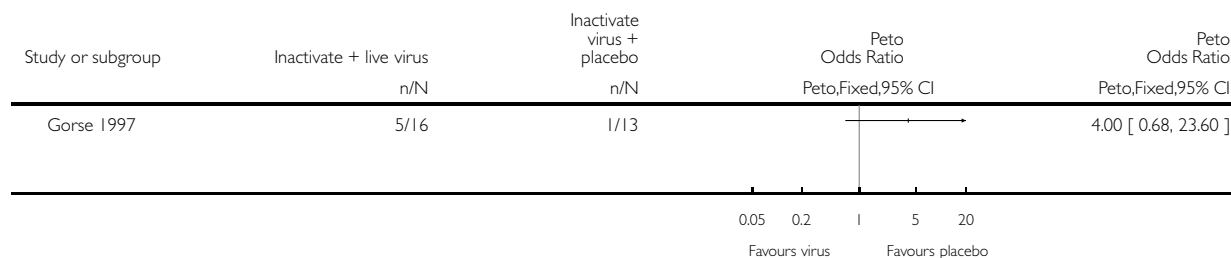


Analysis 2.11. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 11 Participants with increased lung function (1 category)

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 11 Participants with increased lung function (1 category)

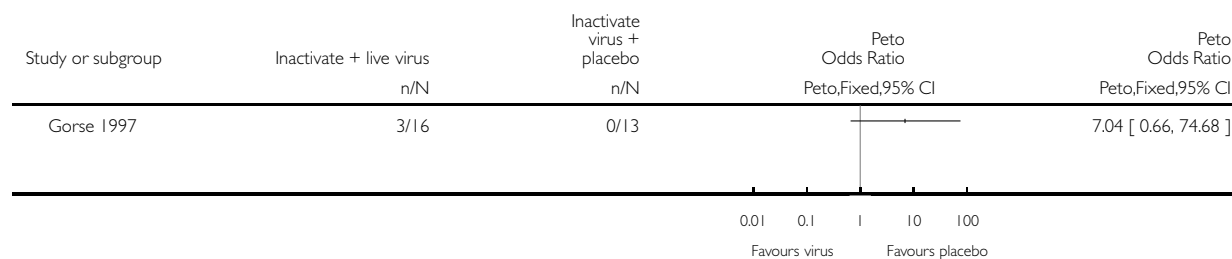


Analysis 2.12. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 12 Participants with decreased lung function.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 12 Participants with decreased lung function

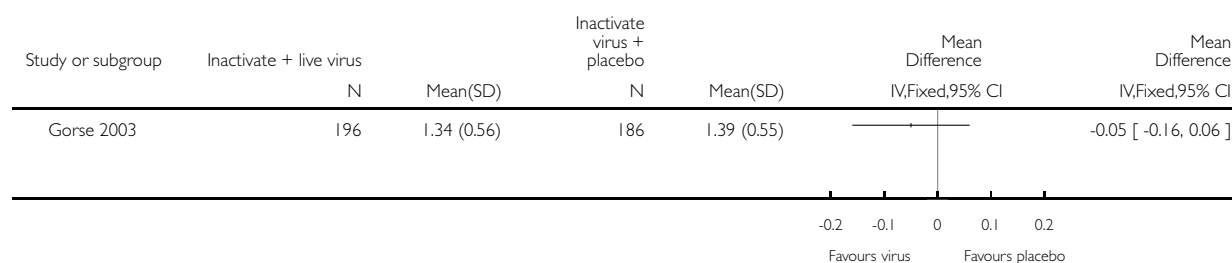


Analysis 2.13. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 13 FEV₁ at end of study.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 13 FEV₁ at end of study

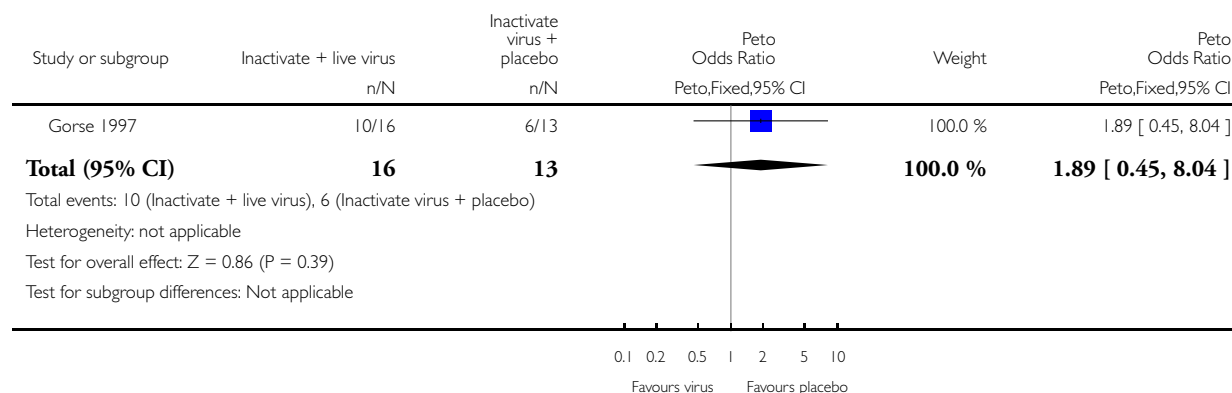


Analysis 2.14. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 14 Participants with adverse effects (new upper respiratory tract symptoms).

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 14 Participants with adverse effects (new upper respiratory tract symptoms)

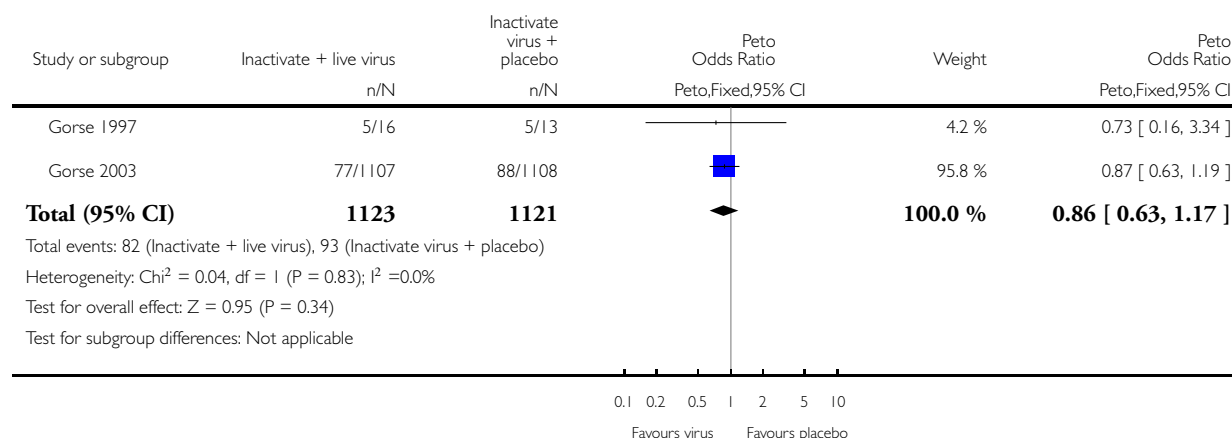


Analysis 2.15. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 15 Participants with early adverse effects.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 15 Participants with early adverse effects

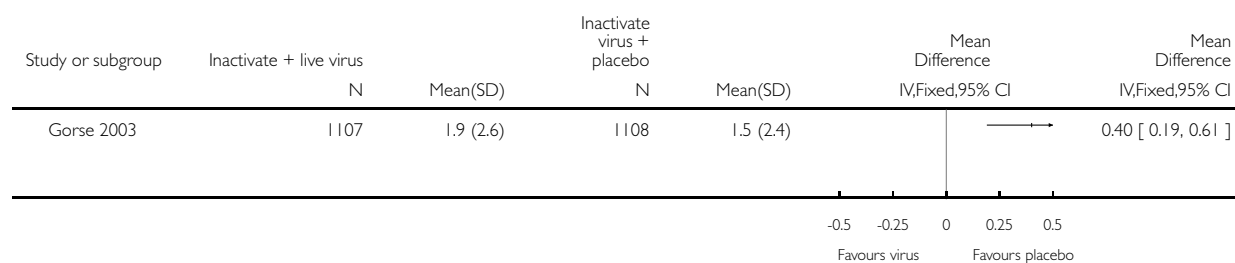


**Analysis 2.16. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 16
Number of days with early symptoms and signs.**

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 16 Number of days with early symptoms and signs

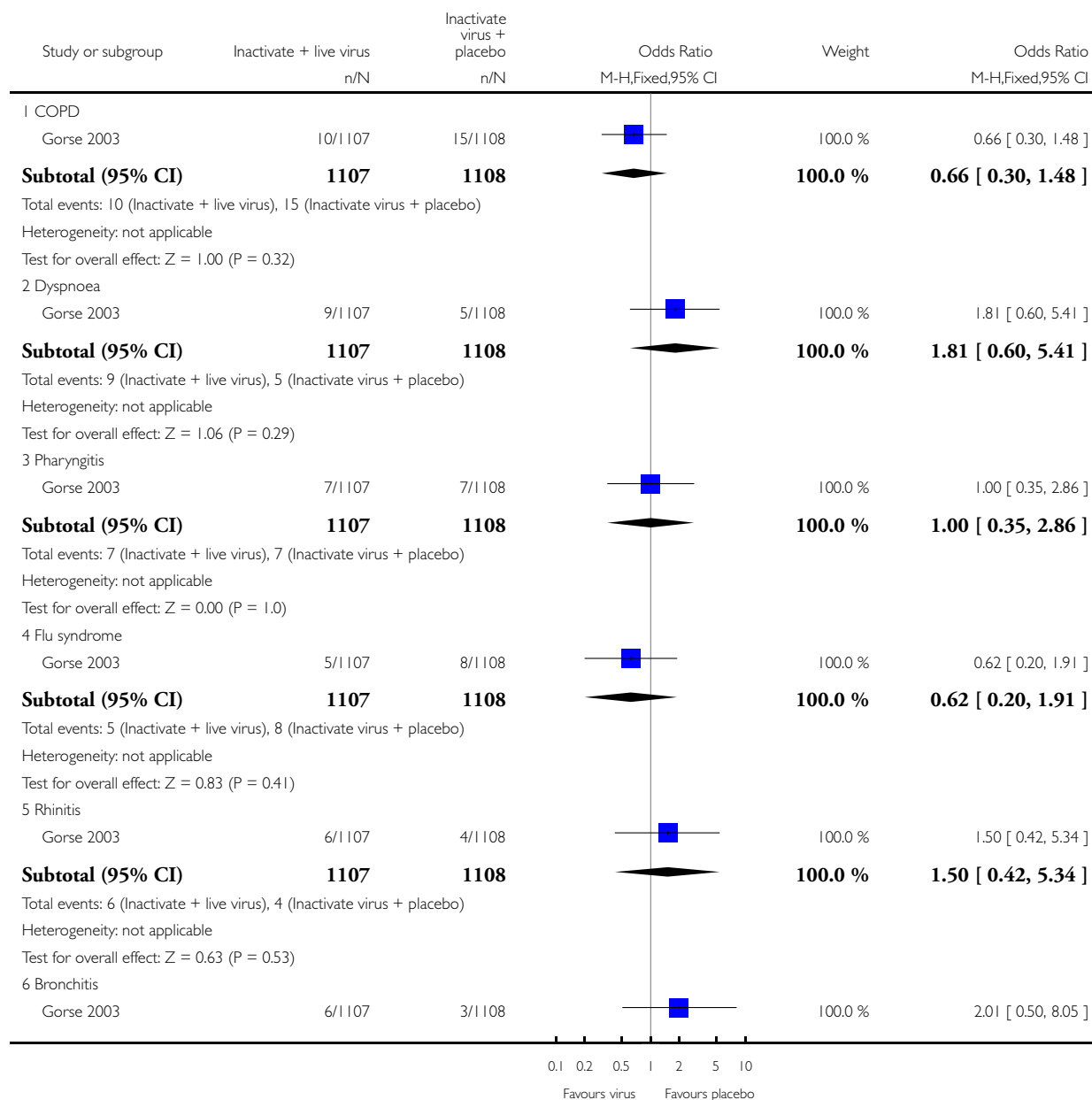


Analysis 2.17. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 17 Number of participants with early adverse effects (by type).

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

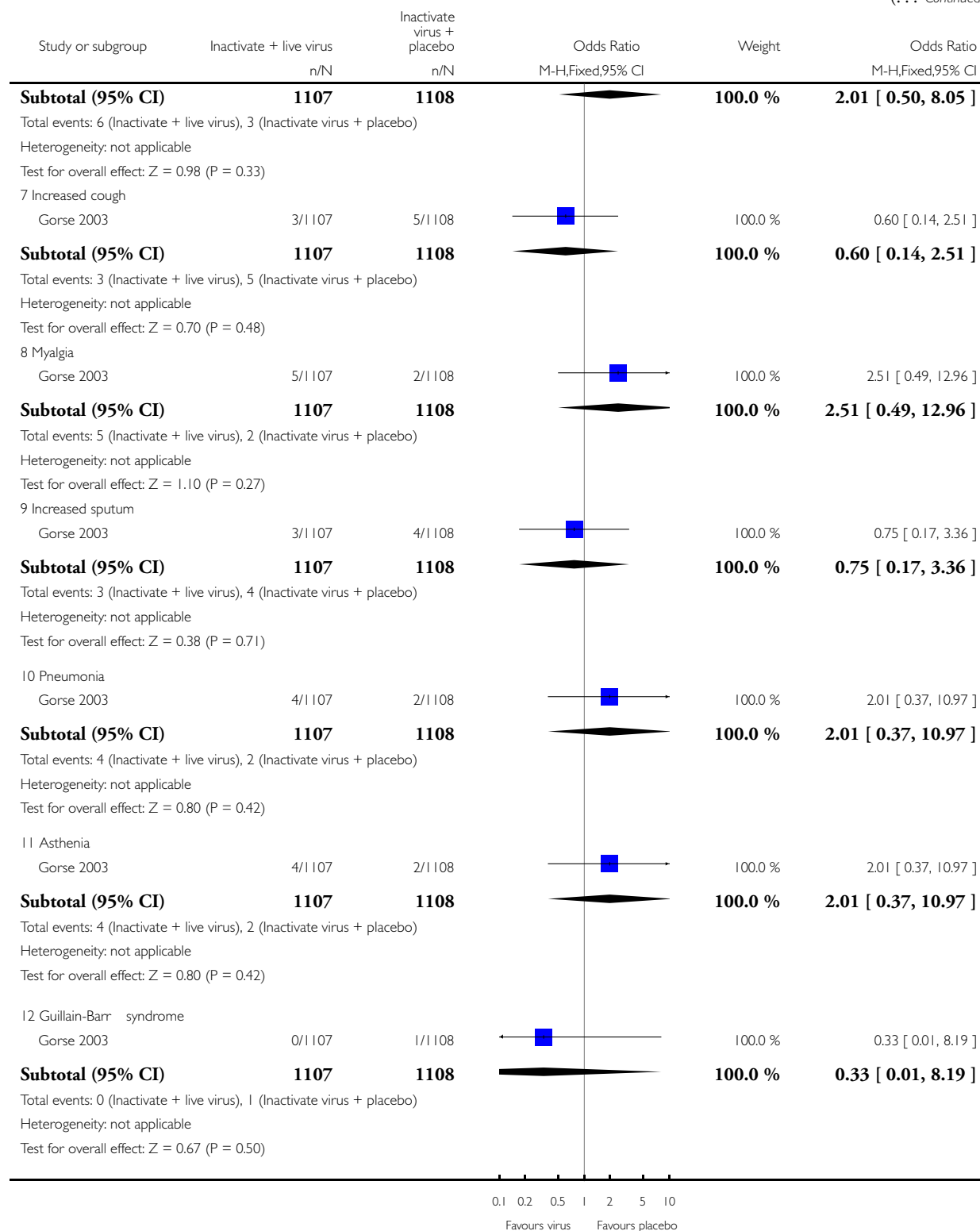
Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 17 Number of participants with early adverse effects (by type)



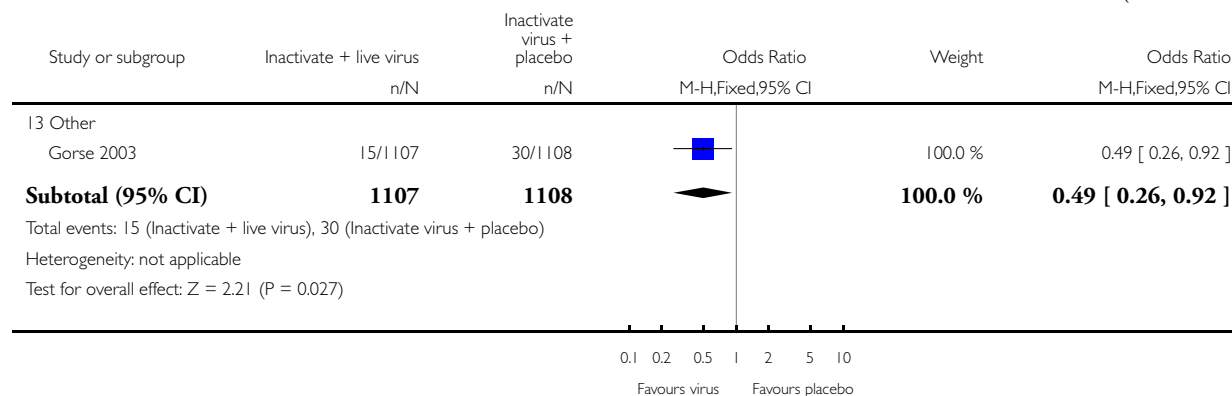
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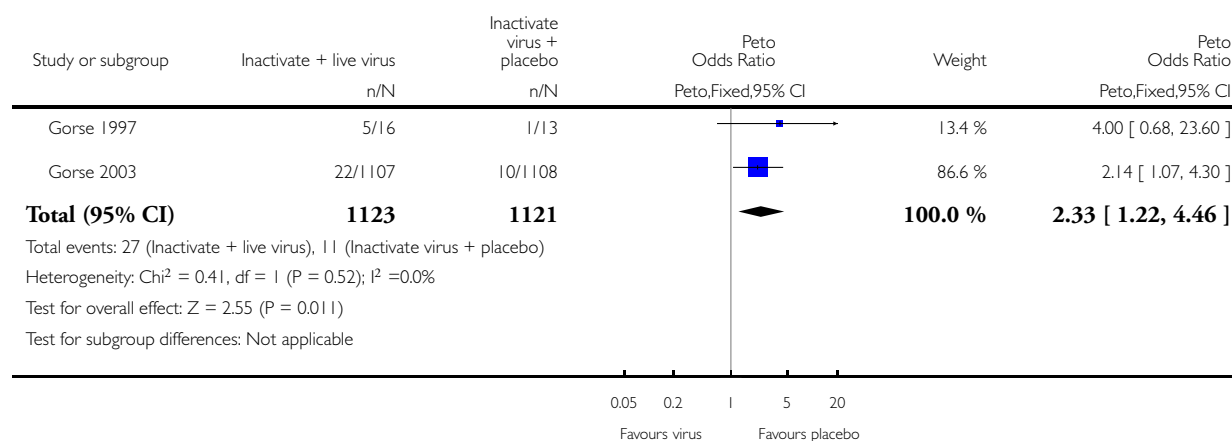


Analysis 2.18. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 18 Participants with late adverse effects.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 18 Participants with late adverse effects

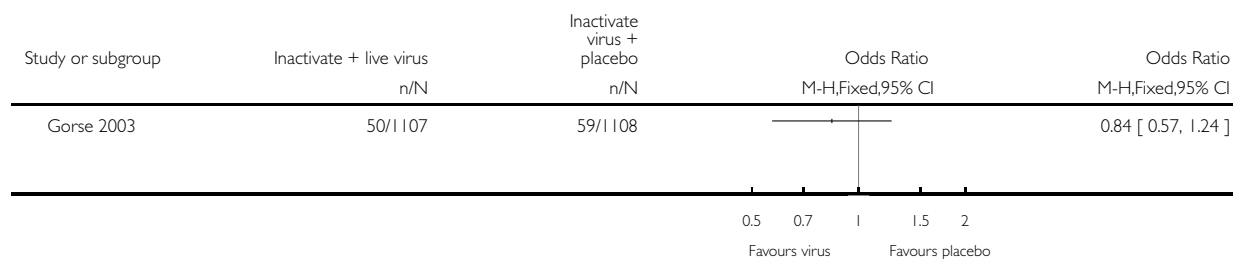


Analysis 2.19. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 19 Acute respiratory illness subsequently documented as influenza-related.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 19 Acute respiratory illness subsequently documented as influenza-related

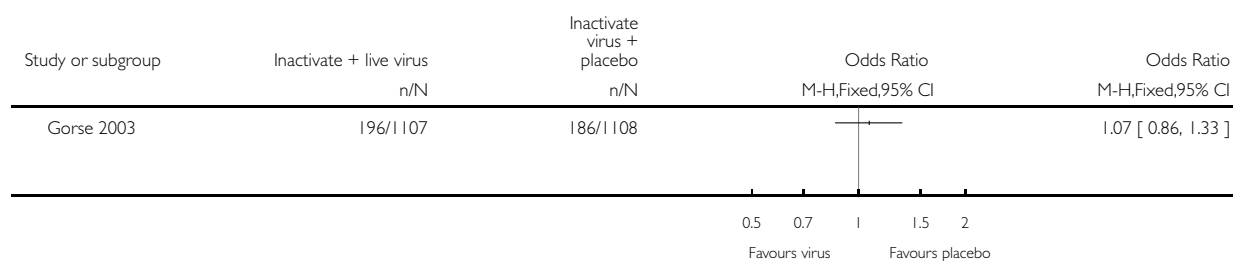


Analysis 2.20. Comparison 2 Inactivated + live virus versus inactivated virus + placebo, Outcome 20 Participants with at least one influenza-like illness.

Review: Influenza vaccine for chronic obstructive pulmonary disease (COPD)

Comparison: 2 Inactivated + live virus versus inactivated virus + placebo

Outcome: 20 Participants with at least one influenza-like illness



APPENDICES

Appendix I. Sources and search methods for the Cochrane Airways Trials Register

Electronic searches: core databases

Database	Frequency of search
CENTRAL (<i>the Cochrane Library</i>)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify trials for the Cochrane Airways Trials Register

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema\$.mp.
4. (chronic\$ adj3 bronchiti\$).mp.
5. (obstruct\$ adj3 (pulmonary or lung\$ or airway\$ or airflow\$ or bronch\$ or respirat\$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

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

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

Appendix 2. Search strategy to identify relevant trials from the Cochrane Airways Trials Register

Search via Cochrane Register of Studies (CRS Web)

- #1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
- #2 MeSH DESCRIPTOR Bronchitis, Chronic
- #3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
- #4 COPD:MISC1
- #5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
- #6 #1 OR #2 OR #3 OR #4 OR #5
- #7 MeSH DESCRIPTOR Influenza Vaccines
- #8 MeSH DESCRIPTOR Vaccines
- #9 (influenza* or flu*) NEAR (vaccin* or immuni* or inoculat*)
- #10 flumist
- #11 trivalent
- #12 CAIV
- #13 LAIV
- #14 medimmune
- #15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
- #16 #6 AND #15

WHAT'S NEW

Last assessed as up-to-date: 5 December 2017.

Date	Event	Description
5 December 2017	New search has been performed	Literature search keywords updated and search re-run
5 December 2017	New citation required but conclusions have not changed	No new studies included. Updated to current review format including summary of findings table and risk of bias

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 3, 2000

Date	Event	Description
11 June 2010	New search has been performed	Literature search re-run; no new studies found.
23 June 2009	New search has been performed	Literature search re-run; no new studies found.
28 July 2008	Amended	Converted to new review format.
14 May 2007	New search has been performed	Literature search conducted, no new studies found. Second published report of Gorse 2003 located via searching added, and consequential text changes made
15 August 2006	New citation required and conclusions have changed	There are two new trials (five reports). Gorse 2003 included 2215 people with COPD and Wongsurakiat 2004 included 132 people with COPD. New outcomes have been included: *Acute infection subsequently documented as influenza-related *Cost effectiveness *Number of people with exacerbations A significant protective effect has now been shown of influenza vaccine on exacerbations of COPD

CONTRIBUTIONS OF AUTHORS

Kopsaftis Z: conducted 2018 update: updated search terms, assessed search results, led write up.

Wood-Baker R: protocol, literature search, reviewed papers for inclusion, format of data extraction sheet, analyses, and discussion.

Poole PJ: initial protocol, literature search, reviewed papers for inclusion, contributed to format of data extraction sheet, review write up, analyses, and discussion. Conducted 2006 update. Assessed results from 2007, 2009, and 2018 search updates and contributed to writing each version. Remains the senior and contact author.

DECLARATIONS OF INTEREST

Kopsaftis Z: none known

Wood-Baker R: none known

Poole PJ: none known

SOURCES OF SUPPORT

Internal sources

- The authors declare that no such funding was received for this systematic review, Other.

External sources

- Health Research Council of New Zealand Summer Studentship, New Zealand.
- NHS Executive Eastern Region, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Update in 2018 included a change in format to reflect current Cochrane practice; including a revision of risk of bias assessment for all included studies and development of a 'Summary of findings' table; split outcomes into primary and secondary; searched clinical trials registries; added all required headings for methods and used either existing, revised, or standard text provided by Cochrane Airways.

Major update 2004-5, following searches in 2003 and 2004, located two further trials (5 reports).

New outcomes have been included:

- Acute infection subsequently documented as influenza-related
- Cost effectiveness
- Number of people with exacerbations

INDEX TERMS

Medical Subject Headings (MeSH)

Influenza Vaccines [adverse effects; *therapeutic use]; Influenza, Human [prevention & control]; Lung Diseases, Obstructive [*complications]; Randomized Controlled Trials as Topic; Vaccines, Attenuated [adverse effects; therapeutic use]; Vaccines, Inactivated [adverse effects; therapeutic use]

MeSH check words

Aged; Humans

Chapter 4.

Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease

(Systematic review and meta-analysis)

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Statement of authorship for jointly authored papers within the thesis

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Author contributions:

By signing the Statement of Authorship, each author certifies their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

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Contribution to the paper	Updated the Cochrane protocol, screened the literature search based on titles and abstracts, performed second full text screening to identify studies for inclusion, extracted study data for characteristics, risk of bias and results, analysed the data including meta-analysis and narrative synthesis, drafted manuscript and sent to co-authors for input, made changes based on co-author, peer review and editorial feedback and approved final version.		
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Contribution to the paper	Agree with manuscript results and conclusions, approved final version and supervised the process.		
Signature		Date	4/3/19

Often people with COPD experience acute exacerbations resulting in a worsening of symptoms including breathlessness, which necessitated transport to hospital for management. Treatment is often initiated in transit where oxygen therapy is frequently administered. However, people with COPD are prone to retaining carbon dioxide which may be potentiated by delivery of oxygen at a higher flow rate. There is scarce literature evaluating this key area of COPD management and in 2006 an empty Cochrane Review was published on the area to further illustrate this fact. An update of this review was undertaken in order to identify any new evidence and bring it to light.

The Cochrane Database of Systematic Reviews is frequently used to underpin policy, practice and provide recommendations for future evaluations and research based on a methodologically rigorous systematic appraisal of the available published and unpublished evidence. Cochrane practices not only ensure that a broad cross-section of resources are searched to identify relevant studies for inclusion, it also safeguards the quality of evidence with risk of bias evaluations alongside each study, to identify any possible issues with interpretation of results. Therefore, to systematically consolidate evidence to underpin a best-practice clinical resource, it was necessary to perform a Cochrane review to establish an evidence base of current interventions globally and to determine what has been effective, ineffective and build recommendations based on this available data.

Only one randomised controlled trial involving 214 participants was identified in the global literature for inclusion in the review. The study is dated at almost ten years old, however, results were alarming. The available evidence suggests that the use of a titrated approach to oxygen delivery significantly reduces mortality in individuals transported to hospital for AECOPD. No difference between the titrated approach and high-flow oxygen delivery was identified for other important clinical outcomes including treatment failure requiring ventilation, arterial blood gas and hospital utilisation. Other important outcomes (e.g., quality of life, lung function and dyspnoea) remain unexplored.



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Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease (Review)

Kopsaftis Z, Carson-Chahhoud KV, Austin MA, Wood-Baker R, Smith BJ

Kopsaftis Z, Carson-Chahhoud KV, Austin MA, Wood-Baker R, Smith BJ.

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD), a leading cause of morbidity and mortality in the developed world, is characterised by acute deterioration in symptoms. During these exacerbations, people are prone to developing alveolar hypoventilation, which may be contributed to by the administration of high inspired oxygen concentrations.

Objectives

To determine the effect of different inspired oxygen concentrations (“high flow” compared to “controlled”) in the pre-hospital setting on outcome for people with acute exacerbations of COPD.

Search methods

The Cochrane Airways Group Specialised Register, reference lists of articles and online clinical trial databases were searched. Authors of identified Randomised Controlled Trials (RCTs) were also contacted for details of other relevant, published and unpublished studies. The most recent search was conducted on 14 March 2018.

Selection criteria

RCTs comparing oxygen therapy at different concentrations or oxygen therapy versus placebo in the pre-hospital setting for treatment of acute exacerbations of COPD (AECOPD) were eligible.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

The search identified a total of 824 citations; one study was identified for inclusion and two studies are awaiting classification. Participants involved in the included study were adults receiving treatment by paramedics en route to hospital with AECOPD. A statistically significant reduction in mortality was observed in favour of the titrated oxygen group (two deaths in the titrated oxygen group compared

to 11 deaths in the high-flow control arm; Relative risk 0.22 95%CI 0.05 to 0.97). No statistically significant differences were observed between groups for arterial blood gas, treatment failure requiring invasive or non-invasive ventilation or hospital utilisation. No data were reported for quality of life, lung function or dyspnoea. Risk of bias within the included study was largely unclear with high risk in domains relating to performance and attrition bias. Evidence was GRADED as low certainty.

Authors' conclusions

The one included study found a significant reduction in mortality for the titrated oxygen arm compared to high-flow control arm. However, the paucity of evidence limits the reliability of these findings. There is an urgent need for robust, well-designed randomised controlled trials to investigate the effect of oxygen therapies in the pre-hospital setting for people with AECOPD.

PLAIN LANGUAGE SUMMARY

Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease

Background

Chronic obstructive pulmonary disease is a chronic condition characterised by progressively worsening reduction of airflow through the lungs. People with COPD are prone to sudden episodes where their symptoms become worse (e.g. persistent increase in shortness of breath and changes in sputum volume and consistency) and oxygen levels may fall. Initial treatment during these episodes when patients are being transported to hospital usually includes oxygen; however, this may cause a rise in the carbon dioxide levels that can be harmful.

Review question

This review aimed to investigate if oxygen therapy delivered at different concentrations based on the patient needs would be less-harmful, more-harmful or have no change when compared to a control group using high-flow oxygen.

Study characteristics

To investigate this question we looked for randomised controlled trials that involved patients being transferred to hospital because of COPD symptom flare-ups. We were interested in trials that compared different flow rates (concentrations) of oxygen delivered in an ambulance.

Key results

Only one study was found that answered the review question. The study randomised participants to either have titrated oxygen or high-flow oxygen. Titrated oxygen targets SpO₂ between 88 and 92%,

There were fewer deaths in the titrated oxygen group compared to the control group using high-flow oxygen.

Certainty of evidence

Due to inclusion of only one study we are very uncertain about the effectiveness of this intervention. We GRADED the evidence as low certainty.

Bottom line

The one included study found that titrated oxygen applied when people are being transported to hospital reduces the risk of death compared to using high-flow oxygen. However, there is a lack of evidence to confidently claim that titrated oxygen is safer and more effective than high-flow oxygen.

This plain language summary is current to 14 March 2018.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

High flow compared to Titrated oxygen therapy for acute exacerbations of chronic obstructive pulmonary disease						
Patient or population: acute exacerbations of chronic obstructive pulmonary disease Setting: pre-hospital setting Intervention: High flow Comparison: Titrated oxygen therapy						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with high flow oxygen therapy	Risk with titrated oxygen therapy				
Mortality			RR 0.22 (0.05 to 0.97)	214 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	A significant difference in mortality was observed with 11 deaths in the high flow oxygen arm compared to two deaths in the titrated oxygen arm (p = 0.05). All deaths occurred after arrival at the hospital and two in intensive care. Respiratory failure was the cause of mortality in all cases, with approximately 70% of deaths occurring within the first five days following admission for both treatment arms. Quality of evidence very low due to the inclusion of only one included study

	94 per 1,000	21 per 1,000 (5 to 91)				
Arterial Blood Gas (pH)	The mean arterial Blood Gas (pH) was 7.29 pH	MD 0.06 pH higher (0.04 lower to 0.16 higher)	-	214 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	Based on the intention to treat analysis for the COPD sub-group no significant difference between treatment arms for blood gas measurements was observed between groups (p = 0.23). Quality of evidence very low due to the inclusion of only one included study
Ventilation of any type			RR 0.67 (0.30 to 1.50)	189 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	No significant difference observed between treatment arms for ventilation requirement for per protocol or intention-to-treat analyses. Quality of evidence very low due to the inclusion of only one included study
	143 per 1,000	96 per 1,000 (43 to 215)				
Length of stay	The mean length of stay was 6.3 days	MD 0.88 days lower (2.25 lower to 0.49 higher)	-	214 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	No significant difference was observed between treatment arms in length of hospital stay for the intention-to-treat analysis (p=0.21)
Quality of life	-	-	-	-	-	Outcome not reported as an outcome in the single included study

Lung function	-	-	-	-	-	Outcome not reported as an outcome in the single included study
Dyspnoea score	-	-	-	-	-	Outcome not reported as an outcome in the single included study

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

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^a Downgraded once for indirectness because there was a single included study with moderate sample size (n = 214). The study was conducted in one state within Australia only.

^b Downgraded twice for imprecision because a low number of events led to a wide 95% CIs, with upper limit of the 95%CI approaching or exceeding one.

BACKGROUND

This is an update of a previously published review (Austin 2006) in The Cochrane Database of Systematic Reviews (Issue 3, 2006).

Description of the condition

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide (Lozano 2013) and contributes to global morbidity and mortality, particularly in those over 45 years of age. This burden is expected to continue to rise for the foreseeable future. By 2020, COPD is expected to be the third leading cause of death in the world (GOLD 2018; Lozano 2013; Mendis 2014; Vos 2012). COPD is not one single condition, but instead is an umbrella term used to describe a combination of chronic lung diseases that cause inflammation, including chronic bronchitis, emphysema and asthma (WHO 2018). Tobacco smoking is known to be the most common cause of COPD with lifelong smokers having a 50% probability of developing COPD in later life (Laniado-Laborin 2009). Other modifiable risk factors include: exposure to environmental smoke, such as fumes from carbon-based cooking (including early childhood exposure) and heating fuels used for cooking like charcoal and gas, occupational hazards such as exposure to chemicals and pollutants, poor nutrition and pneumonia or other respiratory infections during childhood (AIHW 2016). Non-modifiable risk factors include age, as COPD is more common as people age and genetic predisposition (AIHW 2016).

The disease is characterised by irreversible and progressive destruction of lung parenchyma and structural change to small airways owing to a chronic inflammatory process (GOLD 2018). This results in breathlessness (initially with exertion), chronic cough and sputum production that gradually worsen as the condition progresses over time (WHO 2018). An acute, abnormal deterioration of respiratory symptoms is termed an acute exacerbation of COPD (AECOPD) (GOLD 2018). These are serious episodes of increasing breathlessness, cough and sputum production that can last from several days to weeks that can require hospitalisation and result in death (WHO 2018). COPD patients may develop alveolar hypoventilation, which results in an elevation of the partial pressure of arterial carbon dioxide (PaCO_2), known as hypercapnia, and a reduction in partial pressure of arterial oxygen (PaO_2), known as hypoxaemia (Abdo 2012). The combination of a PaO_2

below 60 and PaCO_2 above 45 is referred to as hypoventilatory (hypercapnic) respiratory failure. It is associated with poor outcomes in AECOPD (Groenewegen 2003). As COPD is a heterogeneous condition, different pathological processes predominate in different areas of the lung, resulting in wasted perfusion and differentially oxygenated blood on return to systemic circulation (Brill 2014; Cooper 2008).

Description of the intervention

In healthy non-smoking adults oxygen saturations of 94 to 98% are considered normal, with levels diminishing as people age (Brill 2014; Kane 2013). For example, a 70 year old may have an oxygen saturation of less than 94%, which may still be considered normal, particularly in the presence of co-morbidities such as heart failure (Kane 2013). People experiencing AECOPD typically present to hospital with lower levels of oxygen saturation in the blood due to the destruction of lung parenchyma and structural changes resulting in poor gas exchange (GOLD 2018). Thus, administration of oxygen at concentrations greater than that found in the surrounding air will help to increase oxygen saturation, or carbon dioxide excretion, or both (Brill 2014). Oxygen is one of the most commonly administered drugs in the pre-hospital and emergency setting, with an estimated 34% of people being transported by ambulance receiving it (Hale 2008). Thus administration in the pre-hospital setting typically occurs via medical or paramedical assistance, such as during ambulance transport. Its administration should be delivered with a targeted oxygen saturation rate and regular monitoring of patient response (Beasley 2015). In the context of COPD, supplemental oxygen delivered at moderate concentrations is typically adequate to overcome hypoxia related to an AECOPD (Brill 2014). A target SpO_2 (arterial oxygen saturation measured by pulse oximeter) range of 88 to 92% is recommended by Australian (Beasley 2015), European (Kane 2013), British (O'Driscoll 2017) and American (Rochwerg 2017) guidelines, for the treatment of AECOPD. Moreover, a greater than two-fold reduction in mortality with pre-hospital oxygen therapy titrated to this target has been demonstrated, compared with higher concentrations of oxygen therapy. Oxygen can be administered via nasal cannulae or face masks, with nasal cannulae reported to be the simplest mode of administration as they are less likely to fall off and allow patients to speak while undergoing treatment (Brill 2014). Disadvantages to nasal cannulae, however, include patient reports of nasal dryness/epistaxis and discomfort as well as ineffectiveness due to mouth breathing, degree of nasal congestion and respiratory rate and/or minute volume (Brill 2014).

How the intervention might work

The administration of oxygen for people with COPD is intended to relieve hypoxaemia, not breathlessness and as a mainstay of treatment for exacerbations is often delivered in conjunction with other treatments including inhaled bronchodilators (Beasley 2015; Kane 2013; O'Driscoll 2017). Impairment of gas exchange and the development of respiratory failure may be precipitated by a variety of factors, one of which is the administration of oxygen at high concentrations. In this group of patients, the administration of high inspired concentrations of oxygen may cause a worsening of respiratory function, leading to further elevation of arterial carbon dioxide concentration (Donald 1949; McNicol 1965; Plant

2001). In addition, high dose oxygen may cause injury to other organs, such as the heart, and lead to morbidity and mortality through other mechanisms. Therefore, it is important for oxygen to be delivered at moderate concentrations (controlled oxygen therapy) with monitoring to overcome hypoxia and prevent oxygen-induced hypercapnia (Brill 2014). Oxygen titration can be achieved through altering the oxygen flow rate or administering a mixture of air and oxygen in set proportions, with certain delivery devices, to allow the patient to breathe a known fraction of inspired oxygen (Brill 2014). When the appropriate level of oxygen is administered to reach the target SpO_2 of 88 to 92% in the pre-hospital setting, this will relieve hypoxaemia and reduce the risk of mortality (Brill 2014).

Why it is important to do this review

Supplemental oxygen therapy in the emergency situation has traditionally been administered using “high-flow” oxygen. This approach has been adopted on the basis that the population as a whole are at greater risk from failure to correct oxygenation than from its excessive administration. Indeed, for people with AECOPD, oxygen driven nebulisers via mask at flows of 6 to 8 L/min will often be used to achieve nebulization of bronchodilator. A retrospective study found that the administration of an inspired oxygen concentration above 28% was associated with a 14% in-hospital mortality, compared to a 2% in-hospital mortality for those administered a concentration of oxygen less than 28% (Denniston 2002). This has raised questions about the optimal delivery of oxygen to people with AECOPD in the pre-hospital setting. One prospective prevalence study in the United Kingdom identified that one in five patients out of 983 admitted to hospital with AECOPD had respiratory acidosis (Plant 2000). A more recent cohort study of 415 patients with AECOPD conducted across Asia, Australia and New Zealand identified low compliance with blood gas testing, particularly in South East Asia, suggesting the potential for under-diagnosis of clinically important hypercapnia, which may have implications for oxygen therapy (Kelly 2018). Therefore, the potential for high-flow oxygen administration in the pre-hospital setting coupled with lack of blood gas testing to identify acidosis in the emergency department presents a need for evidence consolidation around the application of oxygen therapy in the pre-hospital setting. The results of this review will provide updated evidence for clinical practice guidelines and raise awareness of this important clinical issue.

OBJECTIVES

To determine the effect of different oxygen therapies in the pre-hospital setting (prior to casualty/emergency department) of AECOPD.

METHODS

Criteria for considering studies for this review

Types of studies

We considered RCTs for inclusion within this review, with full text and abstracts both accepted. There was no language or publication date restriction.

Types of participants

Studies were included that evaluated adults with AECOPD requiring medical or paramedical assistance in the pre-hospital setting. AECOPD was defined as any combination of: an increase in breathlessness, sputum volume, sputum purulence, cough or wheeze. Spirometric evidence of airflow obstruction (forced expired volume in one second (FEV_1)/Forced Vital Capacity (FVC) < 0.7) plus a smoking history of greater than 10 pack history years or fulfilling an accepted standard definition (e.g. Global initiative for chronic Obstructive Lung Disease (GOLD) or American Thoracic Society (ATS)). Studies were excluded if they investigated patients with acute asthma.

Types of interventions

Studies were included that evaluated high fractional inspired concentration (FIO_2) (> 28%) oxygen therapy compared to either:

- 1) placebo;
- 2) low fractional inspired concentration (FIO_2) (< 28%) oxygen therapy;
- 3) titrated oxygen therapy; or
- 4) standard care.

In acknowledgement that oxygen therapy is rarely seen in isolation when treating AECOPD, additional treatment interventions (e.g. bronchodilators and corticosteroids) were accepted but were required to be standardised to both groups.

Types of outcome measures

Primary outcomes

Mortality from respiratory and all causes.

Secondary outcomes

1. Quality of life
2. Arterial blood gas
3. Lung function (FEV_1 /FVC)
4. Dyspnoea score

5. Treatment failure requiring invasive or non-invasive ventilation
 6. Hospital utilisation (length of stay, readmission rate, emergency department presentations)
- Reporting in the publications of one or more of the outcomes listed above was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

The previously published version of this review included searches up to August 2008 and did not find any studies for inclusion. The search period for this update is August 2008 to March 2018. For this update we searched the Cochrane Airways Specialised Register of trials up to 14 March 2018 through contact with the information specialist for the Group, using search terms relevant to this review. The Cochrane Airways Specialised Register contains studies identified from several sources:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS Web);
2. weekly searches of MEDLINE Ovid SP;
3. weekly searches of Embase Ovid SP;
4. Monthly searches of PsycINFO Ovid SP;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. handsearches of the proceedings of major respiratory conferences.

Studies contained in the Specialised Register are identified through search strategies based on the scope of Cochrane Airways. Please see [Appendix 1](#) for details of these strategies, as well as a list of handsearched conference proceedings. See [Appendix 2](#) for search terms used to identify studies for this review.

A search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) were also conducted. All sources were searched from inception, with no restriction on language of publication.

Searching other resources

We handsearched reference lists of all available included studies and review articles to identify potentially relevant citations and we made inquiries to authors of included studies regarding other published or unpublished trials known to them.

Data collection and analysis

Selection of studies

Two review authors (ZK and KVC) independently screened the titles and abstracts returned from the literature search and separated them into the following groups 'potential inclusion' or 'exclude not relevant'. Full-text was obtained where possible for the studies in the 'potential inclusion group' and the same two review authors independently assessed them for inclusion. Excluded studies were either tagged as 'exclude not relevant' or 'exclude but relevant' with reasons for exclusion recorded. The authors encountered no disagreement during the study selection process, however, had there been disagreements this would have been resolved in consultation with a third review author (BJS). A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram was used to demonstrate the study selection process.

Data extraction and management

Two review authors (ZK and KVC) independently extracted data for each included trial into a standardised, pilot tested data extraction form. Data extracted in duplicate included: study characteristics, outcome and risk of bias data. Any disagreements were resolved through discussion. One review author (KVC) entered the data into Review Manager and this was double-checked by ZK to ensure it was transferred correctly.

Assessment of risk of bias in included studies

Two review authors (ZK and KVC) assessed each study for risk of bias, in line with recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), for: random sequence generation, allocation concealment, blinding of participants and outcome assessors, handling of missing data, selective outcome reporting and other threats to study validity. An assessment of either high, unclear or low risk of bias was assigned to each domain with supporting justification recorded in the 'Risk of Bias' table. Disagreements during the risk of bias assessment process were resolved through discussion.

Assessment of bias in conducting the systematic review

This review has been revised to reflect current Cochrane reporting standards. All steps taken are described in the methods section of this publication. The original authors of this review (MA and RWB) are also the authors of one of the included studies ([Austin 2010](#)), neither of them were involved in the extraction or interpretation of data from this study; this was solely completed by ZK and KVC.

Measures of treatment effect

Meta-analyses was to be conducted where it would provide a meaningful outcome e.g. studies had sufficiently homogeneous methodology. Had there been sufficient studies for meta-analysis, continuous and dichotomous data would have been extracted and analysed in accordance with standard statistical techniques with a fixed-effects model for all studies deemed homogeneous enough to be pooled. In the presence of significant heterogeneity (I^2 -statistic $\geq 50\%$), a random-effects model would have been used. Had meta-analysis been possible, mean differences (MDs) with 95% confidence interval (CIs) and pooled MDs for standardised mean differences (SMDs) for continuous outcomes would have been calculated. Risk ratios (RRs) with 95% CIs would have been calculated for dichotomous outcomes.

Given there was only a single study for inclusion, a qualitative synthesis was conducted and all data was entered and synthesised using Review Manager 5.3 software, as per the pre-specified protocol. Despite no meta-analysis being conducted the data for all reported, relevant outcomes were used to create individual forest plots for visualisation of the data.

Unit of analysis issues

The unit of analysis was considered to be the participant. Had there been sufficient studies for meta-analysis, unit of analysis issues would have been addressed through the use of generic inverse variance (GIV) and entering effect estimates and their standard errors, as per Section 7.7.7 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Dealing with missing data

Should there have been a need, missing information regarding participants on an available case analysis basis would have been conducted, as described in Chapter 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If statistics essential for analysis were missing (e.g. when group means and standard deviations for both groups were not reported) and could not be calculated from other data, attempts would have been made to contact study authors to obtain missing data. In the event of loss of participants that occurred before baseline measurements were obtained, an assumption would have been made that this would have no effect on the final outcome.

Assessment of heterogeneity

We planned to assess statistical heterogeneity using a combination of tests including I^2 statistic $\geq 50\%$ and visual inspection of data. Statistical significance would have been determined by the Der-Simonian and Laird method of analysis presented with a P-value less than 0.05 (Der Simonian 1986). In the presence of significant heterogeneity (as per the criteria above), data would have been re-analysed using both fixed-effects and random-effects models. Given no meta-analyses were conducted in this review, heterogeneity was not assessed.

Assessment of reporting biases

We planned to explore potential reporting biases using a funnel plot had there been ten or more studies available for meta-analysis. Instead, this was extrapolated as a possible risk of bias within the "other bias" section in the risk of bias tables.

Data synthesis

Data were combined from included trials using Review Manager 5.3 software. Studies were reported by using intention-to-treat analysis when all participants who were randomly assigned during the study were assessed, regardless of whether they received the intervention/study treatment to which they were allocated.

Summary of findings table

A 'Summary of findings table' was constructed from the available data using the following outcomes:

1. Mortality
2. Quality of life
3. Arterial blood gas
4. Lung function (FEV_1 /FVC)
5. Dyspnoea score
6. Treatment failure requiring invasive or non-invasive ventilation
7. Hospital utilisation (length of stay, readmission rate, emergency department presentations)

Quality of the body of evidence was assessed according to the five GRADE considerations:

1. Study limitations
2. Indirectness
3. Inconsistency of results
4. Imprecision of results
5. Publication bias

This was undertaken in accordance with guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions*, section 8.5 and chapter 12 (Higgins 2011) using GRADEpro software (GRADEpro GDT). Justification for decisions regarding the up-grading or downgrading of evidence quality for each outcome was provided through footnotes.

Subgroup analysis and investigation of heterogeneity

Planned subgroups included:

- High fractional inspired concentration oxygen therapy VERSUS placebo
- High fractional inspired concentration oxygen therapy VERSUS low fractional inspired concentration oxygen
- High fractional inspired concentration oxygen therapy VERSUS titrated oxygen therapy
- High fractional inspired concentration oxygen therapy VERSUS standard care

A single study was included, so subgroup analyses could not be performed.

Sensitivity analysis

Had there been sufficient studies for meta-analysis, a sensitivity analysis based on risk of bias would have been conducted.

RESULTS

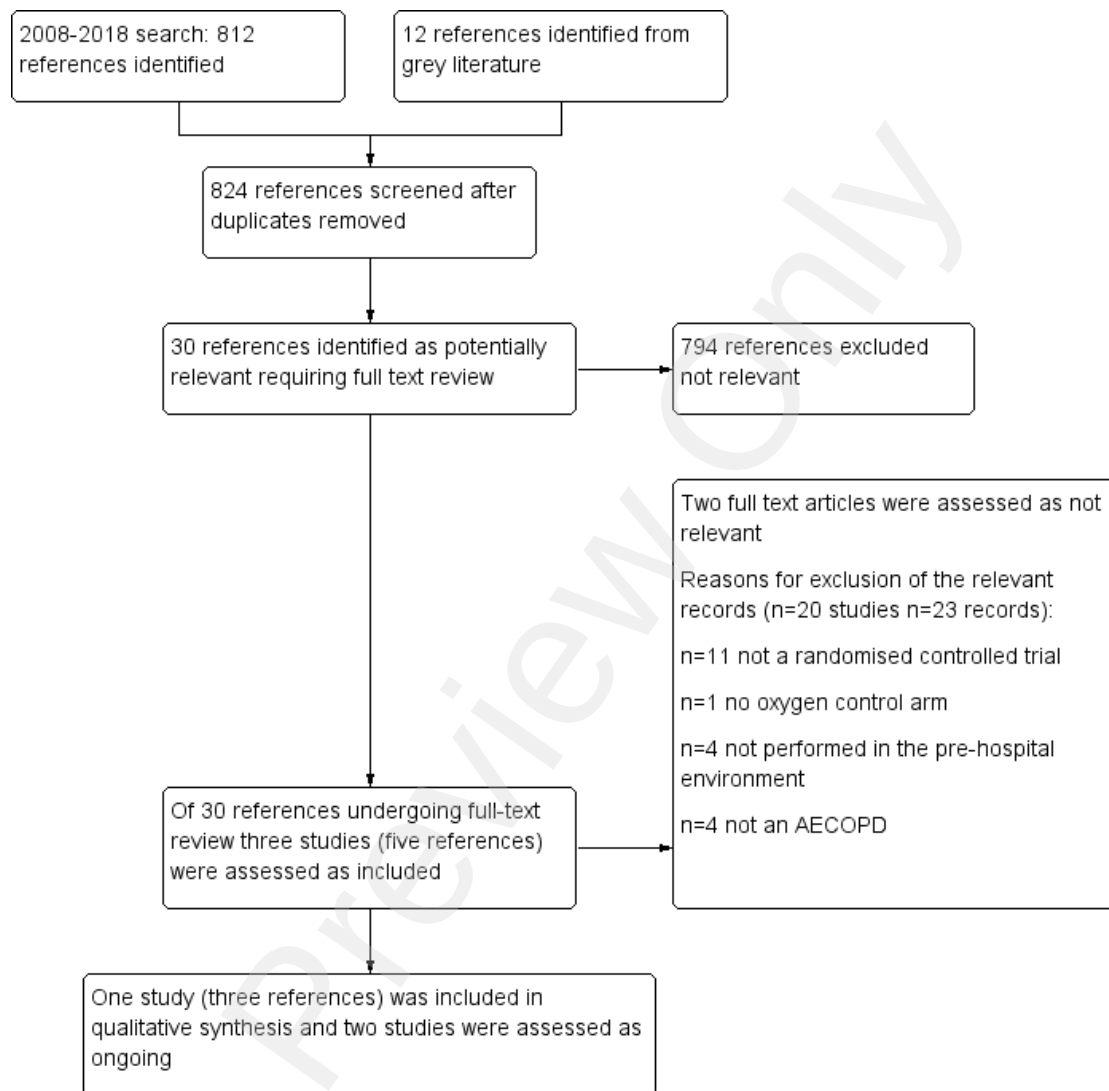
Description of studies

See [Characteristics of included studies](#), [Characteristics of excluded studies](#) and [Characteristics of ongoing studies](#) for additional information.

Results of the search

The previous version of this review did not identify any included studies. Through database searches conducted for this updated version which covered the period from 2008 to 2018 we identified a total of 812 records for screening. Twelve additional records were identified through screening of grey literature such as online clinical trial registries, producing a total of 824 records for review. On the basis of title and abstract 794 records were excluded and found not to be relevant. Full text was obtained for the remaining 30 records. Five records for three studies were found to be relevant and were included in the review (one complete and two ongoing) with the remaining 23 records assessed as excluded but relevant. For further details of screening processes, see the study flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.



Included studies

One study (three records) was identified for inclusion (Austin 2010). While this study enrolled 405 patients, only 214 of these had a diagnosis of AECOPD and it is this subset that has been included in analyses for this review. This study was a cluster randomised controlled parallel group trial undertaken with the ambulance service in Hobart, Tasmania, Australia. The study population were comprised of people aged 35 years or older with breathlessness and a history or risk of COPD. They were treated by paramedics, transported and admitted to the Royal Hobart Hospital.

Intervention

Patients received titrated oxygen treatment delivered by nasal prongs to achieve arterial oxygen saturations between 88% and 92%, with concurrent bronchodilator treatment delivered by a nebuliser driven by compressed air and delivered via a facemask over the nasal prongs. Pulse oximeters were used to measure oxygen saturations and titrate oxygen to target saturations. All patients received other standard treatment according to Tasmanian Ambulance Service guidelines, including basic support, nebulised bronchodilators (salbutamol 5 mg made up in 2.5 mL normal saline, ipratropium bromide 500 µg made up with 2.5 mL normal

saline), dexamethasone 8 mg intravenously and where necessary salbutamol 200 to 300 mg intravenously or 500 mg intramuscularly.

Control

Control patients received high flow oxygen treatment (8 to 10 L/min) administered by a non-rebreather face mask and bronchodilators delivered by nebulization with oxygen at flows of 6 to 8 L/min. Oximeters were used to measure oxygen saturation in the high flow oxygen arm. All patients received other standard treatment according to Tasmanian Ambulance Service guidelines, including basic support, nebulised bronchodilators (salbutamol 5 mg made up in 2.5 mL normal saline, ipratropium bromide 500 µg made up with 2.5 mL normal saline), dexamethasone 8 mg intravenously and where necessary salbutamol 200 to 300 mg intravenously or 500 mg intramuscularly.

For more information about study characteristics see [Characteristics of included studies](#).

Ongoing studies

Two ongoing studies were identified from the literature search ([Eiser 2004](#) and [Elliott 2004](#)), but no data were available after contacting the authors. Description of these ongoing studies are in Characteristics of ongoing studies.

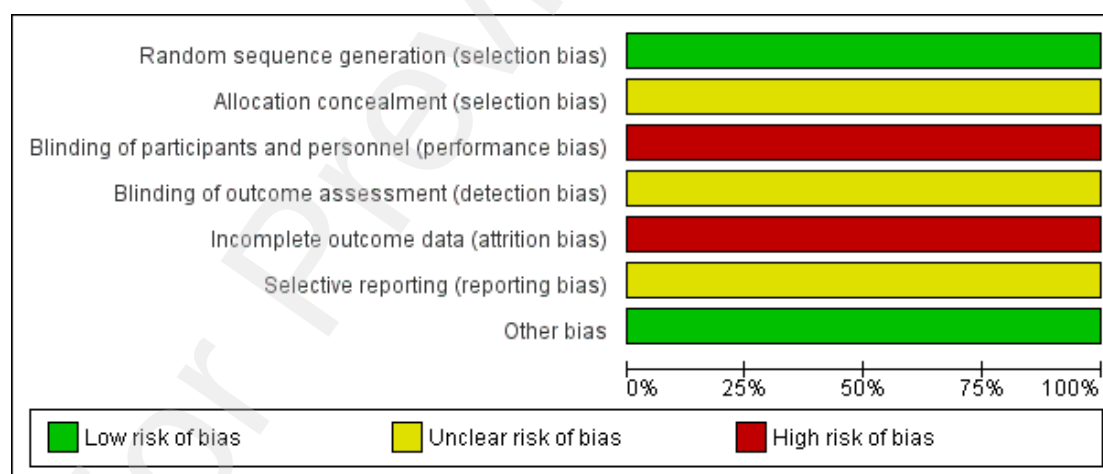
Excluded studies

Twenty studies were identified as excluded but relevant to the review (23 records). The primary reason for exclusion was the lack of RCT design, found in 11 studies ([Characteristics of excluded studies](#)). Three of these studies were reviews, one a clinical audit and the remaining studies were not randomised. Four studies were not conducted in the pre-hospital setting, but instead undertaken once patients were admitted to hospital, one did not have an oxygen comparator arm and the remaining four studies were not conducted in patient cohorts with a majority diagnosis ($\geq 60\%$) of AECOPD.

Risk of bias in included studies

Risk of bias is reported for the [Austin 2010](#) study and is displayed visually in [Figure 2](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Sequence generation was assessed as low risk of bias since computer random number generation after stratification by rurality was performed. Allocation concealment was assessed as unclear risk of bias as method of allocation was not reported, however, the

authors state that stratification by rurality was performed to reduce differences associated with transportation time between urban and rural areas, ensuring that treatment allocation was concealed before randomisation.

Blinding

Authors report that paramedics, the research team and hospital staff were not blinded to treatment after randomisation and as such, blinding for participants was assessed as a high risk of bias. A respiratory physician blinded to treatment allocation reviewed lung function data and smoking history, from private and public medical records; however, no mention was made regarding the blinding for other outcome assessors. Therefore, binding of outcome assessors was classified as an unclear risk of bias.

Incomplete outcome data

Data were reported to be missing from both the ambulance and hospital patient records, resulting in denominators varying among analyses. Intention-to-treat analysis occurred, however, this domain was assessed as a high risk of bias.

Selective reporting

No pre-specified protocol available to determine selective reporting, therefore this was assessed as an unclear risk of bias.

Other potential sources of bias

No other biases were identified.

Effects of interventions

See: [Summary of findings for the main comparison High flow compared to Titrated oxygen therapy for acute exacerbations of chronic obstructive pulmonary disease](#)

All data below are reported for the one included [Austin 2010](#) study.

Primary outcome

Mortality from respiratory and all causes

Among the cohort with confirmed AECOPD, a significant difference in mortality was observed with 11 deaths in the high flow arm compared to two deaths in the titrated oxygen arm (RR 0.22, 95% CI: 0.05 to 0.97; participants = 214; studies = 1, [Analysis 1.1](#)). All deaths occurred after arrival at the hospital, including two in the emergency department and two in intensive care. As reported in the paper, the cause of mortality was respiratory failure in all cases with approximately 70% of deaths occurring within the first five days following admission for both treatment arms.

Secondary outcomes

Quality of life

Quality of life was not reported as an outcome in this study.

Arterial blood gas

Based on the intention to treat analysis for the AECOPD subgroup no significant difference between treatment arms for blood gas measurements was observed between groups (MD 0.06, 95% CI: -0.04 to 0.16; participants = 38; studies = 1, [Analysis 1.2](#)). The per protocol analysis, however, reported in the paper indicates significantly less respiratory acidosis ($p = 0.01$) and acute hypercapnia ($p = 0.02$) between patients receiving titrated oxygen (intervention) compared to patients receiving high flow oxygen (control).

Lung function

Lung function was not reported as an outcome in this study.

Dyspnoea score

Dyspnoea was not reported as an outcome in this study.

Treatment failure requiring invasive or non-invasive ventilation

No significant difference was observed between treatment arms for ventilation of any type in the intention-to-treat analysis (RR 0.67, 95% CI: 0.30 to 1.50; participants = 189; studies = 1, [Analysis 1.3](#)); the split between invasive and non-invasive ventilation is available in [Analysis 2.1](#), however, this is not adjusted for clustering.

Hospital utilisation (length of stay, readmission rate, emergency department presentations)

No significant difference was observed between treatment arms in length of hospital stay for the intention-to-treat analysis (MD - 0.88 days, 95% CI: -2.25 to 0.49; participants = 214; studies = 1, [Analysis 1.4](#)). Other types of hospital utilisation were not reported as outcomes in this study.

DISCUSSION

Summary of main results

This review update identified one new study that satisfied the pre-defined inclusion criteria ([Austin 2010](#)). [Austin 2010](#) compared high flow oxygen therapy to a titrated approach in people with AECOPD in the pre-hospital setting. Two studies identified as ongoing in the original review were marked as awaiting classification ([Eiser 2004](#); [Elliott 2004](#)) as there were no data available for analysis and attempts to contact the authors were unsuccessful. The included study was a well-reported, well-conducted Australian cluster RCT ([Austin 2010](#)). For the primary outcome of mortality

(respiratory or all cause) a significantly higher risk of death (9%) was reported with a high flow treatment approach compared to a titrated oxygen approach (2%). All deaths were reportedly caused by respiratory failure and occurred once the patient arrived at hospital; 15% of reported deaths occurred in the emergency department and 15% occurred in the intensive care unit. With regard to arterial blood gas, [Austin 2010](#) reported no evidence of an effect with high flow compared to titrated oxygen therapy in the intention to treat analysis; however, participants who were treated per protocol with a titrated oxygen therapy approach were less likely to have respiratory acidosis due to acute hypercapnia. There was no evidence of a difference between high flow and titrated oxygen therapy for the outcomes treatment failure requiring invasive or non-invasive ventilation or hospital utilisation.

Overall completeness and applicability of evidence

The overall completeness and applicability of evidence was low given that only one study was identified for inclusion in this review, covering only one potential comparison (high flow versus titrated oxygen therapy) with a total of 214 participants with AE-COPD. The included study reported the primary outcome pre-specified in our review (mortality) and some of our secondary outcomes (arterial blood gas, hospital utilisation and treatment failure); however, several important secondary outcomes were not measured (e.g. quality of life, lung function and dyspnoea). While perhaps difficult to measure in a pre-hospital/emergency setting, these outcomes are nevertheless clinically relevant and important when considering the impact of this intervention on the patient's burden of disease. No studies were identified that compared high flow oxygen to placebo or standard care, though this is not surprising considering the ethical considerations of withholding first-line treatment from a participant suffering with AECOPD. No studies were found evaluating the effect of low flow oxygen therapy. The findings of this review are therefore limited by a paucity of available data and an inability to assess all pre-defined outcomes.

Quality of the evidence

Quality of evidence was low given the inclusion of only one study. The moderate sample size of $n = 216$ and methodologically rigorous study design, however, does facilitate the ability to draw some conclusions for clinical practice in the absence of other available data.

Potential biases in the review process

Every effort was made to reduce the impact of bias on this review. A pre-specified methodology was adhered to based on Cochrane standards ([Higgins 2011](#)). The systematic search for this review

was conducted through diverse means (i.e., electronic databases, conference proceedings, author contact and online clinical trial registries) by an experienced information specialist and experienced review team in order to identify all available and potentially relevant studies. However, considering the lack of available evidence returned by this search, it is likely that some publication bias was introduced leading to over or underestimation of the intervention effects, or indeed the inability to report on some outcomes altogether. From the original publication of this review, two studies have been moved from ongoing to awaiting classification ([Eiser 2004](#); [Elliott 2004](#)). This is likely illustrative of the difficulty authors face in having their results published and the ultimate lack of evidence available for inclusion in this review. Attempts were made to overcome this by contacting the authors and/or listed contact persons for these studies; however, no responses were received. While there may have been potential for false exclusion of relevant studies and data entry error, steps were taken to mitigate this by having two independent authors screen, extract and check data entry performed. The only included study was written by the two original authors of this review (MA and RW). The publication of the [Austin 2010](#) study occurred subsequent to this review. As a result, this may have been a source of bias, however, to mitigate this issue MA and RW were not involved in any capacity for protocol revision, study screening and selection, data extraction and analysis of the included and excluded studies.

Agreements and disagreements with other studies or reviews

The traditional approach to treatment of patients with shortness of breath is 'high flow' oxygen adopted on the basis that the population as a whole are at greater risk from failure to correct oxygenation than from its excessive administration ([Kane 2013](#)). The results of this review somewhat support a retrospective study by [Denniston 2002](#), that found that the administration of an inspired oxygen concentration above 28% was associated with a higher in-hospital mortality (of 14%) than administration of a concentration of oxygen less than 28% (mortality of 2%). Though [Denniston 2002](#) did not directly assess titrated oxygen therapy, it suggested that the continued use of a high flow approach was no longer appropriate. Although the non-randomised design meant that the results could have been confounded by the severity of illness influencing the choice of oxygen concentration used. The studies identified in this review as awaiting classification have, as with many pre-hospital studies, experienced difficulties with design, implementation and compliance of staff. This observation, however, should not prevent researchers, health professionals and policy makers from striving to obtain evidence based medicine to identify the optimal oxygen treatment for AECOPD.

AUTHORS' CONCLUSIONS

Implications for practice

Only one relevant randomised controlled trial has been published on this topic to date, thus there is a paucity of evidence to conclude that different oxygen therapies in the pre-hospital setting (prior to casualty/emergency department) alters outcomes in patients with AECOPD. However, given the strong results seen with a titrated oxygen therapy approach (via nasal prongs to achieve arterial saturation of 88% to 92%) as opposed to high flow (mask delivered 8 to 10 L/min) particularly with respect to reduced risk of death and respiratory acidosis, it would be responsible to consider the former as the new standard of care. Organisational policies should be amended to reflect this safety risk and an effort to train clinicians to shift their thinking away from the 'more is better' approach to prescribing titrated oxygen for AECOPD.

Implications for research

There is a paucity of well-designed and appropriately powered RCTs investigating the effect of different oxygen therapies in the pre-hospital setting. This evidence is required to optimise the management of people with AECOPD and provide increased generalisability to the findings of this review. Given it may be considered unethical to conduct placebo controlled trials within this context, however, it is unlikely that future studies will take this ap-

proach. Furthermore, the study included in this review was well-conducted and the results of this single trial have impacted practice and current guidelines such that further evaluation of high flow oxygen therapy may also be deemed unethical.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Austin 2010

Methods	<i>Country:</i> Australia <i>Design:</i> Cluster randomised controlled parallel group trial <i>Objective:</i> To compare standard high flow oxygen treatment with titrated oxygen treatment for patients with an AECOPD in the pre-hospital setting <i>Methods of analysis:</i> Log binomial regression to compare the risk of death for patients in two treatment arms (primary outcome). Secondary outcomes were analysed using Student's t-tests after transformation to remove skewness. Ventilation categories were combined with log binomial regression used to compare them due to a small number of observations. Both intention-to treat and per protocol analyses were used (initial analyses were intention to treat) <i>Clustering adjustments made:</i> Cluster randomisation used to assign paramedics to one of the treatment groups. Standard errors were adjusted to account for correlation between observations for the same paramedic (clustering) <i>Was the significance of any affect altered due to clustering:</i> Not reported
Participants	<i>Eligible for study:</i> n = 63 full time paramedic staff eligible; n = 405 eligible patients <i>Randomised:</i> Intervention: n = 32 paramedics; n = 179 patients with breathlessness; n = 97 with AECOPD; Control: n = 30 paramedics; n = 226 patients with breathlessness; n = 117 with AECOPD <i>Completed:</i> Intervention: n = 117 for intention to treat; n = 92 for per protocol analysis; Control: n = 97 for intention to treat; n = 43 for per protocol analysis <i>Age:</i> Intervention: Mean 67.9 + 10.3; Control: Mean 68.0 + 10.2 <i>Gender:</i> Intervention: n = 45 male; n = 52 female; Control: n = 57 male n = 60 female <i>COPD diagnosis definition:</i> Paramedics determined diagnosis based on appropriate acute symptoms, history of COPD (or emphysema) from the patient or a greater than 10 pack year history of smoking; The COPD cohort had a definite diagnosis of COPD defined by national guidelines; Patients without lung function data or who did not fulfil spirometric criteria for COPD were excluded from the COPD subgroup analysis <i>Diseases/co-morbidities included:</i> Not reported <i>Reasons for subject exclusion:</i> Aged less than 35 years
Interventions	<i>Intervention description:</i> Patients received titrated oxygen treatment delivered by nasal prongs to achieve arterial oxygen saturations between 88% and 92%, with concurrent bronchodilator treatment delivered by a nebuliser driven by compressed air and delivered via a facemask over the nasal prongs. Pulse oximeters were used to measures oxygen saturations and titrate oxygen to target saturations. All patients received other standard treatment according to Tasmanian Ambulance Service guidelines, including basic support, nebulised bronchodilators (salbutamol 5 mg made up in 2.5 mL normal saline, ipratropium bromide 500 µg made up with 2.5 mL normal saline), dexamethasone 8 mg intravenously and where necessary salbutamol 200-300 mg intravenously or 500 mg intramuscularly <i>Control description:</i> High flow oxygen treatment (8-10 L/min) administered by a non-rebreather face mask and bronchodilators delivered by nebulisation with oxygen at flows of 6-8 L/min. Oximeters were used to measure oxygen saturation in the high flow oxygen

	arm. All patients received other standard treatment according to Tasmanian Ambulance Service guidelines, including basic support, nebulised bronchodilators (salbutamol 5 mg made up in 2.5 mL normal saline, ipratropium bromide 500 μ g made up with 2.5 mL normal saline), dexamethasone 8 mg intravenously and where necessary salbutamol 200-300 mg intravenously or 500 mg intramuscularly <i>Duration of intervention:</i> During ambulance delivery from patients location to hospital <i>Setting:</i> Pre-hospital setting (ambulance)	
Outcomes	<i>List of pre-specified outcomes:</i> Pre-hospital and in-hospital mortality, length of hospital stay, blood gas measurements (pH, arterial carbon dioxide, bicarbonate and arterial oxygen) <i>Follow-up period:</i> Pre-hospital duration	
Notes	Funding: Provided by the Australian College of Ambulance Professionals (ACAP), nebulisation air compressors donated by FlaemNova. Authors note that neither sponsor had a role in the study conduct or publication of results	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random number generation after stratification by rurality
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported, however, authors state that stratification by rurality was performed to reduce differences associated with transportation time between urban and rural areas, ensuring that treatment allocation was concealed before randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Paramedics, the research team and hospital staff were not blinded to treatment after randomisation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	A respiratory physician blind to treatment allocation reviewed lung function data and smoking history, from private and public medical records. No mention of blinding for other outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Data was reported to be missing from both the ambulance and hospital patient records, resulting in denominators varying among analyses. Intention-to-treat analysis occurred
Selective reporting (reporting bias)	Unclear risk	No pre-specified protocol available to determine selective reporting

Austin 2010 (Continued)

Other bias	Low risk	No other biases identified

Abbreviations. COPD; chronic obstructive pulmonary disease.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bell 2015	Not a pre-hospital study
Costello 1997	Clinical Audit of outcomes, not an RCT
Curtis 1994	Narrative review, not an RCT
Dennston 2002	Not an RCT
Emerman 1989	Not compared with oxygen
Esteban 1993	Not a pre-hospital study
Gomersall 2002	Not a pre-hospital study
L'Her 2017	Not AECOPD
McNally 1993	Not an RCT of oxygen levels
Moloney 2001	Not an RCT
Murphy 2001	Not an RCT
Murphy 2001a	Not an RCT
O'Driscoll 2003	Not an RCT
O'Reilly 2003	Narrative review, not an RCT
Rittayamai 2015	Not AECOPD
Schumaker 2004	Review, not an RCT
Small 2000	Not an RCT
Van der Elst 1982	Not AECOPD

(Continued)

van der Elst 1985	Not AECOPD
Wu 2014	Not a pre-hospital study

AECOPD: Acute exacerbations of chronic obstructive pulmonary disease

RCT: Randomised controlled trial

Characteristics of studies awaiting assessment [ordered by study ID]

Eiser 2004

Methods	Consenting patients will be randomised to receive either standard oxygen therapy or an adjusted oxygen flow rate to achieve a saturation between 88% and 92%. Half of ambulance crews will be trained to administer controlled oxygen and randomisation will be based on which ambulance crew is called to the patient
Participants	All patients presenting with symptoms of exacerbation of COPD conveyed to Lewisham Hospital by London Ambulance Service Emergency Medical Technicians meeting the following criteria: Age; 45 years, have inhaler/nebuliser for regular home use, breathless on exertion of MC grade 2 or above when well, have a current or past smoking history
Interventions	Oxygen therapy to maintain oxygen saturation between 88% and 92%
Outcomes	Primary: Blood pH Secondary: need for intubation and mechanical ventilation, need for non invasive ventilation, hospital length of stay and survival
Notes	Previously listed as ongoing in Austin 2006. No publication was found despite searching; authors were contacted with no response

Elliott 2004

Methods	Randomised controlled trial Random allocation to [A] usual oxygen therapy [B] the oxygen flow rate adjusted to achieve a saturation between 88 and 92%
Participants	Patients who may have an exacerbation of COPD. Patients who can answer "yes" to the following questions 1) Age > 45 2) having an inhaler or nebuliser for regular home use 3) breathlessness on exertion of MRC grade 2 or above when well 4) a current or past of smoking
Interventions	Oxygen therapy to maintain oxygen saturation between 88% and 92%
Outcomes	To establish whether oxygen delivery given to achieve a specific oxygen saturation and nebulised drugs given via a compressor (standard practice on Respiratory wards at St James's) results in fewer patients presenting to hospital acidotic or needing ventilation

Elliott 2004 (Continued)

Notes	Previously listed as ongoing in Austin 2006 . No publication was found despite searching; authors were contacted with no response

DATA AND ANALYSES

Comparison 1. High flow versus titrated oxygen therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (Fixed, 95% CI)	Totals not selected
2 Arterial Blood Gas (pH)	1		Mean Difference (Fixed, 95% CI)	Totals not selected
3 Ventilation of any type	1		Risk Ratio (Fixed, 95% CI)	Totals not selected
4 Length of Stay (days)	1		Mean Difference (Fixed, 95% CI)	Totals not selected

Comparison 2. Use of invasive or non-invasive ventilation

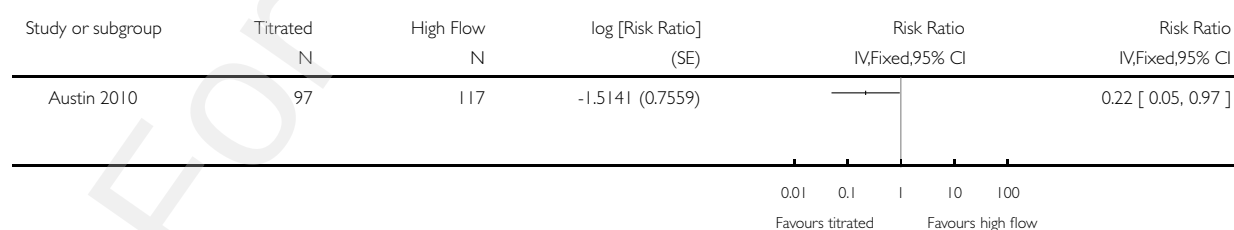
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ventilation type	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Invasive ventilation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Non-invasive ventilation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 High flow versus titrated oxygen therapy, Outcome 1 Mortality.

Review: Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease

Comparison: 1 High flow versus titrated oxygen therapy

Outcome: 1 Mortality

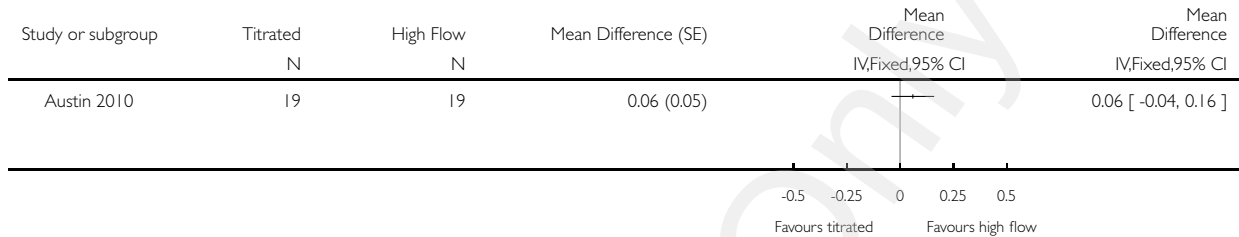


Analysis 1.2. Comparison 1 High flow versus titrated oxygen therapy, Outcome 2 Arterial Blood Gas (pH).

Review: Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease

Comparison: 1 High flow versus titrated oxygen therapy

Outcome: 2 Arterial Blood Gas (pH)

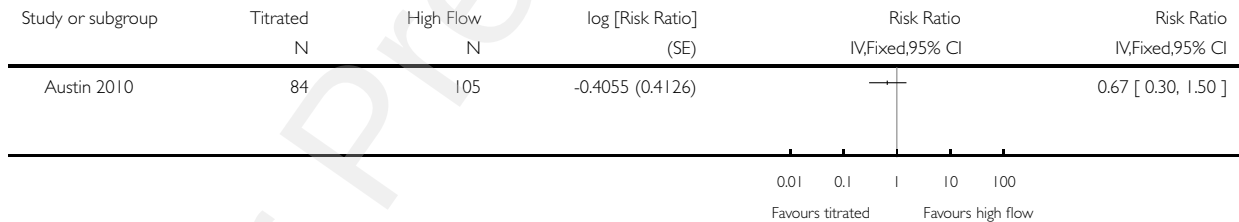


Analysis 1.3. Comparison 1 High flow versus titrated oxygen therapy, Outcome 3 Ventilation of any type.

Review: Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease

Comparison: 1 High flow versus titrated oxygen therapy

Outcome: 3 Ventilation of any type

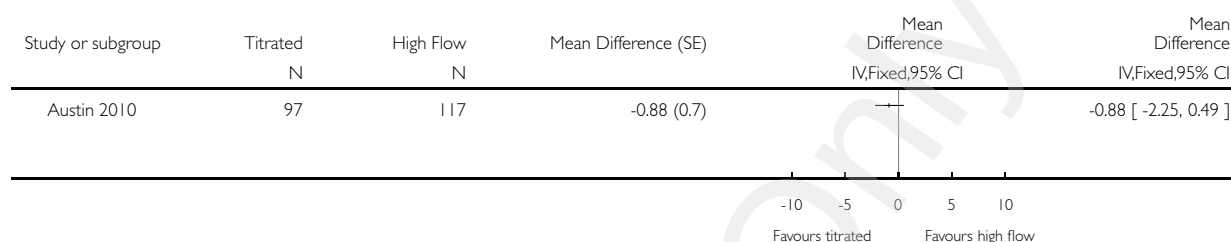


Analysis 1.4. Comparison 1 High flow versus titrated oxygen therapy, Outcome 4 Length of Stay (days).

Review: Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease

Comparison: 1 High flow versus titrated oxygen therapy

Outcome: 4 Length of Stay (days)

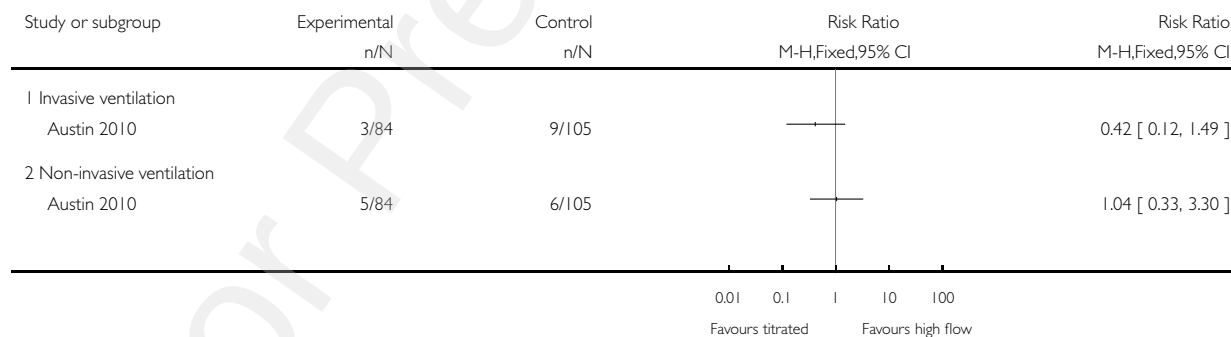


Analysis 2.1. Comparison 2 Use of invasive or non-invasive ventilation, Outcome 1 Ventilation type.

Review: Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease

Comparison: 2 Use of invasive or non-invasive ventilation

Outcome: 1 Ventilation type



APPENDICES

Appendix I. Sources and search methods for the Cochrane Airways Specialised Register of Trials

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly
EMBASE (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema\$.mp.
4. (chronic\$ adj3 bronchiti\$).mp.
5. (obstruct\$ adj3 (pulmonary or lung\$ or airway\$ or airflow\$ or bronch\$ or respirat\$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

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

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

Appendix 2. Search strategy for the Cochrane Airways Group Register

Cochrane Register of Studies (CRS)

- #1. MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
- #2. MeSH DESCRIPTOR Bronchitis, Chronic
- #3. (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
- #4. COPD:MISC1
- #5. (COPD OR COAD OR COBD):TI,AB,KW
- #6. #1 OR #2 OR #3 OR #4 OR #5
- #7. MeSH DESCRIPTOR Emergency Medicine
- #8. MeSH DESCRIPTOR Emergency Medical Services Explode All
- #9. emergenc* or emergent* or emergi-cent* or prehospitat* or pre-hospital*
- #10. ambulance* or (patient* NEAR transport*)
- #11. first-aid* or first NEXT aid*
- #12. #7 or #8 or #9 or #10 or #11
- #13. (inhal* or respiratory*) NEAR therap*
- #14. oxygen*
- #15. "nasal cannula*" or "nasal prong*" or NRM or venture* or Hudson* or mask*
- #16. MeSH DESCRIPTOR Oxygen Inhalation Therapy Explode All
- #17. MeSH DESCRIPTOR Respiratory Therapy ambulance*
- #18. MeSH DESCRIPTOR Oxygen
- #19. #13 or #14 or #15 or #16 or #17 or #18
- #20. #6 and #12 and #19

WHAT'S NEW

Date	Event	Description
14 March 2018	New search has been performed	Literature search re-run.
14 March 2018	New citation required and conclusions have changed	One study included in update. Change to included studies criteria to include standard care and titrated oxygen therapy. Methods updated to meet current Cochrane standards

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 3, 2006

Date	Event	Description
18 September 2008	New search has been performed	Literature search re-run; no new studies found
15 August 2008	Amended	Converted to new review format.
4 April 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

MA and RW wrote and developed the initial protocol and published the first version of the review in 2008. ZK and KC updated the protocol, screened literature, conducted data extraction, analysed the evidence and drafted the manuscript for the 2018 review update. MA and BS provided clinical input and reviewed the draft manuscript for the 2018 update.

DECLARATIONS OF INTEREST

MA and RW were authors on the one included study ([Austin 2010](#)). Thus they were not involved in any capacity for protocol revision, study screening and selection, data extraction and analysis of the included and excluded studies.

SOURCES OF SUPPORT

Internal sources

- Cochrane Airways Group (Tasmania), Australia.

External sources

- The authors declare that no such funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review has undergone a significant style and methodological revision from the original review ([Austin 2006](#)). This was undertaken to ensure the review reflects current Cochrane methodological standards. For example we used the Cochrane risk of bias tool instead of the Jadad scale, added a PRISMA diagram and a summary of findings table. We removed some of the outcomes including mental status score and admission to ICU. We also defined some of the outcomes such as FEV₁/FVC instead of lung function.

Chapter 5.

Short-acting bronchodilators for the management of acute exacerbations of chronic obstructive pulmonary disease in the hospital setting: Systematic review

Zoe A. Kopsaftis^{1,2,3}, Nur S. Sulaiman², Oliver D. Mountain¹, Kristin V Carson-Chahhoud^{1,4}, Paddy A. Phillips^{5,6}, Brian J Smith^{1,2,3}

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BMC Systematic Reviews 2018

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Statement of authorship for jointly authored papers within the thesis

Statement of authorship

Short-acting bronchodilators for the management of acute exacerbations of chronic obstructive pulmonary disease in the hospital setting: Systematic review

Publication status: Published

Publication details: Kopsaftis Z, Sulaiman NS, Mountain OD, Carson-Chahhoud KV, Phillips PA, Smith BJ. Short-acting bronchodilators for the management of acute exacerbations of chronic obstructive pulmonary disease in the hospital setting: Systematic review; Systematic Reviews; 2018; 7:213 (p1-13)

Author contributions:

By signing the Statement of Authorship, each author certifies their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of principal author (candidate)	Zoe A Kopsaftis		
Contribution to the paper	Conceived and designed the methods and manuscript, analysed the data, wrote the first draft, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions and approved final version.		
Signature		Date	21/02/2019
Name of co-author	Nur S. Sulaiman		
Contribution to the paper	Screened studies for inclusion, extracted data, interpreted results, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions.		

Signature		Date	21/02/2019
Name of co-author	Oliver D. Mountain		
Contribution to the paper	Screened studies for inclusion, extracted data, interpreted results, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions.		
Signature		Date	21/02/2019
Name of co-author	Kristin V Carson-Chahhoud		
Contribution to the paper	Interpreted results, analysed data, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions..		
Signature		Date	10/01/2019
Name of co-author	Paddy A. Phillips		
Contribution to the paper	Contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions, approved final version and supervised the process.		
Signature		Date	6/3/19
Name of co-author	Brian Smith		
Contribution to the paper	Contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions, approved final version and supervised the process.		
Signature		Date	4/3/9

Despite routine administration of short acting bronchodilator agents in the inpatient setting, there is no standardised guideline or protocol for their use. The differences in clinical practice can be extrapolated down from geographic variances, between hospital differences and then the differences in practice between individual physicians. The current evidence underpinning use of short acting bronchodilators for COPD in the acute setting is extrapolated from studies based in the community setting. Overall, the evidence underpinning the use of SABD for inpatients is unspecified to the inpatient setting and unsurprisingly there were no available systematic review to collate whatever evidence was actually in existence. Given that people with COPD are admitted to hospital frequently optimisation and standardisation of the administration of short acting bronchodilators is important for quality care as it is currently routine practice.

Systematic reviews of randomised controlled trials are ranked as level I evidence by the National Health and Medical Research Council. They are well regarded in evidence based medicine for their rigorous, methodical approach to synthesis and critical appraisal of the available evidence for the topic of interest. Best-practice guidelines are generally comprised of a compilation of systematic reviews and as such a systematic review of the literature was undertaken in order to underpin use of short acting bronchodilators in the hospital setting for COPD with a more applicable evidence base than currently exists.

A search up to November 2017 was conducted in online databases and trials registries to identify evidence for both published and ongoing studies. Ten randomised controlled trials or controlled clinical trials met all of the eligibility criteria for this narrative synthesis. Based on available evidence, there were no significant differences in most outcomes of interest relative to dose, delivery via inhaler or nebuliser, and type of β_2 -agonist used. However, increased dosage of β_2 -agonist was associated with increased cardiac side effects as demonstrated in some evidence. The available evidence, though limited, suggest that a low dose of short acting β_2 agonist delivered via metered dose inhaler (if tolerated by the patient) is sufficient to relieve symptoms. Anything additional confers no additional clinical benefit and may expose the patient to increased risk of cardiac adverse events.

RESEARCH

Open Access



Short-acting bronchodilators for the management of acute exacerbations of chronic obstructive pulmonary disease in the hospital setting: systematic review

Zoe A. Kopsaftis^{1,2,3*} , Nur S. Sulaiman², Oliver D. Mountain¹, Kristin V. Carson-Chahhoud^{1,4}, Paddy A. Phillips^{5,6} and Brian J. Smith^{1,2,3}

Abstract

Background: Currently, there is a lack of guidelines for the use of short-acting bronchodilators (SABD) in people admitted to hospital for acute exacerbation of chronic obstructive pulmonary disease (AECOPD), despite routine use in practice and risk of cardiac adverse events.

Aim: To review the evidence that underpins use and optimal dose, in terms of risk versus benefit, of SABD for inpatient management of AECOPD and collate the results for future guidelines.

Methods: Medline, Embase, the Cochrane Central Register of Controlled Trials, clinicaltrials.gov and International Clinical Trials Registry Platform were searched (inception to November 2017) for published and ongoing studies. Included studies were randomised controlled trials or controlled clinical trials investigating the effect of SABD (β_2 -agonist and/or ipratropium) on inpatients with a diagnosis of AECOPD. This review was undertaken in accordance with PRISMA guidelines and a pre-defined protocol. Due to heterogeneous methodologies, meta-analysis was not possible so the results were synthesised qualitatively.

Results: Of 1378 studies identified, 10 met inclusion criteria. Narrative synthesis of 10 studies revealed no significant differences in most outcomes of interest relative to dose, delivery via inhaler or nebuliser, and type of β_2 -agonist used. However, some evidence demonstrated significantly increased cardiac side effects with increased dosage of β_2 -agonist (45% versus 24%), $P < 0.05$.

Conclusion: This review identified a paucity of methodologically rigorous evidence evaluating use of SABD among AECOPD. The available evidence did not identify any additional benefits for participants receiving higher doses of short-acting β_2 -agonists compared to lower doses, or based on type of delivery method or β_2 -agonists used. However, there was a small increase in some adverse events for participants using higher doses of β_2 -agonists.

Keywords: Chronic obstructive pulmonary disease, Short-acting bronchodilators, SABA, SAMA, Systematic review, Hospital, Exacerbation, Dose, Delivery

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Introduction

The high prevalence of cardiac comorbidity and cardiac death in people with chronic obstructive pulmonary disease (COPD) [1, 2] may be exacerbated by the adrenergic effects of the routine frequent use of short-acting bronchodilators in clinical practice [3]. As a result, current guideline recommendations are to avoid prolonged use of β_2 -agonists [4]. Hence, there is a need to synthesise existing evidence for its use given that these agents are a mainstay of COPD exacerbation management, with some consideration of the risk/benefit, and optimal dosing.

Periods of acute exacerbation of COPD (AECOPD) often result in hospitalisation, wherein patients are at increased risk of decreased quality of life and death [5–8]. People suffering AECOPD experience an abnormal deterioration of respiratory symptoms defined as increased dyspnoea, sputum production and/or sputum purulence which may be infective or non-infective in origin [7].

The severity of an exacerbation is, in part, determined by the degree of dyspnoea experienced by the patient, largely driven by bronchoconstriction [9]. It is a universally accepted practice to administer rescue doses of short-acting β_2 -agonists and/or ipratropium known collectively as short-acting bronchodilators (SABD) to reduce this bronchoconstriction in AECOPD [9, 10].

However, cardiac markers, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and troponin T, are noted to be elevated in people suffering AECOPD and predict 30-day mortality independently of disease severity and prognosis [11]. Furthermore, the high prevalence of cardiovascular disease in people with COPD is well documented; despite this, the common comorbidity remains largely underdiagnosed [1, 2, 12–19]. Hence, unregulated, frequent administration of SABD in the hospital setting is concerning, given the adrenergic and pro-arrhythmic effects. There is some evidence of positive correlation between levels of short-acting β_2 -agonists and increased cardiac stress markers, specifically NT-proBNP [20].

Despite routine administration of SABD in the inpatient setting and the potential risk, there is no clearly evidence-based, standardised guideline for their use, particularly in terms of optimal and safe dosage [21]. Differences in clinical practice can be extrapolated down from geographic variances, between hospital differences and the dissimilarities in practice between individual physicians. Consultation of major international COPD guidelines provides little elucidation, with recommendations for SABD being underpinned by weak evidence, some of which has been extrapolated from studies of asthma patients and stable COPD [22, 23]. Overall, the evidence supporting the use of SABD for inpatients is unspecified to the inpatient setting [7, 22, 23]. Given that

people with COPD are admitted to hospital frequently [24–26], optimisation and standardisation of COPD management, which includes SABD administration, is important to address large variability identified in current treatment [27, 28].

This systematic review was undertaken in order to evaluate the existing literature relating to SABD use for the inpatient management of AECOPD. Subsequently, these findings may be used as the foundation for clinical practice guidelines regarding specifications for the inpatient administration of SABD, including the use of one or a combination of agents, optimal and safe dose, most effective delivery method and duration of treatment.

Methods

This systematic review was undertaken in accordance with the guiding principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see Additional file 1) [29]. Prior to commencing the review, a protocol was defined by the authors. This was not registered online in Prospective Register of Systematic Reviews (PROSPERO), and therefore, the review protocol will be described in detail in this section.

Eligibility criteria

Studies were eligible for inclusion if they were randomised controlled trials or controlled clinical trials investigating the effect of SABD (short-acting β_2 -agonist and/or ipratropium) when administered to adult inpatients with a diagnosis of AECOPD. The comparison group could be either placebo, usual care, delayed intervention or another SABD (agent, dose or delivery method). Studies were included if the SABD was part of a wider treatment regime. The protocol stipulated that a study may be included if a maximum of 25% of the participants had a primary diagnosis other than COPD (e.g. participant is asthmatic or has secondary diagnosis of AECOPD) and if the data for COPD could be isolated. This parameter was implemented in acknowledgement of the high prevalence of comorbid conditions in patients with COPD [30–32]. Full-text and conference abstracts were eligible for inclusion where relevant outcomes were reported. In the case of abstracts with no published full text, authors were contacted in an effort to access more complete data for review.

Outcomes

The authors selected both primary and secondary outcomes which were deemed to be the most clinically relevant to the topic. The primary outcome was selected, according to the clinical expertise of the clinician-authors, as the primary consideration for use of SABD to treat AECOPD in the hospital setting.

The primary outcome in this review was treatment failure. For the purposes of this review, this was defined as (1) mortality as a result of AECOPD, (2) intensive care unit/critical care unit (ICU/CCU) admission or (3) respiratory failure requiring non-invasive or mechanical ventilation. Secondary outcomes included spirometric values, i.e. forced expiratory volume in 1 s (FEV¹) and forced vital capacity (FVC), dyspnoea, sputum production/purulence and quality of life. Other outcomes of interest were hospital utilisation (length of stay, hospital admission/readmission rate, emergency department presentations) and adverse events related to β_2 -agonist and anticholinergic agents (including cardiovascular events).

Search strategy

A keyword search strategy for systematic literature searching was devised and refined after a preliminary search by ZK and NS in consultation with a senior Reference Librarian, with the goal of identifying all relevant studies (see example in Additional file 2). Both keywords and MeSH terms were used where appropriate; hence, a combination of the following was used: COPD, inpatient, hospital and bronchodilator agents; all variants of these terms were also included. Electronic databases searched (all years up to 2017) for published literature were Medline (OVID), Embase (OVID) and the Cochrane Central Register of Controlled Trials (CENTRAL). Grey literature was searched online via ClinicalTrials.gov and the International Clinical Trials Registry Platform to identify relevant ongoing studies. Supplementing this, alerts were set for the searched databases to ensure any recently published studies were identified prior to publishing this review. Screened studies were not restricted by language or date. Bibliographies of included articles and reviews were hand searched for identification of any other studies potentially eligible for inclusion. Online searches are current as of November 2017.

Data extraction

Screening was undertaken by two independent reviewers. First, titles and abstracts of identified citations were appraised, after duplicates were removed. Following this, full text was obtained for the remaining studies and compared to the pre-established inclusion criteria, before final inclusion in the review. Data pertaining to the above-mentioned primary and secondary outcomes as well as participant and study design characteristics were extracted into a standardised, pilot-tested form (see Additional file 3). This was done independently by a combination of two authors (ZK and either NS or OM). If any disagreements had occurred during this process that could not be resolved by consensus, a third member of the author team would have been consulted.

Methodological quality

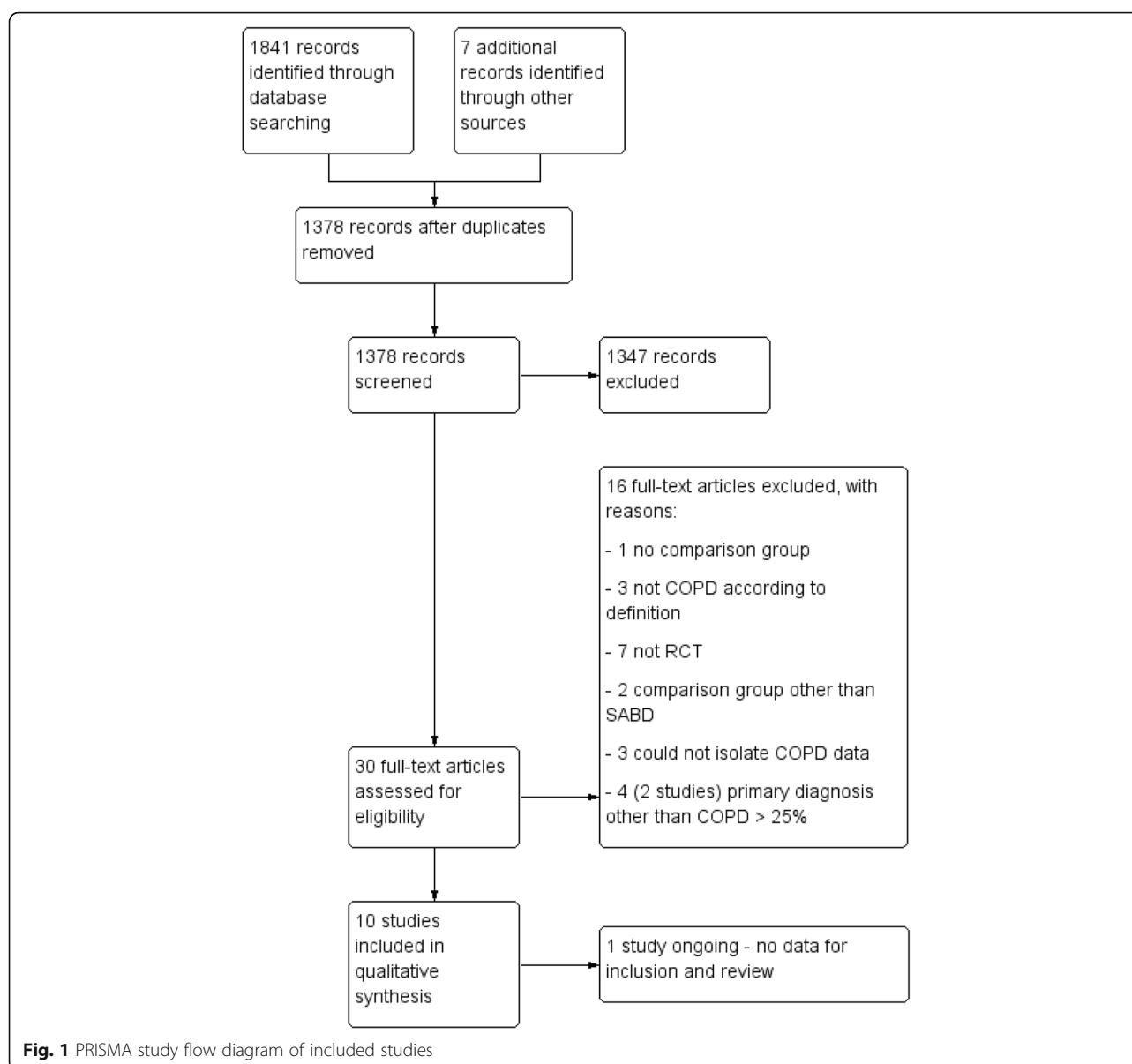
Consensus was reached regarding methodological quality of the included studies after independently evaluating each of them in keeping with the Cochrane Collaboration's tool for assessing risk of bias [33]. Using this method, each study was rated as having low, unclear or high risk of bias for domains including "selection bias", which is split into two sub-groups relating to the appropriateness of the randomisation procedure and allocation of participants to study groups. Presence of "performance bias" and "detection bias" relating to the blinding of participants, personnel and outcome assessment was also assessed, in addition to "attrition bias" and "reporting bias" which relate to incomplete outcome data and selective reporting. The domain "other bias" relates to any potential sources of bias which are not covered by the aforementioned categories, for example, contamination between intervention and control groups or bias arising from particular study designs (e.g. lack of wash-out period in a cross-over trial).

Data analysis

Extracted data was synthesised descriptively based on published data only. The data presented in the included studies were reviewed critically by the authors, taking into account the outcome of the risk of bias assessment when synthesising the evidence. Meta-analysis would have been undertaken according to the predefined protocol, if two or more studies were sufficiently similar in methodology to result in a meaningful outcome. However, included studies used heterogeneous methods specifically relating to the measurement of outcomes and intervention delivery, and hence, a meaningful quantitative analysis was not possible in this instance.

Results

The systematic literature search returned 1848 citations; after de-duplication, 1378 studies were screened, and 10 met all criteria for inclusion in this review (Fig. 1). One study was identified via a search of online clinical trials registries and was deemed to be relevant for inclusion; however, it is still ongoing and no data were available for this review [34]. Included studies originated from six different countries and were dated from 1989 to 2016. Of these, two studies were available in abstract form only despite attempts to contact the original authors for further details [35, 36]. Characteristics of the included studies can be seen in Table 1. Overall, the pool of included studies comprised of eight RCTs [35–42], a randomised crossover trial [43] and a controlled clinical trial [44]. Study participants were people with COPD with average age above 60 years for all.



Risk of bias assessment

The overall quality of the included studies was assessed as average to poor, despite the majority of studies being randomised controlled trials. This was mainly due to inadequate reporting of methodology, which gave many studies an unclear risk of bias. There was a low risk of bias with regard to the randomisation and sequence generation. When it was specified, participants were usually randomised in 1:1 ratio blocks and one study randomised using the Latin square design. One study [44] had a high risk of bias for this domain as there was a change to protocol during the study, such that randomisation was not possible. Blinding was performed variably among the studies, with many studies having incomplete blinding or open label testing. Studies

where only the abstract was available were particularly susceptible to incomplete or brief descriptions of methodology. Risk of bias for individual studies is presented in Fig. 2, and a summary of risk of bias is presented in Fig. 3.

Included studies were of small sample size (range $n = 15$ to $n = 86$), and justification for sample size and relevant power calculations were not reported in the publications across the board.

Treatment failure

Although treatment failure was the primary outcome of this review, only two studies [41, 42] reported it, with heterogeneous research methodologies; thus, meta-analysis was not possible. One of these studies, with 50 participants,

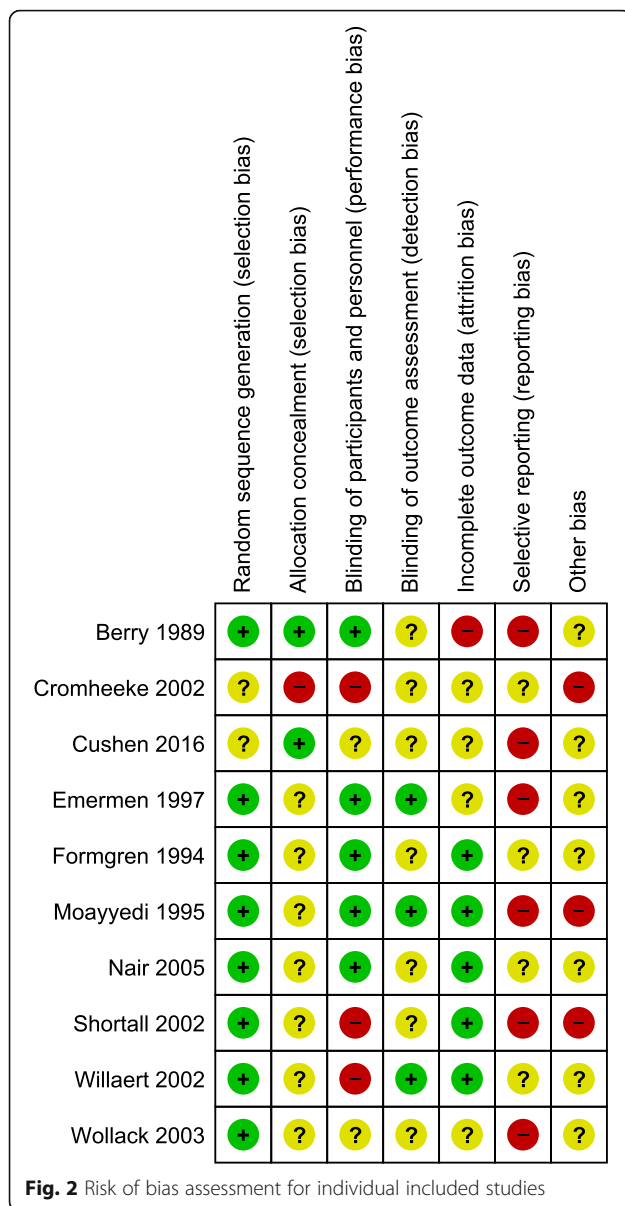
Table 1 Characteristics of included studies

Study	Setting	Design	Sample size	Participants		Intervention		Group 2	Outcomes
				Baseline FEV1 mean (SD)	Age, years mean (SD)	Gender	Group 1		
Berry [43]	USA, single centre	Double blind RCT	20	0.69 ± 0.28 L	67.9 ± 7.1	20M	MDI + spacer placebo 4 puffs and nebulized albuterol 2.5 mg over 10–15 min	MDI + spacer albuterol 4 puffs of 0.36 mg and nebulized placebo	FEV ¹ FVC Dyspnoea (Borg) Adverse events
Cromheecke [44]	The Netherlands, single centre	CCT	42	Group 1 47.39 ± 2.94% Group 2 50.48 ± 3.75%	Group 1 26M 71.1 ± 1.9 Group 2 16F 71.7 ± 1.6		Nebulized salbutamol 10 mg	Nebulized salbutamol 5 mg	FEV ¹ FVC Adverse events Dyspnoea (Borg)
Cushen [36]	Ireland, single centre	RCT	31	48 ± 18%	NR	NR	Combined salbutamol 2.5 mg/ipratropium bromide 0.5 mg via vibrating mesh nebuliser	Combined salbutamol 2.5 mg/ipratropium bromide 0.5 mg via jet nebuliser	FEV ¹ FVC Dyspnoea (Borg)
Emmerman [37]	USA, single centre	RCT	86	Group 1 24.5 ± 11.7% Group 2 24.9 ± 11.2%	63.9 ± 8.9	42M 44F	Albuterol 2.5 mg MDI every 60 min (total 2) with saline MDI at other treatment times (total 4)	Albuterol 2.5 mg MDI every 20 min (total 6 doses)	FEV ¹ FVC Hospital utilisation Adverse events
Formgren [38]	Sweden, single centre	Double blind RCT	15	35.6% (SD NR)	61 ± 9	11M 4F	Placebo turbuhaler + placebo MDI	1) Terbutaline 1 mg via turbuhaler + placebo MDI 2) Terbutaline 1 mg via MDI + placebo turbuhaler 3) Terbutaline 2.5 mg via turbuhaler + placebo MDI with spacer 4) Terbutaline 2.5 mg via MDI with spacer + placebo turbuhaler	FEV ¹ FVC
Moayyedi [39]	UK, single centre	RCT	62	Group 1 0.77 ± 0.34 L Group 2 0.78 ± 0.41 L	Group 1 70.4 ± 9.1 Group 2 67.8 ± 6.7	NR	5 mg nebulised salbutamol 4 times per day + standard of care	5 mg nebulised salbutamol + 500 µg ipratropium bromide 4 times per day + standard of care	FEV ¹ FVC Dyspnoea (subjective) Hospital utilisation
Nair [40]	UK, multicentre	Double-blind RCT	86	0.82 ± 0.41 L	69.3 ± 9.3	39M 47F	2.5 mg nebulized albuterol 4 hourly	5 mg nebulized albuterol 4 hourly	FEV ¹ Hospital utilisation Adverse events

Table 1 Characteristics of included studies (Continued)

Study	Setting	Design	Participants		Intervention		Outcomes
			Sample size	Baseline FEV1 mean (SD)	Age, years mean (SD)	Gender	
Shortall [41]	USA, multicentre	Non-blinded RCT	34	0.75 L (0.5–2.02 L)	Group 1 67 Group 2 71	25M 9F	FEV ₁ Hospital utilisation Treatment failure Dyspnoea (Borg) Adverse events
							Group 1: 40 mg oral methylprednisolone 6 hourly until asymptomatic then 40 mg daily + MDI albuterol (maximum of 20 puffs 4 hourly) and ipratropium bromide (maximum 8 puffs 4 hourly) + cefuroxime 500 mg twice daily Group 2: 40 mg IV methylprednisolone every 6 h until asymptomatic then 40 mg oral daily + 2.5 mg nebulized albuterol and 0.5 mg ipratropium bromide 4 hourly + cefuroxime 1.5 g IV 8 hourly for 36 h then 500 mg orally twice daily
Willaert [42]	Belgium, single centre	RCT	48	Group 1 0.70 ± 0.27 L Group 2 0.82 ± 0.46 L	Group 1 71 ± 8 Group 2 72 ± 6	42M 6F	FEV ₁ FVC Treatment failure Hospital utilisation Dyspnoea (subjective) Quality of life (CRQ)
							Group 1: 32 mg oral methylprednisolone for 7 days before tapering off + 1.6 mg fenoterol and 640 µg ipratropium bromide daily via MDI + spacer Group 2: 40 mg IV methylprednisolone daily for 10 days before tapering off + 10 mg salbutamol and 1 mg ipratropium bromide aerosolised daily
Wollak [35]	USA, single centre	RCT	15	NR	NR	NR	FEV ₁ FVC
							Group 1: 2.5 mg nebulized albuterol 4 hourly + standard of care Group 2: 5 mg/h continuous nebulized albuterol for 4 h, then 2.5 mg intermittently every 4 h + standard of care

Key: SD standard deviation, USA United States of America, RCT randomised crossover trial, M male, MDI metered dose inhaler, FEV₁ forced expiratory volume in 1 s, FVC forced vital capacity, CCT controlled clinical trial, F female, RCT randomised controlled trial, NR not reported, UK United Kingdom, CRQ chronic respiratory questionnaire



demonstrated a similar rate of treatment failure with oral/metred dose inhaler (MDI) (32%) and intravenous (IV)/nebuliser (33%) ($P = 1.0$) [41]. However, these treatment failures were considered to be minor (defined as a subjective perception of clinical deterioration by either participant or physician) and did not satisfy the definition stated in the protocol of this review. The other study [42] noted incidences of treatment failure as defined by our criteria; however, these participants were withdrawn from the original sample of 48 and excluded from analysis. Despite this, the authors reported treatment failure as one of their outcomes in their description of methods. In the case of different treatment regimes, IV/aerosol therapy resulted greater ICU admissions compared to oral/MDI (3 vs 1) [42].

Forced expiratory volume in 1 s

Of the 10 included studies which reported FEV¹ as an outcome, nine reported that all groups experienced an increase from baseline with administration of SABD [36–44]; the improvement from baseline could not be determined from one of the included abstracts [35]. None of the studies reviewed showed a significant difference between groups for FEV¹ regardless of variances in types of SABD, delivery method or dose [35, 40–44]. However, for one study ($n = 42$), authors reported a non-significant average increase in FEV¹ of 11.2% with 10 mg of salbutamol versus 6.9% with 5 mg [44]. Another study, with 86 participants, demonstrated higher percentage increase in FEV¹ at 120 min compared to baseline with a higher dose regimen of albuterol (29.2 ± 35.9 vs 15.1 ± 36.2 ; $P = 0.09$) though again this was non-significant [37]. From one small RCT ($n = 20$), use of a nebuliser appeared to improve the percent change in FEV¹ at 1 h post-treatment compared to MDI plus spacer ($16.7\% \pm 17.0$ vs $13.4\% \pm 20.5$). However, authors reported that this was a non-significant and both groups' improvements appear to be clinically relevant compared to pre-treatment values [43].

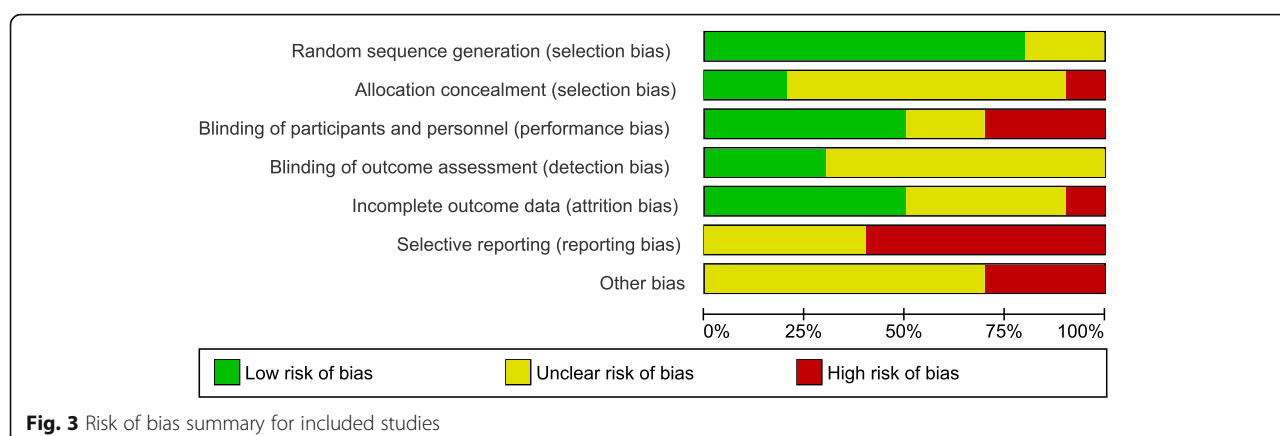
Forced vital capacity

Of the 10 included studies, seven reported FVC as an outcome, all of which reported an improvement from baseline regardless of group.

Four studies reported a statistically significant difference between intervention and control groups. Salbutamol at 10 mg compared to 5 mg was reported to have significantly improved FVC at 10 min post-administration; although the exact p value was not reported for this time point, the magnitude of difference between the two groups was approximately 11.5% [44]. However, after 10 min, authors reported the statistical significance of the between groups difference was not sustained for subsequent time points up to 240 min [44]. Other studies investigating different dosing approaches did not report any evidence of an effect on FVC with a higher versus lower dose [37, 40]. Both of these studies had a sample size of 86 and were the two largest studies included for review.

In a study of 62 people with COPD, monotherapy (salbutamol 5 mg) alone compared to combination therapy (salbutamol 5 mg plus ipratropium 500 μ g) demonstrated a significantly higher mean change in FVC at 3 days post-administration (0.25 L (0.42) vs 0.04 L (0.41), 95% CI -0.42 to 0.001 ; $P = 0.05$); this difference was no longer significant on days 7, 14 and discharge [39].

In terms of delivery method, continuously nebulised albuterol ($-0.85\% \pm 73.38$) appeared inferior to intermittently nebulised albuterol ($21.22\% \pm 30.73$) for percentage change in FVC at 4 h, $P = 0.043$, reported as absolute change in FVC [35]. Nebulised albuterol



resulted in a higher mean change in FVC 1 h after treatment ($310 \text{ mL} \pm 370$) compared to albuterol via MDI plus spacer (190 ± 360); however, this difference was not significant [43]. Furthermore, vibrating mesh nebuliser (salbutamol 2.5 mg plus ipratropium 0.5 mg) demonstrated a greater increase in FVC ($0.40 \text{ L} \pm 0.39$) compared to standard hospital jet nebuliser (same drug regime) ($0.19 \text{ L} \pm 0.19$); however, this was not significant, $P = 0.06$. A subsequent study reported that the addition of a spacer and/or an increase in dose from 1.0 to 2.5 mg (terbutaline) did not confer any additional benefit to FVC [38]. A differing treatment regime including nebulised salbutamol plus ipratropium compared to fenoterol plus ipratropium via MDI with spacer also failed to demonstrate a difference between the groups [42].

Dyspnoea

Dyspnoea was reported in six of the included studies: four utilising the Borg scale [36, 41, 43, 44] while the remaining two studies [39, 42] used subjective description including visual analogue scale. All six studies demonstrated improvement in dyspnoea post-intervention compared to baseline. The only study investigating differing doses found no difference between administration of 5 mg or 10 mg of salbutamol [44].

Similarly, the two studies that investigated oral/MDI versus IV/nebuliser showed no significant differences between groups with $P = 0.75$ [41] and $P = 0.15$ [42] respectively. There was a greater change in dyspnoea measured by Borg scale when MDI plus spacer albuterol was administered (-1.08 ± 2.01) compared to nebulised albuterol (-0.73 ± 1.75), but this did not reach statistical significance [43]. Another study comparing two different types of nebulisers (vibrating mesh versus standard hospitalised jet) showed no statistical difference between group comparison [36]. The addition of ipratropium to nebulised salbutamol was not found to be more effective in reducing self-reported dyspnoea than nebulised salbutamol alone [39].

Sputum production/purulence

None of the included studies evaluated effect of SABD on sputum production or purulence.

Quality of life

Only one study reported on quality of life as an outcome. Using the chronic respiratory disease index questionnaire [42], the study did not demonstrate a significant difference when comparing oral/MDI versus IV/nebuliser (86 ± 20 vs 90 ± 24 , $P = 0.73$) for this outcome. However, both groups improved in quality of life from baseline regardless of intervention; the IV/nebuliser group by approximately 20% ($P = 0.036$) and the oral/MDI group by approximately 45% ($P = 0.0069$).

Adverse events

Five of the included studies reported adverse events relating to β_2 -agonists including changes to heart rate [40, 41, 43, 44], palpitations [40], tremor [40, 44] and changes to blood pressure [43, 44]; one study reported on albuterol-related side effects as a general outcome without further qualification [37]. One study found no difference between 2.5 mg and 5 mg of albuterol [40] with regard to heart rate and palpitations, but tremor was common with the higher dose (5 mg). This study reported overall adverse events were similar in both groups ($P = 0.506$) [40]. Another study comparing 10 mg salbutamol versus 5 mg salbutamol demonstrated higher increase in heart rate with 10 mg salbutamol dose at 30 min post-administration (76.9 ± 4.3 versus 74.7 ± 3.27 bpm). While this was reported as significant, there was no supporting p value [44]. Salbutamol 10 mg led to an earlier maximal change in heart rate ($t = 30$ min) compared to salbutamol 5 mg ($t = 120$ min). Furthermore, there was a significant decrease in systolic blood pressure in the 10 mg salbutamol at $t = 10$ min (10.2 ± 13.7 mmHg). Similarly, diastolic blood pressure was also significantly lower with 10 mg salbutamol compared to baseline, reaching nadir $t = 30$ min; 5 mg salbutamol also

significantly decreased from baseline, but the reduction occurred later at $t = 60$ min and the minimum was smaller (5.8 ± 2.0 mmHg versus 10.2 ± 1.7 mmHg). Area under curve for tremor was greater in the 10 mg salbutamol (1139.9 ± 95.5) compared to 5 mg salbutamol (892.4 ± 61.0), p value not reported [44]. A study looking at cumulative dose of 15 mg versus 10 mg albuterol showed significantly higher adverse events in the higher cumulative dose (45% versus 24%) ($P < 0.05$). However, this study did not specify the type of adverse events other than to say “side effects consistent with albuterol treatment” [37].

There was no difference in heart rate (2.7 ± 9.0 bpm versus 2.9 ± 7.4 bpm) with administration of SABD via MDI plus spacer or nebuliser [43]. Similarly, there was no difference in systolic/diastolic blood pressure 5 min post-treatment with MDI plus spacer ($2.7 \pm 11.8/2.5 \pm 12.5$ mmHg) compared to nebuliser ($0.8 \pm 15.2/3.7 \pm 13.2$ mmHg) [43].

In a single study where participants received therapy via either oral/MDI or IV/nebuliser regime ($n = 50$), there was no significant difference reported between groups in terms of heart rate post-treatment [41]. Any differences noted by the authors, from baseline, were consistent with an expected physiological response to SABD administration (i.e. increase < 10 bpm) [41].

The only study reporting use of ipratropium did not report adverse events [39].

Hospital utilisation

Six of 10 studies investigated hospital utilisation as an outcome [37, 39–43].

The study comparing cumulative higher dose regime to lower overall dose resulted in equal rates of hospitalisation (69% for both groups) [37]. The addition of ipratropium to salbutamol did not improve the hospital length of stay in one study [39]. However, it appears administering an oral/MDI SABD treatment regime compared to an IV/nebuliser regimen may have some (though non-significant) reductive effect on length of stay (10.6 ± 2.8 vs 15.5 ± 10.3 , $P = 0.06$) [42].

Dosing with 2.5 mg versus 5 mg of albuterol produced a reduced length of stay (6 vs 9 days) though this was not statistically significant ($P = 0.084$) [40]. Adding ipratropium to salbutamol resulted in additional, though non-significant, mean length of stay: 11.8 ± 4.4 vs 10.5 ± 4.7 days (95% CI -1.02 to 3.62) ($P > 0.05$) [39]. Two studies demonstrated a reduced but non-statistically significant length of stay with an oral/MDI with spacer treatment regime (antibiotics, steroids and SABD) compared to IV/nebuliser 11 ± 3 versus 16 ± 10 days ($P = 0.06$) [42] and 4.3 vs 5.1 days ($P < 0.56$) [41].

A 5-mg vs 2.5-mg regimen of albuterol resulted in higher cumulative cost £8665 versus £4048 (£188.37 vs £101.20 per patient) [40].

Only one study reported hospital readmissions as an outcome, following up participants 20 weeks post-discharge [42]. At this time, 42% of the 23 participants (approximately 10 individuals) in the IV/nebuliser treatment group experienced a readmission versus 66% of 25 participants (17 individuals) in the oral/MDI with spacer treatment group.

Discussion

Established guidelines for the management of COPD exacerbations recommend the use of SABD [7, 23]. The effectiveness of SABD in stable COPD is well established [45, 46], and it is this evidence that has been generalised for use in the inpatient setting [47–50]. However, inpatient administration of SABD is underpinned by weak evidence and is not specific to patients with AECOPD [7, 22, 23]. As such, this review aimed to evaluate the existing evidence for the effectiveness of SABD for patients admitted to hospital due to AECOPD. A paucity of data was identified with only 10 studies meeting the eligibility criteria for inclusion, the majority of which had small sample size, poor methodological quality and/or lacked adequate reporting of the study design. This is likely a reflection of looser reporting standards for older studies (only one included study was published after 2005). Further, there appears to be a lack of interest within the clinical and research space toward focussing new endeavours and funding on what is widely considered a well understood, mainstream treatment for AECOPD. However, as evidenced by the findings of this review, there are still gains to be made particularly for outcomes relating to hospital utilisation, spending and a baseline for standardisation of care. The prevalence of COPD and subsequent high levels of hospitalisations warrant a renewed interest in this fundamental area of inpatient management of these patients [51]. Through evaluation of patient and hospital-based outcomes, we attempted to determine the optimal dose, delivery method, duration and types of agents for the hospital setting, as described in the proceeding sections.

Dose evaluation

Comparison of dosages of SABD for inpatient application demonstrated no added clinical bronchodilatory benefit with doses above 2.5 mg of salbutamol per administration [35, 40, 44]. In fact, there was some indication that a higher dose may result in a higher number of adverse events, with hypotensive and arrhythmic effects noted with > 10 mg of salbutamol [44]. This finding is consistent with a recent study demonstrating a positive correlation between blood salbutamol levels and N-terminal prohormone of brain natriuretic peptide in

people treated with rescue relief for AECOPD [20]. Furthermore, this review indicates that with 5 mg, there was a trend towards increased incidence of tremors, though this was not significant [40]. The evidence suggests that using a lower dose of SABD (e.g. salbutamol 2.5 mg) is just as effective as a higher dose (e.g. 5 mg) in achieving relief of symptoms of breathlessness associated with AECOPD and may prevent unnecessary risk to patients due to drug-related adverse events. Moreover, the use of less medication may potentially result in cost savings with reduced dose delivery per patient for the same clinical benefit [40].

Similarly, the sole study looking at terbutaline did not confer additional benefit beyond dose of 1 mg compared to 2.5 mg [38].

Delivery method

Of the five studies [36, 38, 41–43] reporting different delivery methods for SABD, two were embedded into a wider treatment regime [41, 42]. Both of these studies used a similar approach, differing mainly in the use of either IV or oral steroids [42] or IV/oral antibiotics [41]. The combination of IV steroid with nebulised SABD is likely a model for treating a high-dependency patient requiring more support than a patient who can tolerate an oral steroid and navigate an MDI with spacer [42]. While consistent use of either oral or IV steroid would have been preferable in methodological terms for clarity of comparison, unpacking the results of this study with reference to other research offers interesting and practical insights into clinical decision-making across the diverse spectrum of patients. A systematic review concluded that in the treatment of AECOPD, there is no discernible difference between treating with and IV or oral steroid approach [52]. Furthermore, a recent Cochrane Review concluded, much like the results of this review, that while there is a dearth of large well-conducted studies in this area, there does not appear to be a difference between treating with nebulised or MDI with spacer SABD when considering FEV¹ [53]. The lack of conclusive results in favour of one or the other suggests that clinicians can feel comfortable using whichever delivery method best suits the needs and capabilities of their individual inpatients. One study investigated MDI with spacer versus nebulised SABD with both groups receiving equivalent standard therapy which included use of IV aminophylline and corticosteroids and additional oral or inhaled sympathomimetics [43]. The standard therapy outlined in the latter study is now considered outdated and no longer considered standard practice.

Overall, despite variations in methodology, all five studies demonstrated no significant difference between delivery of SABD via either nebuliser or MDI with spacer. In this instance, clinicians may be guided more by

the patient presentation and tolerability when determining which device to use, rather than potential efficacy of the device.

Duration of treatment

No studies investigated the optimal time frame for duration of SABD administration before termination in the inpatient setting for AECOPD. This is an important aspect of the treatment regime and requires further investigation.

Mono- versus co-intervention therapy

All studies showed an improvement from baseline with administration of SABD; this is not surprising given established evidence of effectiveness in stable COPD [46]. There appeared to be no difference between mono- and co-intervention therapy with regard to FEV¹. As a result of these findings, it is possible to suggest that monotherapy with a β 2-agonist for inpatients with AECOPD to be sufficient and addition of anticholinergic agents is of no additional clinical benefit and a potential waste of resources. However, this is based on a single included study with only 62 participants, and as such, results should be interpreted with caution. Further research in this area is required prior to considering changes to practice.

Type of short-acting β 2-agonist

Most included studies reported the use of either salbutamol or albuterol which are the same agent [35, 39–41, 43, 44]. One study investigated a treatment regime which delivered albuterol to one group and fenoterol to the other group [42]; while both are short-acting β 2-agonists, the latter has a slightly longer duration of action [54]; another study examined terbutaline [38]. There appeared to be no difference between agents used. Interestingly, fenoterol has been withdrawn from the pharmaceutical market due to its association with increased risk of death [55]. Based upon this observation, a choice may be made according to clinical preference, safety profile and drug availability.

Limitations of this review

The limitations of this review owe mainly to the quality and quantity of included studies. The majority of the included studies were published before 2008, bar one [36]. Hence, recommendations based on these findings may not be a true reflection of current clinical practice. This is perhaps an indication that clinical practice is evolving quickly, with research and the evidence-base lagging behind. Furthermore, the wider literature on this general topic is also somewhat lacking in recency; it appears that perhaps the profession has just accepted SABD as a relatively non-threatening and straight forward treatment for AECOPD and is happy to focus research efforts on

other, more exciting things. This is of concern given that administration of SABD is considered a core therapy during AECOPD and standardisation of practice is desirable. The heterogeneity of reported methodologies and outcomes made meta-analysis of the data impossible. Furthermore, as indicated by the risk of bias assessment, the included studies were of average to poor methodological quality with small sample sizes, again limiting generalisability of the findings. It is also desirable to be able to assess the pooled effect of these studies to be able to provide a more objective assessment of effectiveness through meta-analysis; however, this was precluded in this review.

Recommendations for clinical practice and future research

Given that a clear clinical benefit was not identified with use of higher doses of SABD, it is important to consider the risk of frequent and sustained use, while questioning continued acceptance of the status quo. A moderated approach is recommended, especially when administering four hourly nebulisations; extra care in the case of people with known or possible unknown comorbid cardiac disease is necessary as in these patients, risk may outweigh benefit.

Methodologically rigorous evaluations are required that evaluate the current use of SABD in the hospital setting following patient admission for AECOPD, particularly given the lack of recent evidence identified in this review. Future studies should report on all the outcomes pre-specified in this review, as these outcomes reflect not only patient level variables, but also those necessary for policy and guideline decision-making. Detailed description of dose, delivery method, duration and types of agents need to be described in detail to facilitate accurate evidence-based recommendations for the use of SABD in the inpatient setting.

Conclusion

Despite the routine use of SABD in the hospital setting for the management of AECOPD, a paucity of data pertaining to the inpatient applications of this medication was found. Though the evidence is limited, it appears consideration of the use of a single short-acting β_2 -agonist such as salbutamol/albuterol at a dose of 2.5 mg may be sufficient to get the desired clinical outcome. Co-intervention therapy and higher dose regimens were not associated with any discernible clinical benefit for the outcomes reported in this review. Delivery method may be prescribed based on patient preference given the equivalence observed in delivery method for available data. However, despite the somewhat interesting results presented in this review, interpretation should be made with care as the quality of the evidence underpinning these outcomes were overall low.

The gap in evidence highlights the need for methodologically rigorous, appropriately powered studies to address the use of SABD specifically in the inpatient setting, to allow for improved patient- and hospital-based outcomes, and the basis of standardised practice with regard to prescription of mainline therapy of AECOPD.

Additional files

Additional file 1: PRISMA checklist. (PDF 214 kb)

Additional file 2: Search strategy and search terms. (PDF 287 kb)

Additional file 3: Standardised data extraction template. (PDF 82 kb)

Abbreviations

95%CI: 95% confidence interval; AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; CENTRAL: Cochrane Central Register of Controlled Trials; COPD: Chronic obstructive pulmonary disease; FEV₁: Forced expiratory volume in 1 s; FVC: Forced vital capacity; ICU/CCU: Intensive care unit/critical care unit; IV: Intravenous; MDI: Metered dose inhaler; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; P: Probability value; PRISMA: Preferred Reporting Items for Systematic Reviews And Meta-Analyses; SABA: Short-acting β_2 -agonist; SABD: Short-acting bronchodilator; SAMA: Short-acting muscarinic agent; vs: Versus

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Authors' contributions

ZK wrote the protocol for the review; screened, extracted and synthesised the data; and drafted the manuscript. NS and OM assisted with screening, extraction and manuscript drafting. KVCC assisted with protocol development and manuscript drafting. PP and BS assisted with interpretation of data and revision of manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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Chapter 6.

Cessation of smokers seeking treatment and advice from health care professionals in the hospital setting

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Contribution to the paper	Invited to write the review, conceived and designed the manuscript, extracted data, interpreted results, analysed the data, wrote the first draft, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions and approved final version.		
Signature		Date	22/02/2019
Name of co-author	Joseph van Agteren		
Contribution to the paper	Screened studies for inclusion, extracted data, interpreted results, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, and made critical revisions.		
Signature		Date	24.2.2019

Name of co-author	Kristin V Carson-Chahhoud		
Contribution to the paper	Extracted data, interpreted results, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, and made critical revisions.		
Signature		Date	10/01/2019
Name of co-author	Tim O'Loughlin		
Contribution to the paper	Agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, approved final version and supervised the process.		
Signature		Date	28/02/19
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Signature		Date	4-/3/19

Cigarette smoking is the single most preventable risk to health and the progression and exacerbation of COPD in particular. Guidelines state that smoking cessation is a priority in the management of COPD, yet delivery of interventions to assist quit attempts is variable in practice. This is despite indications that the decline in prevalence having plateaued in recent years. Hospital admission presents a sizeable opportunity to capitalise on forced abstinence and attempt to facilitate a successful quit attempt. Existing systematic reviews and evidence syntheses in the area appear to have had little impact on change in clinical practice. An invitation was extended to systematically produce a peer reviewed policy document for the Australia and New Zealand School of Government.

Given the potential for wider dissemination of the evidence base to relevant policy makers this invitation was accepted. The journal of the Australia and New Zealand School of Government, *Evidence Base*, is a peer-reviewed online repository designed to put systematic reviews, focusing on interventions that work, at the fingertips of public sector decision-makers. Hence, this invitation was seen as an opportunity to do one better on previous efforts to translate the results of a growing evidence base in to real-world changes to practice.

The analysis of sixty-nine studies in this review identified that high intensity behavioural counselling with one month follow-up and the provision of adjunct pharmacotherapy to be the most effective strategy for assisting quit attempts in the general inpatient population. The addition of pharmacotherapy was not necessary for patients admitted to specialist wards (e.g. cardiac wards), while peri-operative cessation interventions showed effective but transient effects and intervention in the emergency setting was not supported by positive results.

Cessation for smokers seeking treatment and advice from health care professionals in the hospital setting

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Abstract

Cigarette smoking costs Australia and New Zealand billions of dollars per year and is the single most preventable risk to health. Though governments have initiated numerous public health policies which have reduced the incidence of smoking, current usage remains around 15 percent. Making further inroads is likely to require augmenting these interventions with action at the individual level. The hospital setting provides a unique opportunity to assess the efficacy of individual attention. The aim of this study is to make an initial assessment of this efficacy by collating the existing evidence of outcomes achieved by health professionals working with individuals in hospital settings. The systematic literature search resulted in 69 studies (72 citations) for evaluation. Results indicated that a multi-component intervention comprised of high intensity counselling with a minimum of one month of post-discharge follow-up in addition to either nicotine replacement therapy or varenicline tartrate is the most effective combination of individual treatments for improving smoking abstinence, particularly for general inpatients. Further, there was an indication that patients admitted to specialist wards (e.g. cardiovascular) would benefit most from high intensity interventions, regardless of the use of adjunct pharmacotherapy. The evidence for a positive effect on sustained quit smoking rates for peri-operative patients is not definite, but as smoking adversely affects surgical success, implementing multicomponent interventions should still be considered. This review found no clear evidence to support implementation of smoking cessation interventions in the emergency department setting. Overall, interventions throughout the review were heterogeneous, making the estimate of a true effect difficult. Furthermore, there were only low numbers of local studies, with the findings of this review relying mostly upon extrapolation from overseas studies. Given the severity of the burden placed on the health system by smoking, there is a need for continuing endeavours by researchers with the support of the government to identify innovative and effective interventions for smokers that can be delivered by health professionals caring for smokers in the hospital setting.

Cigarette smoke is composed of more than four thousand known chemical species with toxic and carcinogenic properties (Colombo et al. 2014). Smokers breathe this aerosolised gas and particulate cocktail

into their bodies, even though it has been identified as the cause of a long list of diseases and cancers affecting the circulatory, respiratory, reproductive, nervous, urinary and digestive systems (Colombo et al. 2014).

Cigarettes' main psychoactive component, nicotine, has strong reinforcing and rewarding properties, and together with the psychological and environmental cues associated with smoking, makes cigarette smoking an extremely addictive behaviour (Balfour 2009; Laviolette and van der Kooy 2008).

Recent estimates indicate a decrease in the prevalence of smoking, from 29.1 percent of Australians and 25 percent of New Zealanders in the 1990s compared to the most recent figures of 12.8 percent and 16.6 percent respectively (Australian Institute of Health and Welfare 2008; Australian Institute of Health and Welfare 2014; Ministry of Health 2014; Ministry of Health 2015). Though these figures appear to be heading in the right direction there are still many who engage in a behaviour which is the greatest preventable cause of morbidity and mortality, accounting for approximately 15,500 and 5,000 Australian and New Zealander deaths per year respectively (Begg et al. 2007; New Zealand Government 2016).

In common with most other countries, Australia and New Zealand have implemented a range of public policy initiatives targeting cigarette use over the past decades. Key examples include prohibiting the advertisement and promotion of cigarette products, followed by mass media public education campaigns and labelling of cigarette packaging with health warnings, and most recently implementing plain packaging requirements (Cotter 2011; Grace 2016; Miller and Scollo 2016). Financial interventions and methods aimed at increasing quit rates have also been introduced in the form of subsidisation of pharmacotherapy, and price and taxation increases, with the cost of purchasing cigarettes in Australia now almost 10 times more expensive than in the 1990s (Purcell et al. 2012). Perhaps the strongest legislation is the ban on smoking in public places, including (but not limited to) workplaces, bars and restaurants, schools, hospitals and other health-care buildings (New Zealand Drug Foundation 2011; Greenhalgh et al. 2016). These broad public policies and legislature initiatives to date have contributed to a drop in smoking rates (Woodruff et al. 1993; Glasgow et al. 1997; Farkas et al. 1999; Farrelly et al. 1999; Albers et al. 2007; Azagba and Sharaf 2013), and as such have demonstrated the viability of continuing to target smoking cessation on a societal level.

Policy interventions have enjoyed considerable success in reducing smoking. However, smoking reduction is not as great in absolute terms as the percentage decline might imply. That is, the decline in absolute number of smokers is now less, for instance due to population growth. Additionally, smoking rates are influenced by fewer young people taking up the habit, as opposed to reducing current smoker rates. These

recalcitrant smokers are less receptive to changing their behaviour, even with the concerted effort of enforcing the tobacco related policies outlined above (Borland et al. 2012; Australian Institute of Health and Welfare 2014). Hence, additional interventions aimed at the level of individual smokers are required to support these larger scale initiatives. The need to engage the healthcare system in this effort has been outlined in a number of policy documents, including Australia's *National Tobacco Strategy 2012-18*, *Framework Convention on Tobacco* and the *National Preventative Health Strategy* (World Health Organization 2005; National Preventative Health Taskforce 2008, Intergovernmental Committee on Drugs 2012). In broad terms these documents outline the need to improve uptake of existing infrastructure (e.g. Quitline), develop systems where health professionals engage with patients around this issue, and provide policy guidelines on brief interventions for health professionals to implement with smokers in their care (World Health Organization 2005; Greenhalgh et al. 2016). The *National Tobacco Strategy 2012-18* (Intergovernmental Committee on Drugs 2012) specifies that as an industry we must:

Improve management of smoking cessation for all patients in health care facilities, particularly for patients on admission to hospital.

There are a number of evidence-based approaches that have been proven to work in the general smoking population, when attempting to address smoking cessation with patients. One can provide face-to-face counselling (Lancaster and Stead 2005) or can refer to a telephone counselling service (Stead et al. 2013), hereafter referred to as a Quitline. Alternatively, there are a number of smoking cessation medications that can assist during a quit attempt, including varenicline tartrate (varenicline) (Ebbert et al. 2010; Cahill et al. 2013), bupropion hydrochloride (bupropion) (Raupach and van Schayck 2011; Cahill et al. 2013) or nicotine replacement therapy (NRT) (Ferguson et al. 2011; Cahill et al. 2013). Combining pharmacotherapy and counselling, hereafter referred to as a multicomponent strategy, is an additional option, which has been shown to increase quit rates from 10 to 25 percent compared to pharmacotherapy alone (Stead and Lancaster 2012). There are also some alternative methods that often get mentioned when discussing smoking cessation, most notably hypnotherapy, for which conclusive evidence is currently lacking (Barnes et al. 2010).

Healthcare institutes' practices and specific organisational policies in relation to smoking cessation are often underutilised, ad hoc, outdated and

variable between institutions, departments, and even individual healthcare practitioners (Freund et al. 2008; Freund et al. 2009; Bartels et al. 2012; George et al. 2012; Ohakim et al. 2015). In the hospital setting, anecdotal and published evidence suggests that clinical practice guidelines for smoking cessation are sub-optimally translated into practice (Fiore et al. 2012; Freund et al. 2009; Regan et al. 2012; Slattery et al. 2016; Smith et al. 2012), despite a growing evidence base underpinning the recommendations. This is a substantial missed opportunity for effective intervention, with almost 300,000 hospitalisations per year in Australia attributable to cigarette smoking (Hurley 2006). Furthermore, hospitalisation presents a unique opportunity to apply individualised approaches as it:

1. provides a reflection period during an inpatient stay for smokers to reconsider lifestyle factors contributing to their illness/admission, a so-called 'teachable moment' (McBride et al. 2003);
2. makes it difficult (although not impossible) to smoke through enforced initiation of abstinence while in a hospital bed, as a result of widespread smoking bans in hospitals (Rigotti et al. 2000; Purcell et al. 2012), allowing patients to focus on the achievement that they have already quit by the time of discharge; and
3. facilitates the initiation of smoking cessation medication under supervision, which allows monitoring of nausea, craving and titration of medication to avoid adverse events.

Hence, in order to provide a current snapshot of effective quit smoking interventions in the hospital setting, the aim of this review is to evaluate the existing evidence for interventions delivered to smokers admitted or presenting to hospital, who are receiving treatment and advice from healthcare professionals.

The compiled evidence will be discussed with a view to underpin practical and achievable recommendations for policy improvement in this area. Given that smoking is a national and international priority area, there is an opportunity to make a significant impact on patient services for smoking cessation by making a change to current practice approaches.

Methods

Study search strategy

A systematic literature search of the Medline, EMBASE, PsycINFO and The Cochrane Library databases was

conducted in November 2016. Publications investigating smoking cessation policy within the hospital setting (for admitted patients and those attending the emergency department) were examined. We used the following free text search terms to identify relevant records: (smoking cessation) AND (pharmacotherapy OR drug therapy OR counselling OR hypnotherapy OR hypnosis OR aversive therapy OR psychotherapy OR smoke-free policy OR bans OR fines OR penalties OR motivation OR goals).

Grey literature were also searched to identify potentially relevant articles through the International Clinical Trials Registry Platform and ClinicalTrials.gov (searched November 2016), using the key words (smoking cessation) AND hospital. Reference lists of publications meeting all the inclusion criteria were also screened for potentially eligible studies.

Study inclusion criteria

In order to determine the most effective smoking cessation interventions delivered by healthcare professionals in the hospital setting, we reviewed evidence from randomised controlled trials with a minimum three-month follow-up. In the case of perioperative interventions, there was no restriction set at the follow-up period. Trial participants were current smokers admitted to a hospital ward or presenting to a hospital emergency department. Healthcare professionals delivering the intervention were defined as doctors, nurses, pharmacists, physiotherapists, and other clinical professionals providing care within the hospital setting. The intervention could also be delivered by researchers in instances where the procedure would, in practice, be provided by a healthcare professional.

Interventions included were:

1. Behavioural interventions: counselling, support groups, self-help, seminars, motivational lectures, web- and mobile phone-based interventions
2. Pharmacological interventions adjunct to counselling: NRT, bupropion and varenicline. These are generally accompanied by at least minimal counselling by health professionals. When minimal counselling was standardised across each study group, this was considered as isolation of the pharmacological intervention effect
3. Multicomponent interventions: pharmacological and non-pharmacological approaches combined as a package intervention

Comparison groups consisted of usual care, minimal intervention (such as a pamphlet or referral back

to regular General Practitioner for follow-up) or co-intervention (where the control group receives some parts of the intervention but not all).

Analysis methods

From the title, abstract or descriptors, two reviewers screened the retrieved citations to identify potentially relevant trials. Data for included studies were then extracted into standardised templates for trial characteristics and outcome variables. Studies not meeting all the inclusion criteria reported above for study design, subject description, and intervention/comparison group characteristics, were excluded from the narrative synthesis of results. In addition, a risk of bias assessment was conducted to assess the quality of the evidence base. This was undertaken using the report by Tooth et al. (2005) and standard Cochrane risk of bias grading criteria. Bias was categorised as 'high risk of bias' when a particular quality procedure did not occur, 'unclear risk of bias' when data were not reported in the article or when criteria were not relevant and 'low risk of bias' when data for a criterion were reported and adequately addressed in the study design. Review Manager Version 5.3 software was used to generate the risk of bias graphs. Outcome variables of interest were:

- Seven-day point-prevalence smoking abstinence: this refers to whether, at a pre-defined time point, an individual has smoked cigarettes/tobacco in the previous seven days.
- Continuous smoking abstinence: relates to cessation of smoking from the initial quit date to a pre-defined time point.

These outcomes are often measured by the participant's self-report, and may be validated through biochemical measures, e.g. cotinine samples obtained via blood, urine or saliva, or carbon monoxide assessed through expired breath or blood specimen (Benowitz et al. 2002; Hughes et al. 2010).

For this review we will report seven-day point-prevalence in the first instance, and where this is not measured we will report 30-day continuous smoking abstinence. These self-reported measures are highly correlated and will lead to the same conclusion (Velicer and Prochaska 2004). Other outcomes which will be discussed in the review are: number and type of adverse events in case of pharmacological interventions; number and type of postoperative complications in case of interventions focusing on surgical patients; and costs associated with each intervention.

While not *direct* smoking cessation measures, these outcomes are clinically relevant and should be taken under advisement when making recommendations for change of practice.

What kind of research is available?

After duplicates were removed, 2768 citations from the electronic search were screened for eligibility. Of these, 62 citations were eligible for evaluation and a further 10 were identified through hand searching included articles and relevant systematic reviews. Tables 1, 2 and 3 are a summary of the characteristics and findings of the 69 studies (72 citations) included for evaluation, separated into the three main types of intervention.

Initially this document aimed to focus on Australia and New Zealand studies, with reference to international studies. However, the comprehensive literature search identified only seven studies undertaken in Australia and none from New Zealand. As such, all relevant studies have been included together for narrative synthesis; studies from North America and Europe being the main contributors to the current evidence base.

Methodological assessment was undertaken for all 72 citations and a visual summary is provided in Figure 1, while individual study quality is presented in Figure 2. Overall, study quality was determined to be average. There were many studies where a low or high risk of bias judgement was precluded due to poor reporting of study methods in the publication; this resulted in a high volume of unclear bias assessments. High risk of bias assessment was predominantly noted in the performance bias domain; this is likely attributable to difficulty blinding participants with behavioural interventions. For pharmacological interventions this was generally well done.

The results below are split for interventions targeting the general inpatient population and patients on cardiac wards. This decision was made because pharmacological interventions are often perceived to be associated with increased risk and caution for cardiac patients; furthermore, there is a substantial body of research targeting this specific patient group. Upon review of the evidence base, cancer patients were not placed in a dedicated subgroup, as it was hypothesised that they predominantly fall within the pre-operative or outpatient group depending on disease status.

In addition, it is important to note that the 'intensity' of behavioural interventions will be discussed below. This refers not necessarily to the quality of the intervention but to the composition of the intervention itself; for example, duration and number of contacts by health care professionals (longer and more

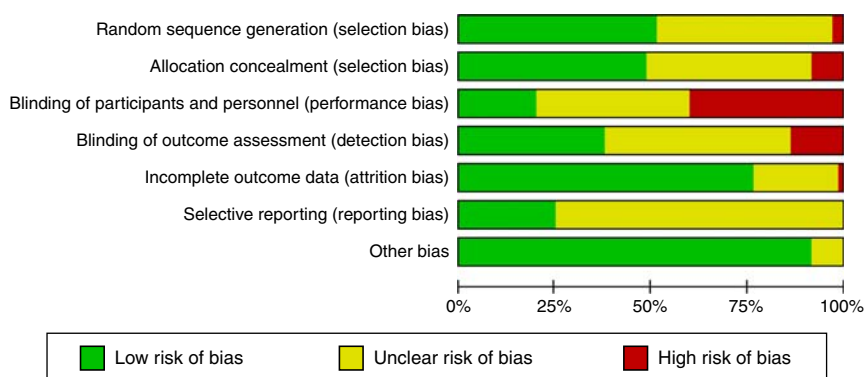


Figure 1: Summary of risk of bias for included studies

equates to a higher intensity). Quality of these interventions is an important factor when considering the results, and may have had a bearing on the relative success or otherwise of the studies included for review. Aspects of the interventions which would facilitate a quality judgement (e.g. delivery of intervention by a specialist or a generalist; training of study personnel to ensure consistent intervention delivery) are reported variably, making it difficult for the authors to rate the intervention quality.

Interventions targeting the general inpatient population

Behavioural interventions

For reasons explained previously, high intensity behavioural interventions are recommended for inpatient smokers to successfully quit their habit. These recommendations are influenced by the results of a Cochrane systematic review and meta-analysis that concluded that high intensity behavioural interventions, being those that consist of a hospital counselling session and a follow-up for at least one month, lead to a significant improvement in quit rates (Rigotti et al. 2012). These recommendations are accurate when behavioural and multicomponent (counselling and access to free pharmacotherapy) interventions are put together, which was the case in the Rigotti et al. (2012) Cochrane review. However, when solely looking at behavioural counselling interventions, specifically split for admitting ward, results point to different conclusions: no clear evidence in favour of either low or high intensity behavioural interventions.

Three studies used lower intensity interventions, and unsurprisingly for such a small pool of evidence, conclusive evidence of effectiveness was lacking. While Meysman et al. (2010) found that a brief

nurse-delivered stage-based intervention using trained nurses was better than a booklet in getting patients to quit, a study by Rigotti et al. (1997) failed to find a significant advantage with a 15-minute bedside counselling session combined with post-discharge counselling over usual care at 6-month follow-up. Similarly, Pederson et al. (1991) did not find any differences when comparing brief quit advice with more intensive counselling consisting of up to eight 15–20 minute sessions while participants were still hospitalised.

Interestingly, studies using higher intensity interventions also showed no significant differences in favour of intervention. De Azevedo et al. (2010) used tailored counselling and up to seven follow-up telephone calls, while Hennrikus et al. (2005) used counselling and up to six follow-up telephone calls, with neither trials showing higher smoking cessation rates compared to brief advice or usual care. Similarly, the study by Smith et al. (2011) did not find significant benefits from a high intensity intervention (bedside counselling, seven telephone follow-ups and minimal intervention package) over minimal intervention. These trials, with a combined sample size of 2228 participants, are only opposed by a small study of 77 participants, which found that an intensive 12-week nurse-delivered relapse management intervention, including eight telephone follow-up calls, showed a 42 percent quit rate compared to 15 percent in the usual care group (Caruthers et al. 2006).

All studies above used either telephone or face-to-face follow-up. Only one study (Harrington et al. 2016) used at a different mode of delivery – a web-based intervention. The intervention focused on quit smoking education and allowed for asynchronous communication with quit smoking counsellors. The authors found that at end of follow-up, results significantly favoured control, 18.5 percent versus 13.8 percent. These results need to be considered in the context of problematic treatment adherence, which may have negatively

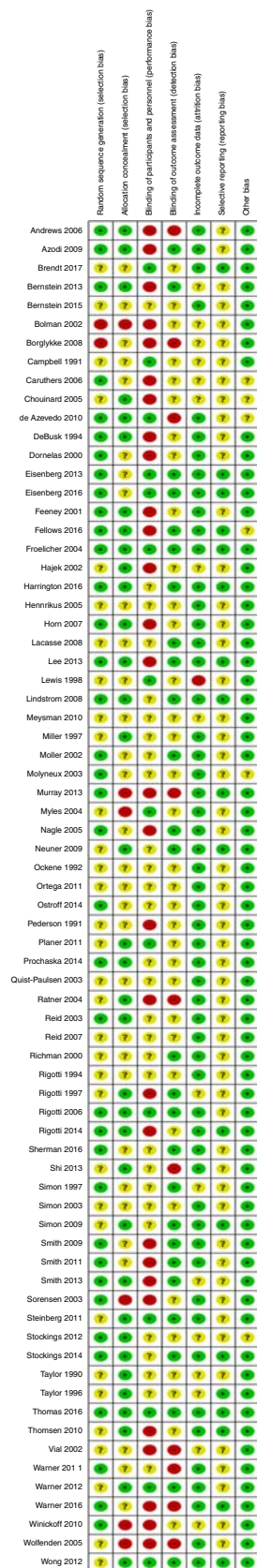


Figure 2: Risk of bias assessment for individual studies

impacted the findings. Treatment adherence problems for web-based and mobile-based interventions in the general population are widely recognised, and can be attributed (among other reasons) to the inexperience of intervention designers in designing engaging solutions (Kelders et al. 2012). This problem will hopefully be solved as the eHealth and mHealth research field matures and interventions become more sophisticated.

Pharmacological interventions adjunct to counselling

Evidence for the effectiveness of bupropion prescribed in the general hospital setting is currently lacking; three trials used bupropion in a cardiac population (see the cardiac section) and two trials targeted pre-operative patients (see pre-operative section). One trial assessed its use in the general population (Simon et al. 2009). The study found no significant improvement in quit rates with bupropion. Interestingly, however, it reported non-significant higher rates of abstinence among the placebo group (31 percent) compared with the bupropion group (15 percent) at six-month follow-up.

The sole study looking at the effect of NRT versus placebo in the hospital setting did not yield significantly higher quit rates when both groups were provided as an adjunct to intensive counselling with five face-to-face follow-up sessions (Campbell et al. 1991). All other NRT studies were either performed in the cardiac or pre-operative setting, or were provided as a multicomponent intervention.

The two studies that tested the use of varenicline in the hospital setting found conflicting results. A well-powered Australian study found that varenicline adjunct to counselling by Quitline significantly increased quit rates to 31.1 percent compared to the 21.4 percent of smoke-free patients treated by Quitline alone (Smith et al. 2013). Alternatively, a much smaller pilot study by Steinberg et al. (2011) found no significant difference between varenicline and placebo adjunct to low intensity counselling. In this trial, only just over half of the participants treated with varenicline were compliant, but those patients who were compliant with the medication showed higher quit rates when treated with varenicline (80 percent versus 56 percent); unfortunately, the study was not sufficiently powered to detect this kind of difference.

Multicomponent interventions

Multicomponent interventions for inpatient smoking cessation are widely encouraged by best-practice

guidelines (Fiore et al. 2000; West et al. 2000; Global Initiative for Chronic Obstructive Lung Disease 2015; Yang et al. 2016). Most studies found in this review evaluated a bedside counselling program combined with NRT and post-discharge telephone and/or outpatient cessation support. Similar to behavioural interventions, counselling can be broken up into high and low intensity. For low intensity interventions, three studies were found that tested the effectiveness of low intensity counselling in addition to provision of NRT, none of which found a significant effect on quit rates (Molyneux et al. 2003; Nagle et al. 2005; Thomas et al. 2016).

The results of eight studies investigating high intensity multicomponent interventions, on the other hand, showed favourable smoking cessation rates. The largest of these studies (Miller et al. 1997), comprising 2024 patients, found that an intervention consisting of counselling, access to an educational video, NRT and one follow-up telephone call was not demonstrably superior to usual care for smoking cessation. However, after increasing the behavioural counselling intensity, by adding three extra follow-up telephone calls and provision of extra face-to-face counselling in the event of relapse, smoking cessation significantly improved by 7 percent over usual care. Similarly, Simon et al. (1997; 2003) conducted two studies evaluating a multicomponent intervention comprised of individual counselling, educational video, provision of three months of NRT, printed resources and five follow-up telephone calls. In the first instance it was compared to a brief pre-discharge counselling session and printed resources and though not significant at six months, abstinence favoured the intervention group by 8 percent, and at 12 months this further improved to 14 percent and became a statistically significant difference (Simon et al. 1997). In the second evaluation, the multicomponent intervention was compared to two months of NRT and a brief counselling session (Simon et al. 2003). Once again results favoured intervention at six months (35 percent vs 21 percent) and 12 months (33 percent vs 20 percent); both differences were statistically significant. This is the first time an identical intervention of this type has been evaluated with reproducible results.

High intensity individually oriented multicomponent interventions may be a resource-intensive exercise, and as such several studies have researched different intervention formats, specifically referring to outpatient services, the use of group-formats, automated telephone counselling, and the use of computers to deliver the interventions.

Simply referring patients to outpatient counselling is not sufficient to maintain high quit rates. Sherman et al. (2016) found that providing patients post-discharge (up to 42 days) counselling via telephone in addition to eight weeks of NRT out-performed a simple referral to Quitline for proactive counselling by almost 10 percent at two months and 5 percent at six months for 30-day point prevalence abstinence.

Delivering inpatient counselling within a group setting is a promising alternative to individual bedside counselling. Borglykke et al. (2008) tested group counselling combined with standard cessation information and provision of NRT compared to standard cessation information alone. Results favoured the multicomponent strategy, where cessation at one-year follow-up was 17 percent superior to control.

Two recent studies investigated the use of innovative technology aimed at automating follow-up counselling and triaging smokers who needed additional human-delivered counselling. Rigotti et al (2014), found significant results when using an automated interactive voice response system to provide follow-up counselling, in addition to free NRT, with superior quit rates of 11 percent higher in the intervention group. They also performed a cost analysis that determined the costs per patient for the intervention were US\$354 for the first 12 months and US\$108 for subsequent years (Rigotti et al. 2014). Fellows et al. (2016) similarly tested an innovative voice recognition intervention in addition to assisted outpatient referrals and a multicomponent inpatient intervention, however, they reported no significant difference in quit smoking rates. Uptake of NRT in the Fellows et al. (2016) trial was considerably lower, which might explain the difference in results. These results indicate that simple voice recognition counselling on its own is not sufficient, but that it proves a promising future research area when tested as a complement to a multicomponent intervention and free NRT.

Only one study assessed the effectiveness of a computer delivered intervention in addition to other familiar components (NRT, print resource, individual counselling and follow-up telephone support) (Prochaska et al. 2014). This multicomponent intervention proved successful compared to usual care, improving smoking abstinence by approximately 10 percent at three-month follow-up. This was sustained at 18-month follow-up with 20 percent of participants reporting smoking abstinence in the intervention group compared to just 7.7 percent in the control. Interestingly, the intervention group also demonstrated decreased risk of hospital readmission. When viewed in combination with the promising results of another web/computer-based intervention, discussed above (Harrington et al. 2016), this is

likely a priority area for further cessation research given its potential for the easy implementation of a standardised program with long-term results.

Summary of smoking cessation treatments for the general inpatient setting

There is insufficient evidence to suggest that the general inpatient population benefits from brief counselling, referral to professional counselling services after discharge or even high intensity behavioural interventions that include telephone follow-up counselling. Furthermore, evidence for the use of pharmacotherapy on its own is inconsistent. The only intervention type that was significantly more effective in increasing quit rates was the use of multicomponent interventions. Specifically, the biggest evidence based interventions involve combining provision of (free) NRT with intensive counselling. Using innovative approaches (automated telephone counselling and computer-delivered interventions) to complement or substitute human-delivered counselling looks promising, but the current evidence base is not strong enough to recommend widespread adoption.

Patients on cardiac wards

Behavioural interventions

Three studies evaluated the effectiveness of low intensity behavioural interventions in patients with a cardiac admission, failing to find sufficient evidence for effectiveness. Neither Bolman et al. (2002) nor Hajek et al. (2002) found superior quit rates for low intensity interventions consisting of brief bedside counselling and other behavioural components (e.g. declaration to commit to quitting). Adding a single one-week follow-up call to an extensive cognitive behavioural intervention was not sufficient in inducing higher quit rates compared to usual care (Rigotti et al. 1994). Quit rates for cardiac patients were, however, higher as compared to the general inpatient setting, despite not being higher than usual care, which does indicate a higher susceptibility to quit smoking for this population.

This notion is further supported by results from studies using higher intensity behavioural interventions. In contrast to the general inpatient population, cardiac patients show significantly higher quit rates of between 39–70 percent as found by five studies. Bedside counselling and education complemented with telephone follow-ups were effective in improving quit rates, with one study finding these results were sustained up to

five years later (Chouinard and Robichaud-Ekstrand, 2005; Dornelas et al. 2000; Feeney et al. 2001; Ockene et al. 1992; Smith and Burgess 2009).

Using a group format as opposed to individual counselling, or targeting smoking cessation as part of a larger cardiac care improvement interventions, are also promising. A bi-weekly group smoking cessation session, combined with telephone follow-up after discharge, resulted in abstinence up to 12 months in 50 percent of patients treated in the group sessions versus 37 percent of patients given no further instruction on how to quit (Quist-Paulsen and Gallefoss 2003). Quit rates of up to 70 percent were found when evaluating a multicomponent intervention focusing on improving case-management of cardiac patients (DeBusk et al. 1994). The intervention assessed smoking and nutritional counselling, the use of lipid-lowering drug therapy and exercise training, and included 12 nurse-initiated telephone follow-ups and 12 patient visits to either the nurse case manager or the laboratory for blood testing.

Pharmacological interventions

Four trials investigated the differences between pharmacotherapy targeting smoking cessation, and placebo as a complement to low intensity counselling. Review of the existing literature demonstrates that there is no definitive evidence to support adding bupropion to counselling for cardiac patients, as two trials failed to find a significant benefit in this population (Eisenberg et al. 2013; Planer et al. 2011). A third trial by Rigotti et al. (2006) only found a significant short-term difference favouring bupropion when looking at a subset of treatment compliant participants; this result was not maintained at one-year follow-up. A further study investigated the use of varenicline as a complement to low intensity counselling, which saw significantly higher rates of non-smokers at the end of the trial – 47.3 percent versus 32.5 percent (Eisenberg et al. 2016).

Multicomponent interventions

Multicomponent interventions for cardiac inpatients were largely led by nurses and included a higher intensity behavioural component. Interventions overall point to increased cessation rates of at least 10 percent up to a period of 3–6 months, but results were in general not sustained at 12 months. Froelicher et al. (2004) found higher point prevalent smoking cessation rates of 10.7 percent at 6 months and overall higher continuous smoking abstinence ($p=0.04$)

for their multicomponent intervention versus brief counselling. Reid et al. (2003) similarly found 11 percent higher quit smoking rates at 6 months, for an intervention that provided extra follow-up care for those patients who had relapsed. These results were replicated when they tested a similar intervention but used voice response technology to take over the follow-up counselling (Reid et al. 2007).

These results were countered on the one hand by a study with significantly higher quit smoking rates, and on the other hand a study that failed to find results. Taylor et al. (1990) found that a multicomponent intervention over usual care almost doubled smoking cessation rates (61.6 percent vs 32 percent). Conversely, a recent three-arm study (Berndt et al. 2017) comparing usual care to follow-up counselling performed by telephone or follow-up counselling done face-to-face did not find significant between-group differences. However, when the latter split the groups into low socioeconomic status and high socioeconomic status, telephone counselling and face-to-face counselling outperformed usual care.

Summary of smoking cessation treatments for the cardiac setting

High intensity behavioural as well as multicomponent interventions are effective in increasing quit smoking rates for patients with cardiac conditions. While behavioural interventions were heterogeneous in their intervention designs, making it difficult to nominate the exact program which would be most effective, it can be said that any inpatient smoking cessation intervention for cardiac patients should include a behavioural component extending into the post-discharge period. Where possible and appropriate, the provision of free quit smoking medication could be considered as results show overall favourable short to medium term results.

Emergency department patients

There is no clear evidence to support the use of behavioural smoking cessation interventions in the emergency department. The only trial available failed to find a difference between two-minute generic advice and a more intensive intervention, including a self-help workbook and three follow-up telephone calls, when targeting smoking youth aged 14–19 years old. Quit rates were 2.5 percent for the intervention and 2.9 percent for control (Horn et al. 2007).

There appeared to be no difference between provision of a multicomponent intervention with either

low or high intensity behavioural counselling in the emergency department setting. Three trials studied multicomponent interventions including low intensity behavioural support. Bernstein et al. (2013) and Bernstein et al. (2015) tested brief counselling, six weeks of NRT and referral to Quitline (for general smokers) or a single follow-up telephone call (for substance abusers). Though these results were promising at the three-month follow-up, they were not sustained at 12 months. Richman et al. (2000) failed to find even short-term positive results for a similar program compared to an educational pamphlet, with quit rates of 10.9 percent versus 10.4 percent.

Only one emergency department initiated a multi-faceted intervention including a higher-intensity behavioural component, consisting of four follow-up telephone calls (Neuner et al. 2009). Contrary to results of higher-intensity interventions in the general and cardiac inpatient settings, this study demonstrated similar results between groups when compared to usual care: 14.2 percent versus 11.3 percent respectively.

Lack of successful outcomes in the emergency department, even for multi-faceted interventions including a higher-intensity behavioural component, is inconsistent with results seen in other hospital settings. Given the inundation of patients in the emergency department and the need to triage patients according to urgency, as well as costs associated with intervention delivery, this may not be the most suitable opportunity for dedicated smoking cessation interventions.

Peri-operative patients

Providing a personalised letter from a consultant in combination with nurse quit smoking advice and a referral to a stop smoking service improved quit rates pre-operation (18 percent), as opposed to providing a general quit smoking booklet and nurse advice (8 percent) (Andrews et al. 2006). The only other peri-operative behavioural intervention did not detect a difference between brief advice and brief advice plus a carbon monoxide check on the day of surgery (Shi et al. 2013).

Only two pharmacological studies were identified for the peri-operative setting. Myles et al. (2004) did not find bupropion to be more effective than placebo prior to elective surgery in terms of overall abstinence rates at hospital admission and six-month follow-up (this trial started two months before surgery was scheduled and encompassed two face-to-face counselling sessions, as well as weekly telephone

follow-up). Alternatively, a 12-week course of varenicline as part of a perioperative intervention including standardised counselling identified a significant 10 percent improvement in smoking abstinence with varenicline compared to placebo which was sustained up to 12 months (Wong et al. 2012).

Multicomponent interventions that included higher-intensity behavioural support found favourable quit rates for the peri-operative setting overall. Lindström et al. (2008) and Lee et al. (2013) used similar interventions consisting of weekly long counselling sessions, referral to Quitline and free NRT, with both trials finding significantly higher quit rates. The Lindstrom trial found that 33 percent versus 15 percent of smokers had quit at 12-month follow-up, and the Lee trial found 30 percent versus 11 percent had quit at three-month follow-up, for intervention compared to control. A study comparing peri-operative nurse-led telephone, computer and in-person support in conjunction with NRT, found that in the two weeks pre-surgery, abstinence was significantly higher than control (89 percent vs 13 percent), which was maintained in the post-surgery period (92 percent vs 50 percent) (Sørensen and Jørgensen 2003). Furthermore, a multi-modal intervention delivered in person, by telephone and computer as well as free NRT resulted in 73 percent pre-surgical abstinence compared to 56 percent in the usual care group. Though these results diminished after the peri-operative period, the intervention group still out-performed the control group (18 percent vs 5 percent) (Wolfenden et al. 2005).

These favourable results were opposed by two studies that failed to find a significant difference between intervention and control. Ratner et al. (2004) found 20 percent more abstinence within 24 hours of commencing the intervention, but failed to find significant differences beyond the post-operative period. Referral to Quitline in combination with NRT and clinician-driven motivation to use Quitline did not lead to significant differences in abstinence rates at one or three-month follow-up (Warner et al. 2011).

Finally, two studies employed a weaning/scheduled quit program to encourage peri-operative smoking cessation. Adding a scheduled quit date and cigarette weaning program to best practice care (five nurse-led bedside and telephone counselling and NRT) was ineffective; the control group who received best practice care alone demonstrated similar three and six-month abstinence prevalence (approximately 30 percent) (Ostroff et al. 2014). Moller et al. (2002) provided NRT and a consultation session with a nurse, where the participant received a personalised

nicotine substitution schedule and was encouraged to quit smoking entirely, or at least reduce consumption by 50 percent. Though this study did not record smoking abstinence outcomes, it demonstrated a significant improvement in post-surgical complications, particularly wound healing, as well as, a non-significant improvement in the need for second surgery and cardiovascular complications, compared to the control group (Møller et al. 2002).

The evidence for long-term abstinence when targeting peri-operative patients is not clear-cut. Overall, high intensity multicomponent interventions seem to point to sustained quit smoking rates compared to usual care, but more research is still needed. Referring to Quitline and placing patients on a weaning schedule, however, did not lead to significant longer-term quit rates. Overall, higher quit rates were demonstrated in this population as compared to the general inpatient population. While control often comprised basic cessation advice, it also resulted in an increase in abstinence from baseline. This effect is likely attributable to the 'hard deadline' and gravity of impending surgery followed by enforced smoke-free environments during post-operative hospital stays. Although results are not definitive, implementing multicomponent interventions should be considered, due to the adverse effects smoking has on the success of surgical procedures and related potential post-operative complications.

Adverse events related to pharmacological interventions

Out of the 13 pharmacological studies, 11 reported information pertaining to adverse events as part of their investigation. Five studies used bupropion, four used varenicline and four used NRT in forms of gum, lozenges and/or patches. Among the five studies reporting on bupropion, only one reported a significant increase in adverse events between the intervention and comparator population, finding dizziness to be more common among bupropion participants compared to placebo (14 percent vs 1.4 percent; $p = 0.005$) (Planer et al. 2011). Other common adverse events reported among all five studies and across both arms (intervention and placebo) include insomnia, dry mouth, vomiting, sleep disturbance and re-hospitalisation. An increased risk of suicidal thoughts, changes in thinking and behaviour and worsening of depression are known to occur with antidepressants including bupropion. However, none of the five studies evaluated found this to be significantly worse among the bupropion participants.

Among the four studies reporting on varenicline, three found a statistically significant increase in nausea and two reported an increase in abnormal dreams, both among varenicline users. Nausea occurred in 13.9–25 percent of participants on varenicline compared to 1.5–8.6 percent of comparator participants. Other common side effects include insomnia, headache and irritability. A black box warning did exist for varenicline related to possible development of serious neuropsychiatric symptoms including suicidal thoughts, hostility and agitation. However, in December 2016 the US Food and Drug Administration approved dropping the warning due to recent evidence from the EAGLES publication (Evaluating Adverse Events in a Global Smoking Cessation Study) (Anthenelli et al. 2016). This study compared the safety of varenicline, bupropion, NRT and placebo in approximately 8000 smokers with and without psychiatric disorders, finding that varenicline did not increase neuropsychiatric events among those with a history of psychiatric disorders. Although the black box warning has been lifted, the labelling still states that post-marketing studies have reported serious or clinically significant neuropsychiatric adverse events. None of the four studies evaluating varenicline in this review found any significant increase in neuropsychiatric events, cardiovascular events or serious skin reactions between groups.

Among the four NRT studies only two reported information about adverse events and none of these were found to be significantly different between groups. The most common side effects were gastrointestinal such as nausea and vomiting. Of the 35 multicomponent interventions, only six studies reported that an adverse event had occurred. The most common side effects with use of transdermal nicotine patch were skin reactions such as site irritation and erythema, which resolved with discontinuation of the patch. Other common side effects included nausea, headache, sleep disturbances/nightmares and dizziness. However, among studies using a placebo patch as a comparator there was no significant difference between groups in relation to these outcomes (Lewis et al. 1998; Molyneux et al. 2003; Sørensen and Jørgensen 2003). No adverse events were mentioned specifically for other types of nicotine replacement therapy such as gums, lozenges, inhalers, and mists.

Implications for practice

When considering smoking cessation interventions for the inpatient setting, health institutes need to consider intervention and patient type, as patients

admitting to hospital for different reasons may have variable responses to different types of interventions. Patients admitted to a cardiac ward, as opposed to a general ward, showed higher quit rates when they were offered face-to-face counselling, which needs to be followed by either face-to-face or telephone follow-up for at least one month. A simple one-off counselling session, even if it is extensive, is not sufficient to improve cessation rates. The behavioural counselling program can be supplemented with NRT, but it is not necessary as these patients respond to the intervention with or without NRT. This is welcome news, as treatment compliance to smoking cessation pharmacotherapy and enthusiasm for its use in general is often sub-optimal (Ferguson et al. 2011).

When looking at the general inpatient setting, participants do not show higher quit rates when treated solely with a behavioural intervention, regardless of whether there is intensive follow-up or not. This patient group requires the provision of (free) NRT in order for smoking cessation interventions to become effective. Alternatively, patients can be prescribed varenicline, as this medication has been shown to be effective and safe in the hospital population, as well as the general population (Anthenelli et al. 2016; Sterling et al. 2016).

Smoking cessation counselling interventions can successfully be embedded within already existing models of care, specifically by training ward nurses to counsel and provide follow-up. This is a similar conclusion as that found by the Cochrane review on nursing interventions for smoking cessation (Rice et al. 2013). Health institutes should consider making smoking cessation, and counselling on other health related factors, such as alcohol use and exercise, an official part of the health professional's role. They should ensure that the health professional has enough resources, time and training to ensure they are capable to perform these important duties.

There was no evidence to support quit smoking interventions in the emergency department. While smoking cessation should be discussed as part of the 'teachable moment' that is hospitalisation (McBride et al. 2003), health professionals should carefully consider whether the patient is likely to benefit from a quit smoking intervention (based on admitting reason, access to pharmacotherapy, and feasibility of running a high intensity behavioural intervention), or whether it would be more fruitful to address other health problems or behaviours that would be more likely to change. Similarly, healthcare institutions and individual professionals should weigh the costs and available resources of focusing on smoking cessation in this setting in light of the current lack of evidence.

Implications for research

Though there has been substantial research in the field of interventions for inpatient smoking cessation, a definitive conclusion on the exact elements of the most effective approach is lacking. This is largely attributed to heterogeneous interventions and a large proportion of neutral results. Overall, we may infer that interventions including both high intensity behavioural counselling, and either NRT or varenicline have been most effective.

Previously, diagnosis of a chronic condition has been associated with increased smoking cessation. More specifically, patients with cardiac and cancerous disease demonstrate a greater desire and aptitude for quitting (Hermanson et al. 1988; McWhorter et al. 1990; Novotny et al. 1990; Salive et al. 1992). This is consistent with the findings of this review, where interventions were most successful when implemented in cardiac as opposed to general medical, surgical and emergency units. While it may be that health professionals in specialist units (e.g. cardiovascular) place greater emphasis on the benefits of smoking cessation than general medical units (Emmons and Goldstein 1992), future research exploring patients' attitudes toward the importance of quitting in relation to their type of disease may provide the required insight to close the gap.

Surprisingly, there was only limited evidence for more innovative interventions, with only four studies testing the effectiveness of a computer or web-based solution (Wolfenden et al. 2005; Ostroff et al. 2014; Prochaska et al. 2014; Harrington et al. 2016), and no studies testing the use of smartphone apps. While these studies did not favour an electronic intervention as such, issues with adherence were identified. As this field of research evolves, further understanding of effective implementation strategies could unlock the potential of these interventions. As the burden on our health professionals and the demand for cost-effective care increases, developing, testing and implementing innovative tools to track patient progress on vital health behaviour such as smoking cessation becomes increasingly important. Preliminary results from the general population are promising in terms of feasibility, acceptability and smoking abstinence (Bricker et al. 2014; Ubhi et al. 2015). As this technology becomes ingrained in society's daily life, it presents the greatest opportunity for innovative research.

The current evidence base lacks data for the cost-effectiveness of these hospital-based interventions. A high intensity behavioural intervention in combination with provision of NRT was estimated to

cost US\$354 in the first year of implementation and US\$108 for subsequent years (Rigotti et al. 2014). However, when in-person counselling was replaced with a batch of telephone sessions in combination with NRT, there was an estimated cost of approximately US\$75 per patient (Sherman et al. 2016). While this is by no means sufficient evidence of cost-effectiveness to change policy and practice, it does not exclude the hospital as a viable setting for intervention, suggesting that using existing models of care and infrastructure can keep costs low.

The socioeconomic burden of smoking on the health system, a great deal of which can be attributed to hospital use, is disproportionate to the research effort from Australia and New Zealand. Though smoking cessation is a national priority area and policies recommend that hospital and health care professional intervention is necessary, just seven of the included studies were conducted in Australia and none in New Zealand. Of these, only three demonstrated beneficial effects in favour of intervention; a multicomponent computer based intervention (Wolfenden et al. 2005), inpatient prescription of varenicline and bedside facilitation of Quitline contact (Smith et al. 2013), and high intensity behavioural counselling with an extended period of follow-up telephone calls (Feeney et al. 2001). Translational clinical research can be a lengthy and costly process, and within the hospital system this is often investigator-led with costs coming from already restricted operating budgets. Redirecting some governmental funds into a research grant scheme could and should target two important areas for bridging the knowledge-translation gap that currently exists. The first initiative would be a commitment to the development of an evidence-based hospital smoking cessation program, which also takes into account strategies that support the ongoing provision of this intervention beyond the study period. This should be accompanied by a methodologically rigorous and reproducible evaluation, with a commitment to regular review for currency. Secondly, a grant scheme could invite more interest in continued innovation in this area. Despite the existence of a large body of evidence, hospital cessation research needs to continue to evolve and grow to incorporate such emerging approaches as eHealth and mHealth interventions, which could prove invaluable to the cessation effort.

Overall, this review has provided an evidence base predominantly from overseas, which indicates the merits of ward-based intervention for smoking cessation and provision of post-discharge follow-up by health professionals. Though results are not overwhelmingly favourable, given the current state of socioeconomic burden caused by smoking, perhaps

something is better than nothing. However, it is apparent from this review that local and innovative (web and smartphone-based) research is lacking, and would benefit from a more concerted effort by health researchers with support from the government.

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Appendix 1: Descriptive summary of exclusively behavioural intervention

Table 1. Interventions that compare two behavioural solutions to smoking cessation: none of the participants of either group had free access to pharmacotherapy

Study reference	Participants and sample size	Setting description	Intervention	Control	Short summary of findings	Plain language conclusion
Andrews, Bale et al. 2006	Elective surgery patients • Consultant advice letter $n=51$ • General booklet $n=51$	Single site: General hospital; UK	Individualised letter from consultant general with advice to stop smoking, nurse advice and referral to stop smoking service Model used: not stated	General quit smoking booklet + nurse advice	18% in the intervention compared to 8% in the control group quit smoking before surgery commenced	An individualised letter can contribute to higher quit smoking rates before planned surgery
Bolman, de Vries et al. 2002	Inpatients with cardiovascular disease • Intervention $n=388$ • Usual care $n=401$	Multi-site: 5 received intervention, 6 received control; Netherlands	Initiated during hospital admission and continued after discharge: consisted of stop-smoking advice from cardiologist, short-bedside consultation with a nurse including assessments of readiness to change, additional nurse-led consultations, provision of self-help materials and after care by cardiologist Model: health counselling model	Usual care consisting out of occasional attention to smoking cessation during check-up	Self-reported 7-day point-prevalence data at 3 months indicate a significant small intervention effect (OR=1.4). No significant effect for continuous abstinence was found	Intensive behavioural intervention can lead to small improvements in smoking cessation rates
Caruthers, Perkins et al. 2006	Hospitalised smokers; • Intervention $n=40$ • Usual care $n=40$	Multi-site; three hospitals; USA	12-week nurse delivered relapse management intervention (8 telephone interventions over 11 weeks) Model: Self-efficacy Theory	Enhanced usual care: promotional message + manual for tobacco dependence by the Centre for Disease Control	At 24 weeks, 42% of intervention subjects and 15% of usual care showed 7 day point prevalent smoking cessation (biochemically validated), $p=0.004$	An 11 week intensive intervention can increase cessation rates
Chouinard and Robichaud-Ekstrand 2005	Inpatients with cardiovascular disease • Counselling + follow-up $n=56$ • Counselling $n=56$ • Brief advice $n=56$	Single site: Cardiology unit of regional tertiary hospital; Canada	1 hour inpatient counselling session either with or without telephone follow-up (6 calls) Model: Transtheoretical Model	General smoking cessation advice	Higher validated self-report 7-day point prevalent smoking cessation at 6 months ($p=0.05$), but not continuous ($p=0.21$), with higher point prevalence rates for those receiving follow-up 41.5% versus those who did not 30.2%	Especially inpatient counselling + intensive follow-up seems to improve cessation rates.
de Azevedo, Mauro et al. 2010	Inpatient general hospital admissions • High intensity $n=132$ • Low intensity $n=141$	Single site: public university hospital; Brazil	30-minute tailored motivational interview with trained counsellor tailored to patient needs plus seven routine telephone calls after hospital discharge Models used: motivational interviewing	Low-intensity intervention consisted of 15-minute general counselling	Low and high intensity sessions produced comparable self-reported 7-day point prevalent abstinence rates, 41.7% versus 44.9%, $p=0.03$	No difference in single session low or high intensity intervention
DeBusk, Miller et al. 1994	Patients admitted following acute myocardial infarction; • Intervention $n=131$ • Brief advice $n=121$	Multi-site: 5 Kaiser Permanente Medical Centres in San Francisco Bay area; USA	Intervention focused on multiple risk factors including smoking, nutrition and exercise delivered in hospital. Brief bedside counselling by physician combined with relapse prevention intervention ran by nurses. Telephone follow-up after two days, a week and at monthly intervals was provided. Model used: relapse prevention	Brief smoking cessation counselling by physician	Cotinine confirmed point-prevalent smoking cessation rate was significantly higher for the intervention arm (70%) compared to control (53%), $p=0.03$ at 12 months	Bedside counselling combined with follow-up leads to significantly higher cessation rates at 12 month follow-up

Dornelas, Sampson et al. 2000	Inpatients with myocardial infarction; • Intervention $n=54$ • Minimal care $n=46$	Single site: Hartford Hospital cardiology ward; USA	20 Minutes of bedside cessation counselling by a trained psychologist followed by seven brief telephone calls over 6 months post-discharge Model: motivational interviewing, relapse prevention, transtheoretical model and social-cognitive	Minimal care: a verbal and written recommendation to watch an on-line patient education video	7-day point prevalent smoking cessation rates were 70% for intervention compared to 40% for control at 12 month follow-up, $p<0.005$. Cessation rates at 6 months also favoured the intervention condition over control (73% versus 46%, $p<0.05$)	Bedside counselling with follow-up can improve cessation rates up until 12 months
Feeney, McPherson et al. 2001	Inpatients following acute myocardial infarction; • Intervention $n=96$ • Control $n=102$	Single site: coronary care unit in a Queensland Hospital; Australia	Intervention program consisted of the Stanford Heart Attack Staying Free program: The program included an exercise-based manual, assessment of confidence to quit (patients with low confidence were counselled on coping skills) and weekly telephone follow-up for the first month, and follow-up at 2, 3, 6 and 12 months. Model used: not mentioned	Usual care patients received verbal and printed advice about tobacco cessation and watched an educational video during the coronary care unit stay and were reviewed by an alcohol and drug assessment nurse; The nurse continued to follow-up at 3, 6 and 12 month intervals as outpatients	Analysis shows that of patients who joined the Stanford heart attack staying free and showed up at the 1 month follow-up 39% were abstinent (as validated by cotinine array) at 12 months compared to 2% of patients receiving usual care ($p<0.001$)	The Stanford heart attack program produced superior results compared to usual hospital care
Hajek, Taylor et al. 2002	Inpatients with cardiac event (myocardial infarction or coronary bypass surgery). • Intervention $n=274$ • Brief verbal advice $n=266$	Multi-site: 17 hospitals; UK	Brief verbal advice and access to British Heart foundation booklet as well as 20-30 minute session of CO reading, booklet on smoking and cardiac recovery, a quiz, a buddy, declaration of commitment to quit and a sticker in patient file Model: no model mentioned	Brief verbal advice + British Heart foundation booklet	No difference in continuous abstinence ($p=0.84$), 59% vs 60%, or point prevalent abstinence, 60% vs 60% ($p=0.91$) at 6 weeks, nor at twelve months, 41% vs 37% ($p=0.40$) for continuous and 43% versus 39% ($p=0.35$) for point prevalent, control vs intervention respectively	Single brief behavioural intervention is not enough to promote abstinence. Adherence to intervention components was relatively low
Harrington, Kim et al. 2016	All patient care areas (psychiatric, maternity and ICU were excluded). • Intervention $n=748$ • Control $n=740$	Single site: University Hospital; USA	Usual care and access to quit smoking web intervention using education and asynchronous communication with a Quit advisor Models used: Social-cognitive theory and Transtheoretical model	Usual care: one-pager and verbal message (2-3 minutes) by untrained hospital staff	There was no difference in 30-day point prevalence abstinence ($p=0.55$), 25.4% vs 26.8% at 6 month follow-up. Continuous abstinence was significantly higher for control, 18.5% vs 13.8%, $p=0.020$. Costs were \$53,802 for intervention and \$3,875 for control	Web-based smoking cessation treatment not better than usual care. May be due to adherence problems
Hennrikus, Lando et al. 2005	General medical patients (psychiatric, maternity and substance users were excluded). • Advice (A) $n=703$ • Advice + counselling(AC) $n=696$ • Usual care (UC) $n=696$	Multi-site: 4 hospitals (2 public, 2 private; USA	Advice only group: Usual care and a sticker was placed in the patient's case notes and their health professionals were frequently reminded of the project via newsletters, incentives etc. Advice + counselling group: usual care, brief provider advice and extended bedside counselling at hospital + 3-6 follow-up telephone calls Model: motivational interviewing, relapse prevention, transtheoretical model and social-cognitive	Usual care: two smoking cessation manuals and a directory of quit smoking programs and resources	At 12 month self-reported 7-day abstinence was higher in the AC group (19.8%) compared to UC (15%) and A (15.2%). However, adjusting for cotinine readings, there was no difference between AC (9.9%), A (10.0%) and modified usual care (8.8%) Quit rates were higher in this with smoking-related conditions	No increase in cotinine validated abstinence rates between three conditions (although self-report did go up for intensive condition)

Cessation for smokers seeking treatment and advice from health care professionals in the hospital setting

Horn, Dino et al. 2007	Smokers aged 14 - 19 • Intervention $n=41$, • Brief advice $n=34$	Single site: Suburban, university affiliated ED; USA	Motivational tobacco intervention: 15-30 min face-to-face patient-tailored intervention, stage-matched self-help workbook, handwritten postcard, 3 follow-up telephone calls at 1, 3 and 6 months Models used: client-centred therapy, social cognitive theory, and cognitive behavioural therapy, motivational interviewing	Brief advice (BA): 2 min generic advice, referral to health line. One follow-up telephone call.	No difference in point prevalent abstinence. For intervention (2.5%) or control (2.9%), $p=0.55$. There was no significant difference in reduction either	No difference in responders between brief advice and motivational tobacco intervention
Meysman, Boudrez et al. 2010	Surgery patients from orthopaedics, traumatology, ENT, head and neck and neurosurgery • Intervention $n=178$ • Booklet $n=180$	Multi-site: 4 university hospitals; Belgium	Nurse delivered stage based intervention using the 5 A's Model: Transtheoretical model	Booklet with quit smoking information	Self-reported continuous abstinence at 6 months was 15.7% for the intervention versus 8% for control, $p=0.02$	Significantly more self-reported abstinence at 6 month follow-up for stage based intervention compared to a booklet
Ockene, Kristeller et al. 1992	Inpatients with cardiovascular disease • Intervention $n=132$ • Advice only $n=135$	Multi-site: 3 Cardiac catheterisation laboratories of general hospitals; USA	10 minute quit smoking advice + 30 min inpatient counselling + outpatient telephone follow-up (3-4 sessions). There was also a possibility to return for outpatient face-to-face counselling Model: cognitive and behavioural self-management strategies	Advice only: 10 minute advice session	While validated 7-day point prevalent quit rates were higher for patients receiving the intervention (57%) versus control (48%) at 12 months, this results did not reach significance, $p = .06$, OR = 1.4. These results were maintained at 5 year follow-up. Patients with more significant disease responded better	No significant results for multicomponent intervention versus advice only when using validated tools
Pederson, Wanklin et al. 1991	COPD inpatients • Intervention $n=37$ • Control $n=37$	Single site: Chest unit of a 600-bed teaching ward; Canada	Self-help manual and advice to quit smoking with 3 to 8 15-20 minute counselling sessions while in hospital. Model: authors developed own approach	Advice to quit smoking	There were no significant differences in self-reported smoking cessation at 3 or 6 months, with 33% quitting successfully for intervention at 6 month versus 21.4% for control.	Intensive intervention including booklet and counselling with follow-up did not lead to significantly higher quit rates, however results may be caused by low sample size
Quist-Paulsen and Gallefoss 2003	Inpatients with cardiovascular disease • Intervention $n=118$ • No intervention $n=122$	Single site: general hospital; Norway.	Quit smoking group sessions 2x per week during inpatient stay. Follow-up telephone calls at day 2, 14, 21 and at 3 months and five month. At 6 weeks outpatient consultation was provided Models: relapse prevention and fear arousal	No specific instructions on how to quit smoking	Higher proportion of quitters for the intervention (50%) versus control (37%), $p=0.05$, as determined via validated point prevalence abstinence	Higher proportion of quitters when patients received counselling and follow-up telephone calls versus control
Rigotti, McKool et al. 1994	Patients scheduled for coronary artery bypass surgery • Intervention $n=44$ • Usual care $n=43$	Single site: cardiac surgery hospital unit; USA	Commenced approximately 4 days post-surgery. Cognitive and behavioural techniques via three counselling sessions incorporating video and a written manual + follow-up telephone counselling one week post-discharge from a nurse. Models used: cognitive behavioural theory	Usual post-surgical care: group lecture that included a brief message not to continue smoking	No significant difference between self-reported continuous abstinence rates at any time during 5.5 year follow-up ($p>.62$). Difference in self-reported 7-day abstinence rate was also non-significant ($p>.52$). Cotinine validation was obtained for 94% of those reporting continuous abstinence for one year and 5.5 years, difference between groups remained non-significant ($p>.52$)	Cognitive-behavioural intervention with one week follow-up was not superior to usual care for patients in hospital following cardiac surgery

Rigotti, Arsten et al. 1997	Patients admitted to hospital who had smoked one or more cigarettes in the previous month - Intervention $n=325$ - Usual care $n=325$	Single site: teaching hospital; USA	Bedside counselling session, written self-help resources for in-hospital and at-home use, case note prompt for physician to provide cessation advice and 3 post-discharge telephone counselling Models used: motivational interviewing + cognitive behavioural counselling + relapse prevention techniques	Usual hospital care: not further described	At one month follow-up self-reported seven day abstinence rate was higher for the intervention group compared to control (28.9% vs 18.9%, $p=0.003$). This result was not sustained at six-month follow-up, which was verified by saliva cotinine assay (intervention 17.3% vs control 14.0%, $p=0.26$).	Cognitive behavioural intervention was superior to usual care at one month but not at 6 months in improving smoking cessation for hospitalised patients
Shi, Ehlers et al. 2013	Preoperative surgery patients - Intervention $n=82$ - Control $n=87$	Single site: Mayo Clinic; USA	Brief advice and a check of smoking status via carbon monoxide monitoring at day of surgery, and why it is important to stay smoke free	Brief advice	No difference in carbon monoxide levels at day of surgery between the two groups, $p=0.67$	Informing surgery patients that their carbon monoxide will be measured at the day of surgery does not lead to differences in smoking behaviour
Smith and Burgess 2009	Patients hospitalised for myocardial infarction or coronary artery bypass graft, with minimum hospital admission of 36 hours - Intervention $n=137$ - Control $n=139$	Single-site: 4 cardiac units in large hospital; Canada	Patients received the minimal intervention and 45-60 minute nurse delivered bedside education and counselling session combined with take home resources (video, audio tape, workbook) followed by 7 telephone counselling session post discharge at 2, 7, 14, 21, 30, 45 and 60 days post-discharge Models used: relapse prevention model	Minimal intervention: personalised quit advice based on medical condition, review of 2 written pamphlets delivered by nurse and allocation of a prompt in case notes for physician to deliver standard scripted quit message at bedside during admission	Self-reported 7 day point prevalence abstinence was significantly higher for intervention versus control at all time-points. Quit rates were very high: 3 months, 76% vs 61%, $p=0.009$; 6 months 67% vs 49%, $p=0.003$; and 12 months, 62% vs 46%, $p=0.007$. Quit rates were lower at 12-month when verified by a proxy, but remained significant.	Intensive intervention increased odds of quitting smoking in cardiac patients
Smith, Corso et al. 2011	General hospital patients hospitalised for a minimum of 36 hours - Intensive intervention $n=309$ - Minimal intervention $n=334$	Multi-site: 3 hospitals; Canada	Patients received the minimal intervention and 45-60 minute nurse delivered bedside education and counselling session combined with take home resources (video, audio tape, workbook) followed by 7 telephone counselling session post discharge at 2, 7, 14, 21, 30, 45 and 60 days post-discharge Models used: relapse prevention model	Minimal intervention: personalised quit advice based on medical condition, review of 2 written pamphlets delivered by nurse and allocation of a prompt in case notes for physician to deliver standard scripted quit message at bedside during admission	There were no significant differences at 6 or 12 months between the two groups. At 12 months validated point prevalent smoking abstinence was 28% for the intensive versus 24% for the minimal intervention	There were no significant differences for low intensity versus high intensity in the general population
Winickoff, Healey et al. 2010	Postpartum parents admitted to the maternity ward following birth of a child Counselling intervention $n=48$ Usual care $n=53$	One hospital, USA	Parents received a 15-minute face-to-face counselling session tailored for parental smokers and an offer to be enrolled in a Quitline service, as well as letters faxed to the family's relevant paediatrician, General Practitioner and obstetrician recommending appropriate strategies and ongoing support following discharge Based on the 5As approach to cessation	Usual care: no contact relating to smoking cessation	Self-reported 7-day point prevalence for the intervention group was 31% at baseline and to 25% at 3-month follow-up versus 38% at baseline and 23% at 3-month follow-up in the control group (effect size=9.4%, ns). Self-reported 24-hour quit attempts were significantly higher in the intervention group compared to control (64% vs 18%, $p=0.005$)	Enrolling parents into a smoking cessation program during postpartum hospital admission appears to stimulate quit attempts within the day, though this success does not appear to translate to sustained cessation

Abbreviations: nicotine replacement therapy=NRT, Odds Ratio=OR

Table 2. Combination interventions – Description of pharmacological interventions in adjunct to counselling

Study reference	Participants and sample size	Setting description	Intervention	Comparison	Findings narrative	Conclusion
Campbell, Prescott et al. 1991	Inpatients with smoking-related diseases • Gum + counselling, $n=107$ • Placebo + counselling, $n=105$	Single site: general hospital; UK	Smoking cessation advice + nicotine gum (2 mg) + outpatient follow-up with a research assistant at 2, 3 and 5 weeks, 3 and 6 months where further advice and gum was provided; Stronger gum offered for up to 3-months for individuals still smoking (4 mg or placebo)	Smoking cessation advice + placebo gum + outpatient follow-up with a research assistant at 2, 3 and 5 weeks, 3 and 6 months where further advice and gum was provided	No difference in validated self-reported continuous smoking abstinence between both groups (20%). Abstinence was higher for cardiac patients compared to other (32% vs 13% for lung). Gum adherence was relatively low	No difference in continuous abstinence for NRT gum versus placebo when combined with counselling
Eisenberg, Grandi et al. 2013	Inpatients with acute myocardial infarction; • Bupropion + counselling $n=192$ • Placebo + counselling $n=200$	Multi-site: 38 collaborating centres across 7 countries (USA, Canada, India, Pakistan, Iran, Tunisia and Bangladesh)	Low-intensity counselling and bupropion hydrochloride (Zyban) 150 mg daily for 3 days, 150 mg twice daily for the remainder of the 9 week treatment period	Placebo group received matching placebo administered with the same schedule and low intensity counselling	At 12 months follow-up point prevalence abstinence rates were 37.2% for bupropion group and 32.0% for the placebo group ($p=0.33$)	No difference between bupropion and placebo at 12 months follow-up
Eisenberg, Windle et al. 2016	Hospitalised patients with acute coronary syndrome; • Varenicline + counselling $n=151$ • Placebo + counselling $n=151$	Multi-site: 40 clinical centres across Canada and USA	Intervention consisted low intensity counselling and access to varenicline for 12 weeks	Placebo patients received the same treatment schedule over 12 weeks	Participants treated with varenicline showed higher point-prevalence quit smoking rates at 24 weeks than control (47.3% versus 32.5%, $p=0.01$), results that were not found for continuous abstinence (35.8% versus 25.8%, $p=0.08$)	Varenicline and minimal counselling can result in higher quit rates
Myles, Leslie et al. 2004	Preoperative patients undergoing elective surgery • Bupropion + brief counselling $n=24$ • Placebo + brief counselling $n=23$	Multi-site: two teaching hospitals; Australia	7 Week supply of bupropion that would last until surgery, as well as brief counselling, telephone follow-up 2-4 days after their quit day and a quit smoking booklet	Placebo patients received the same treatment schedule as the active ingredient group	No differences in quit smoking rates at time of hospital admission, but a significant reduction was shown for intervention versus control, $p=0.05$. 6 Months after surgery, no differences were found between the two groups (13% versus 5%, $p=0.61$)	Providing bupropion before surgery can reduce cigarette intake but not quit smoking rates
Ortega, Vellisco et al. 2011	Internal medicine patients • NRT + high intensity counselling $n=924$, • High intensity counselling $n=919$	General hospital in Seville, Spain	Cognitive-behavioural counselling (30-45 minutes) every 3 days until release from hospital. After release, patients could choose to do face-to-face follow-up or telephone follow-up at 1 week, two weeks, month 1,2,3,6, 12. NRT: patches or chewing gum for maximum 12 weeks free of charge	Cognitive behavioural counselling similar to the intervention group	33% of participants treated with NRT continued to smoke compared to 21% of participants who did not have access to NRT as adjunct to counselling, $p=0.002$. Participants who chose to have outpatient face-to-face follow-up compared to telephone follow-up showed higher quit rates in the NRT group, 39% versus 30%, $p=0.03$	Adding NRT to high intensity CBT-based smoking cessation program increases cessation rates

Planer, Lev et al. 2011	Adults hospitalised for acute coronary syndrome (including unstable angina and MI) • Bupropion + counselling n=74 • Placebo + counselling n=75	Single-site: 2 campuses of a medical centre; Israel	Bupropion 150 mg once a day for 3 days, followed by twice a day for 2 month. 15 minute of motivational support was given during hospitalisation. Face-to-face counselling was provided at month 1 and 2. Weekly telephone contact was performed for two months, followed by monthly telephone follow-ups. Total time was 100 minutes of counselling for the first two months and 100 minutes for the remainder of the year	Placebo once a day for 3 days, followed by twice a day for 2 month. Similar counselling was provided to the placebo group as the active drug group	The overall continuous (self-reported) smoking abstinence rate at 1 year was 31% in the bupropion group and 33% in the placebo group ($p=0.86$). There were furthermore no differences at 3 and 6 months	Bupropion compared to placebo did not lead to higher abstinence rates as an adjunct to intensive counselling
Rigotti, Thorndike et al. 2006	Patients hospitalised for acute cardiovascular disease. • Bupropion + counselling n=124 • Placebo + counselling n=124	Multi-site: 5 hospitals; USA	Sustained release bupropion (150 mg) + multicomponent cognitive-behavioural cessation counselling program (12 weeks duration). Treatment commenced during hospital admission	Placebo patients received the same treatment schedule as the active ingredient group	There was no difference in validated seven day point-prevalence abstinence rates at the end of the 12 week treatment period, $p=0.08$ (bupropion 37.1% vs placebo 26.8%), or, one year follow-up, $p=0.49$ (bupropion 25.0% vs placebo 21.3%). Cessation rates were significantly higher in the bupropion group compared to placebo for those who were compliant with medication at twelve weeks ($p=0.04$). This effect was not sustained at one year follow-up ($p=0.23$)	Bupropion may be effective in the short but not long term in increasing quit rates among patients hospitalised with cardiovascular disease
Simon, Duncan et al. 2009	Patients hospitalised for minimum 24 hours and any known patients scheduled for elective admission. • Bupropion + counselling n=41 • Placebo + counselling n=42	Single site: veterans affairs hospital; USA	A 7 week course of sustained release bupropion in combination with a behavioural counselling session + 5 follow-up telephone calls post discharge at 1 and 3 weeks, and then monthly for the first 3 months following enrolment into the study	Placebo patients received the same treatment schedule as the active ingredient group	There was no difference in self-reported 7 day point prevalence abstinence at 6 months between intervention and control (29% vs 41%, $p=0.36$), with similar results found by cotinine validation (15% vs 24%, $p=0.41$)	Results found non-significantly higher quit rates for control
Smith, Carson et al. 2013	Smokers admitted to hospital for smoking related illness • Varenicline + counselling n=196 • Counselling alone n=196	Multi-site, respiratory, vascular, cardiology and neurology wards; Australia	Varenicline tartrate titrated from 0.5mg daily to 1mg twice daily + Quitline counselling	Quitline only	Self-reported continuous abstinence at 12-month follow-up significantly favoured varenicline + Quitline compared to Quitline only (31.1% vs 21.4%, relative risk 1.45; 95%CI 1.03-2.04, $p=0.03$)	Initiating a course of varenicline tartrate and facilitating Quitline contact during hospital admission improves smoking abstinence for up to a year
Steinberg, Randall et al. 2011	General inpatients • Varenicline + counselling n=40 • Placebo + counselling n=39	Single site: university-based hospital; USA	Participants received access to varenicline in hospital and 8 weeks after discharge. They also received low intensity counselling consisting of a 5 to 10 min behavioural intervention and 15 minute long follow-ups during inpatient stay	Placebo patients received the same treatment schedule as the intervention group, as well as the same behavioural counselling	Though not significant, 7 day point abstinence confirmed by expired CO favoured control over intervention at: 4weeks (38% vs 35%); 12 weeks (33% vs 30%) and 24 weeks (31% vs 23%), all, $p>.05$	Pilot study, no significant differences between varenicline and placebo

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Thomsen, Tønnesen et al. 2010	Breast cancer patients scheduled for surgery • NRT + counselling n=58 • Usual care n=62	Multi-site: breast surgery departments; Denmark	Intervention started 3-7 days prior to surgery and continued for 10 days after. It included a single face-to-face counselling session (45-90 minutes), NRT was offered free for the preoperative period and encouragement to remain abstinent for 2 days prior and 10 days following surgery	Routine preoperative advice: inconsistent or no advice regarding risks of smoking in relation to surgery	Self-reported continuous abstinence from 2 days pre to 10 days post-surgery was in favour of the intervention group compared to control; 28% vs 11% (relative risk 2.49; 95%CI 4-37). This difference was not noticeable at 12-month follow-up (13% vs 9%)	45-90 minute one-on-one counselling and the offer of free NRT improved smoking abstinence for the immediate pre and post-operative period, but not long-term
Warner and Kadimpati 2012	Smokers scheduled for elective surgery • Active lozenge+ counselling n=22 • Placebo lozenge + counselling n=24	One hospital; USA	Active 2-4milligram nicotine lozenge in addition to brief cessation counselling. Patients received a supply of 16 lozenges for the pre-surgical admission period (approximately 1 day)	Placebo labelled 2-4milligram lozenge in addition to brief cessation counselling. Patients received a supply of 16 lozenges for the pre-surgical admission period (approximately 1 day)	Pre-operative self-reported abstinence was not different between active and placebo lozenge groups; 73% vs 54% respectively, $p=0.23$	This pilot study indicates that a nicotine lozenge is no more effective than placebo when combined with pre-operative counselling
Wong, Abrishami et al. 2012	Preoperative patients undergoing elective surgery • Varenicline + counselling n=151 • Placebo + counselling n=135	Two hospitals; Canada	Intervention: Varenicline plus 15-minutes of standardised counselling by research coordinators with the first counselling session occurring in the preoperative clinic; varenicline was taken exactly 1 week prior to target quit date and continued for 12 weeks	Placebo tablets for 12 weeks, with initiation 1 week prior to the quit date plus 15-minutes of standardised counselling by research coordinators with the first counselling session occurring in the preoperative clinic	Self-reported 7-day point-prevalence data at 12 months for varenicline versus placebo was 36.4% versus 25.2% (relative risk 1.45; 95%CI 1.01-2.07; $p=0.04$), which was also significant in favour of varenicline at 3 and 6 months follow-up	Varenicline successfully improved long-term (12-month) quit attempts among preoperative surgical patients compared with an identical placebo

Abbreviations: nicotine replacement therapy=NRT, Odds Ratio=OR. In general pharmacotherapy driven interventions do not occur without at least minimal counselling. The following interventions test for the difference between pharmacotherapy versus placebo, but both groups had access to some sort of counselling

Table 3: Descriptive summary of multicomponent interventions

Study reference	Participants and sample size	Setting description	Intervention	Comparison	Findings narrative	Conclusion
Lindström et al. 2008	Hip or knee arthroplasty, inguinal or umbilical primary hernia repair or laparoscopic cholecystectomy patients	Multi-site: university hospitals; Sweden	Intervention started 4 weeks prior to hospitalisation and lasted 4 weeks after. It included weekly face-to-face or telephone meetings, referral to Quitline, free NRT	Brief or no smoking cessation information	Validated up until 3 weeks after surgery shows 36% of intervention participants and 2% of control participants being continuously abstinent, $p < 0.001$. 12 months point-prevalent (non-validated) self-reported smoking cessation rates were 33% versus 15% respectively, $p = 0.03$	A multicomponent approach starting prior to hospital admission can reduce smoking cessation rates short-term and long-term
Azodi et al. 2009	- Intervention $n = 55$ - Control $n = 62$					
Berndt et al. 2017	Inpatients with coronary heart disease: - Usual care $n = 245$ - Telephone counselling + NRT $n = 223$ - Face-to-face counselling + NRT $n = 157$	Multi-site: 8 cardiac wards (8 hospitals); The Netherlands	Both counselling groups included an inpatient and outpatient phase (using the Ask-Advise-Refer strategy: assess smoking behaviour, advice to quit, refer to outpatient cessation counselling; Counselling was tailored for the patient's willingness to quit and was based on Transtheoretical model NRT patches were provided for 8 weeks for both groups Telephone-counselling: provided by the Dutch Expert Centre for Tobacco Control lasting at least 15 minutes per call; Face-to-face: provided by cardiac nurses qualified as smoking cessation counsellors lasting 30-45 minutes	General quit smoking brochure + assessment of smoking behaviour and provision of quit advice by a cardiology or ward nurse	There were no overall significant differences in continuous quit rates between the three groups ($p = 0.17$) at 12 months. Splitting the results for low SES vs high SES showed that there was no difference between the three interventions for high SES, but that patients with low SES had higher quit rates when using face-to-face and telephone counselling compared to usual care, specifically when they have low to moderate intention to quit	More intensive behavioural approach is effective for low SES, but does not lead to higher quit rates for high SES patients
Bernstein et al. 2013	Emergency department smokers with substance use disorders; - Enhanced care $n = 48$ - Usual care $n = 40$	Single site: urban academic hospital emergency department; USA	Enhanced care consisting of quit smoking brochure, 10-15 minute brief motivational interviewing session, 6 weeks of nicotine patches and a telephone follow-up at 48-72 hours after ED discharge	Brochure describing the health risks of smoking and contact information for a cessation programs in the area	No difference in 30-day continuous abstinence at 3 month follow-up, but biochemically validated 7-day point-prevalent abstinence was higher for enhanced care (14.6%) compared to usual care (0%; $p = 0.015$)	Enhanced care including NRT can lead to increased quit rates at 3 month follow-up
Bernstein et al. 2015	Emergency department smokers - Enhanced care $n = 386$ - Usual care $n = 388$	Single site: urban hospital emergency department; USA	Enhanced care consisting of quit smoking brochure, 10-15 minute brief motivational interviewing session, referral to Quitline, 6 weeks of nicotine patches and a telephone follow-up at 72 hours after ED discharge	Brochure describing the health risks of smoking and contact information for a cessation programs in the area	Significant difference in biochemically validated 7-day point-prevalence at 3 months follow-up between intervention (12.2%) and control (4.9%). No significant differences at 1 year follow-up.	Enhanced care including NRT can lead to increased quit rates at 3 month follow-up

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Borglykke et al. 2008	Inpatients with exacerbations of COPD • Group treatment $n=121$ • Usual care $n=102$	Single site: university hospital; Denmark	Standard information on smoking cessation + smoking cessation group treatment consisting of weekly 2-hour sessions over 5 weeks based on materials developed by the Danish Cancer Society and others;. Participant spouses offered participation for supportive effect; complimentary NRT was provided when needed	Standard information on smoking cessation	Self-reported point prevalence smoking cessation (biochemically validated in 84%) at 1 year was higher for intervention (30%) versus UC (13%)	Group training + NRT can increase smoking cessation rates at 1 year
Fellows et al. 2016	Hospitalised adult smokers; • Intervention $n=597$ • Control $n=301$	Multi-site: 3 large community hospitals; USA	Intervention included intensive bedside tobacco use assessment, cessation counselling and proactive assisted referrals to a tobacco treatment specialist consult service for available outpatient counselling programs and medications. Patients received NRT as part of discharge medication and access to an Interactive voice recognition intervention that provided four follow-up calls over 7 weeks.	Usual care included intensive bedside tobacco use assessment and cessation counselling (15 minute), printed and verbal	There was no difference in self-reported 30-day abstinence for the intervention group (18%) versus to control group (17%), $p=0.569$, with similar results for continuous abstinence 13% and 14% for usual care at 6 months follow-up	Assisted referral and access to an interactive voice recognition follow-up system did not lead to an increase in smoking cessation rates compared to usual care
Froelicher et al. 2004	Women hospitalised with cardiovascular disease; • Intervention $n=142$ • Usual care $n=135$	Multi-site: 10 San Francisco Bay area hospitals; USA	Usual care + a nurse-managed cognitive behavioural relapse-prevention intervention at bedside (30-45 minutes) during hospital admission, with telephone contact at intervals post discharge up to 5 times). Counselling included multimedia aids such as educational videos and stress and relaxation audiotapes along with an American Heart Association workbook and videotape on smoking cessation relapse and prevention Note: Subjects in both arms had access to NRT	Usual care: brief counselling by physician, a quit smoking pamphlet and a list of smoking cessation classes. Note: Subjects in both arms had access to NRT	At 6 months follow-up 7 day point prevalence was 51.5% in the intervention group and 40.8% for usual care, with no further significant difference between groups observed for 12 and 24 month follow-up periods. Overall the intervention group showed higher continuous abstinence compared to control, $p=0.04$	Overall high rates of smoking cessation in both groups, but higher rates of continuous abstinence for the more intensive intervention
Lacasse et al. 2008	Cardiac, respiratory and general patients with anticipated duration of >36 hours hospitalisation. • Intervention $n=99$ • Control $n=97$	Single site: tertiary hospital; Canada	Strong quit smoking message, self-help motivational quitting material, cessation counselling based on self-efficacy theory (between 10-20 minutes), use of NRT patches and 4 follow-up telephone calls of about 10 minutes	No cessation advice	No significant differences in point prevalence abstinence between groups at 6 month follow-up, 32.2% for intervention versus 30.0% for control, or 12month follow-up, 30.3% for control and 27.8% for control. NRT was only provided to 18 people	A medium intense intervention with follow-up until 1 month does not lead to higher smoking cessation rates

Lee et al. 2013	Adult surgery patients • Intervention $n=84$ • Standard care $n=84$	Single site: ambulatory and short-stay (<3 days) surgical facility; Canada	Brief counselling, smoking cessation brochures, referral to Quitline, 6 week supply of NRT (transdermal patches). The intervention started 3 weeks before hospitalisation	Standard care: inconsistent smoking cessation advice up to health professionals	At 30 days self-reported abstinence (7-day point prevalence) was 11% in control versus 28.6% in the intervention group, $p=0.008$. By starting the trial before the hospitalisation, self-reported abstinence before surgery (validated by carbon monoxide array) was 6% in control versus 14.3% for the intervention, $p=0.03$	Pre-operative multicomponent smoking cessation intervention leads to peri-operative smoking cessation and 30-day self-reported abstinence
Lewis et al. 1998	All smoking adult inpatients • Counselling + NRT patch $n=62$ • Counselling + placebo patch $n=62$ • Minimal care $n=61$	Single site: university teaching hospital; USA	Counselling + NRT: minimal care and access to patches (3 week 21 mg and 3 week 11 mg) followed by telephone counselling on 4 occasions Counselling + placebo (CPP): minimal care, 6 weeks placebo patches, followed by telephone counselling on 4 occasions Counselling was based on CBT and motivational interviewing	Minimal care: brief 2-3 minute motivational message + self-help booklet	7 day point prevalent cessation + carbon monoxide validation at 6 months did not find a difference between either condition, 4.9% for minimal care, 6.5% for the placebo group and 9.7% for the patch group, $p=0.57$. Those admitted with respiratory diseases had highest quit rate (46%)	Patches did not lead to higher quit rates at 6 months compared to placebo or minimal intervention, but this might be the result of a lack of power
Miller et al. 1997	All smoking inpatients (excluding patients of obstetrical or psychiatric wards) • Intensive intervention $n=540$ • Minimal Intervention $n=460$ • Usual care $n=942$	Multi-site: 4 medical centres; USA	Minimal intervention: 30 minute counselling based on social learning and relapse prevention therapy + 16 minute video and access to NRT when necessary. One follow-up call at 2 days was planned. Intensive care: same as above but with 4 follow-up calls. If relapse occurred, patients could have another 30 minute counselling session	Usual care received 1 to 2 minute counselling provided by the physician, a standard booklet on smoking cessation and the option to do outpatients for co-payment	Self-reported smoking cessation + cotinine validation showed that at 12 months 27% of participants in the intensive intervention, 22% of the minimal intervention and 20% of the usual care group were abstinent, $p=0.02$. The difference was only significant between intensive and usual care, $p=0.009$. Patients who used NRT had lower cessation rates than those without, which is possibly linked to nicotine dependence	Significantly more smokers quit when treated with intensive compared to usual care, but not with minimal care
Moller et al. 2002	primary elective hip or knee alloplasty patients • Intervention $n=56$ • Control $n=52$	Multi-site: three university hospitals; Sweden	Intervention that started 4 weeks prior to surgery. Patients had option to quit cold turkey or reduce intake to at least 50%. NRT was provided free of charge and patients were counselled on side-effects, withdrawal symptoms and weight gain	Standard care	Smoking cessation results not described	Smoking cessation results not described
Molyneux et al. 2003	Medical and surgical patients: Usual care $n=92$ • Counselling alone $n=91$ • Counselling + NRT $n=91$	Single site: metropolitan hospital; UK	Counselling alone: 20 minute counselling by physician or nurse + leaflet. Patients were advised on NRT Counselling + NRT: Counselling as described above + access to a 6 week course of NRT (patch, gum, inhalator, lozenge or nasal spray)	Usual Care: no additional intervention	Continuous validated abstinence rates at 12 months for NRT plus counselling, counselling alone and usual care were 11%, 4%, and 8%, respectively ($p=0.25$), and for validated point abstinence 17%, 6% and 8% ($p=0.03$)	No significant difference in continuous, but a result in point-prevalent abstinence for counselling + NRT compared to usual care and counselling alone

Murray et al. 2013	Self-reported smokers within 4 weeks of admission • Intervention $n=264$ • Control $n=229$	Single site: 18 medical wards of large teaching hospital; UK	Brief advice, standard written information, daily counselling and dual NRT when possible (patch + fast acting product). If contraindicated, varenicline or bupropion was used. Counselling was based on motivational interviewing. Upon discharge patients were offered access to quit smoking service	Usual care: advice given based on discretion of doctors or other HP	Continuous abstinence and carbon monoxide validation at 4 weeks: 38% for intervention versus 17% for control, adjusted odds ratio 2.10 (95% confidence interval 0.96 to 4.61)	No significant results for smoking cessation rates at 4 weeks for delivery of evidence based cessation support by hospital based cessation practitioners
Nagle et al. 2005	All patients excluding patients in accident and emergency, day surgery and dialysis, transplant and intensive care units • Counselling + NRT $n=711$, • Minimal care $n=711$	Single site: metropolitan tertiary teaching hospital in Hunter region, Australia.	Two brief counselling sessions executed by nurses, delivery of patient booklets and depending on nicotine dependency an offer for NRT	No intervention: minimal contact about smoking cessation	Validated self-report 24 hour point prevalence with cotinine and carbon monoxide validation. Did not find a difference at 12 month (19.5% vs. 21.9%) nor was there a difference for continuous abstinence (11.7% vs. 13.9%) at 12 months	Brief nurse-led counselling without a follow-up does not improve smoking cessation rates compared to a minimal intervention
Neuner et al. 2009	Emergency department patients • Intervention $n=515$ • Control $n=529$	Single site: emergency department in Berlin; Germany	Patients received an on-site counselling (1-3 minutes) session and up to 4 telephone booster calls. Counselling was based on motivation to quit. Free NRT was provided on site	Usual care: not described	7-day abstinence at 12 months showed no significant difference for patients in the intervention group (14.2%) versus patients in the control group (11.3%), $p=0.15$	ED initiated brief counselling and access to NRT did not lead to higher quit rates at 12 month follow-up
Ostroff et al. 2014	Cancer patients scheduled for surgery • Intervention $n=37$ • Control $n=37$	Single site: cancer centre; USA	The intervention focused on scheduled reduced smoking before surgery. It contained best practice care (see control column) and pre-surgical tapering using a computer program (Quitpal)	Best practice: telephone and bedside counselling by trained nurse (based on motivational interviewing). 5 sessions + NRT were offered (not obligatory)	There were no significant differences in 7-day point prevalent abstinence at 3 month and 6 month follow-up (36% versus 34%, $p=0.88$, and 32% versus 32%, $p=1.0$, respectively)	No difference between best-practice and best-practice + pre-surgical reduction tool using a computer
Prochaska et al. 2014	Inpatient psychiatric patients (locked ward with smoking ban) • Counselling + NRT $n=113$ • Usual care $n=111$	Single site: Psychiatric ward; USA	Intervention based on Transtheoretical model (TTM). 10 week NRT provision + computer-based TTM intervention with tailored reports, stage-based tailored print material, 15-30 minute counselling session. Follow-up at 3 and 6 month repeated the computer intervention	Usual care: not described	The 7-day point prevalence (verified by CO testing and collateral reports) was 13.9% vs 3.2% at month 3, 14.4% vs 6.5% at month 6, 19.4% vs 10.9% at month 12 and 20.0% vs 7.7% at month 18, with an OR of 3.15, $p=0.018$ for month 18. Retention to the intervention was over 80%	A computerised motivationally tailored intervention reduces smoking cessation rates in psychiatric patients up to 18 months
Ratner et al. 2004	Elective surgery patients • Counselling + NRT $n=117$ • Usual care $n=120$	Single site: teaching hospital; Canada	Pre-operative intervention containing NRT and counselling, emergency kit and a telephone hotline number. Further counselling was provided during admissions and telephone follow-up (up to 9 times) occurred after discharge	No intervention	Significantly higher numbers of 24 hour point prevalent abstinent smokers in intervention group (73%) versus control (53%), $p=0.003$. There were no differences found at 6 month and 12 month follow-up after surgery	Reduction in pre-operative smoking can be achieved by multi-modal intervention

Reid et al. 2003	Patients with coronary artery disease • NRT + counselling $n=126$ • Minimal intervention $n=128$	Single site: tertiary cardiac facility; Canada	Patients would receive brief individual counselling (5-10 minutes), a self-help booklet and a referral to the primary care physician. Patients were called 4 weeks after discharge to provide positive reinforcement. If smoking had started nurse counselling commenced: three 20 minute face-to-face sessions + NRT 4 weeks 10mg 16 hour patches and 2 weeks 5mg/16 hour patches	Patients would receive brief individual counselling (5-10 minutes), a self-help booklet and a referral to the primary care physician	The point-prevalent self-reported abstinence rate in the stepped-care group at 3 month follow-up was 53% in the stepped care group and 42% in the control group, $p=0.05$. This significant difference did not maintain at 12 months, 39% vs 36%, $P=0.36$	Stepped care only resulted in a significant difference at 3 months, but not at 12 month, compared to minimal intervention
Reid et al. 2007	Cardiac patients • Intervention $n=50$ • Control $n=49$	Single site: University of Ottawa Heart Institute; Canada	Standard bedside counselling + access to NRT. + Interactive voice response technology: calls at days 3, 14 and 30 day post-discharge. If chance of relapse was found, the patient was flagged and a nurse specialist would provide counsellor-led telephone sessions (3x 20 minutes over 8-weeks)	Usual care: Standard bedside counselling and access to NRT. No further treatment, but participants were able to join outpatient program or use other resources	At 1 year follow-up 46% in the intervention group ($n=23$) versus 34.7% ($n=17$) were abstinent according to self-reported 7 day point-prevalence, $OR=1.6$, $p=0.25$. At 12 weeks follow-up, 42% versus 35% were abstinent	The trial did not find significant differences between the two groups, but suffered from low power as it was a pilot trial
Richman et al. 2000	Adult smokers presenting to ED • Intervention $n=78$ • Control $n=74$	Single site: emergency department; USA	Two page "Stop Smoking" pamphlet, a comprehensive information package on the use of NRT, standardised scripted counselling by physician incl. written and verbal referral to in-house smoking cessation program (motivational interviewing + education sessions + opportunity to commence NRT) and advice that joining this program is more cost effective than their smoking habit	Two page "Stop Smoking" pamphlet	There were no differences in self-reported three month smoking abstinence for intervention (10.9%) versus control (10.4%), $p=1.0$. None of the intervention group participants contacted or attended the in-house smoking cessation program during the study period.	Physician counselling and referral to a hospital based smoking cessation program had no effect on quit rates or program attendance at three-month follow-up.
Rigotti et al. 2014	Patients admitted to hospital who had already received smoking cessation counselling during hospital stay • Intervention $n=198$ • Control $n=199$	Single site: general hospital; USA	Inpatient cessation services (counselling + access to NRT). At discharge: pharmacotherapy supplied for up to 90 days as discussed by patient and counsellor during inpatient stay, 5 automated interactive voice response telephone calls at 2, 14, 30, 60 and 90 days post discharge (providing support and advice and encouraged them to request counsellor contact if low confidence)	Inpatient cessation services (counselling + access to NRT). At discharge they received Standard care: post-discharge pharmacotherapy recommendation and advice to contact a Quitline	Validated 7-day abstinence at 6 months was significantly greater for the intervention group compared to control (26% vs 15%, $p<.009$). Self-reported continuous abstinence 6 months was also significantly improved (27% vs 16%, $p=0.007$). The costs per patient for the intervention were 354USD for the first 12 months and 108USD for subsequent years	An intervention of free pharmacotherapy for 90 days and follow-up via automated telephone call significantly improved smoking cessation for inpatients planning to quit

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Sherman et al. 2016	Adults admitted to a hospital ward, emergency department or intensive care unit • Intervention $n=805$ • Quitline $n=814$	multi-site: 2 public hospitals; USA	Seven sessions of telephone counselling taking place at 2, 3, 5, 9, 16, 32 and 42 days post-discharge. Cognitive and behavioural approach to supporting participant's chosen quit date and prevent any possible relapse. Eight weeks of NRT provided. Models used: motivational interviewing + problem solving therapy + CBT	Quitline operators instructed to contact participants via telephone to conduct 15-20 minute counselling session and one follow-up call	Self-reported abstinence rates at two month follow-up favoured intervention vs control (18.9% vs 13.6%, RR 1.39, 95%CI 1.11-1.74) and again at 6 month follow-up (25.8% vs 20.5%, RR=1.25, 95% CI 1.05,1.50). The mean cost per participant was 17.84USD for control and 76.62USD for intervention	Intensive telephone counselling leads to higher quit rates than a single Quitline contact
Simon et al. 1997	Patients undergoing non-cardiac surgery. • Intervention $n=168$ • Control $n=156$	Single-site: veterans affairs hospital; USA	Individual counselling session prior to discharge (30-60min) incl. education and advice, behavioural self-management techniques, educational video, an offer of 3 months NRT, written self-help resources and 5 follow-up telephone calls	A 10 min pre-discharge counselling session and provision of written self-help resources	6 month self-reported 7 day abstinence favoured intervention over control, though not significant (22% vs 14%, $p=0.06$). The difference between intervention and control became significant at 12 months (27% vs 13%, $p<.01$). Cotinine validated 7 day abstinence at 12 months was also significantly in favour of intervention compared to control (15% vs 8% , $p=0.04$)	A multicomponent discharge intervention offered to hospital inpatients significantly improved smoking abstinence compared to minimal intervention
Simon et al. 2003	General inpatients (patients with psychiatric or terminal illness were excluded). • Intervention $n=102$ • Control $n=107$	Single-site: veterans affairs hospital; USA	Individual counselling session prior to discharge (30-60min) incl. education and advice, behavioural self-management techniques, educational video, an offer of 2 months NRT, written self-help resources and 5 follow-up telephone calls	Minimal care: 2 months NRT appropriate dose for pre admission cigarette use and a 10 minute counselling session	6 month self-reported 7 day abstinence significantly favoured intervention over control (35% versus 21%, $p=0.02$). The difference for this outcome remained significant at 12 months (33% versus 20%, RR 1.7 95%CI 1.1-2.7, $p=0.03$). Cotinine validated 7 day abstinence at 12 months was not significant with those lost to follow-up considered smokers (29% versus 20%, $p=0.07$)	Higher rates of quitters for more intensive behavioural counselling compared to minimal care
Sørensen and Jørgensen 2003	Pre- and post-operative patients undergoing colorectal surgery • Intervention $n=27$ • Control $n=30$	One hospital; Denmark	Intervention: initiated 2-3 weeks pre-operatively with pre- and post-operative support by project nurse (telephone call, outpatient or home visit the day after expected smoking cessation) and NRT (Nicorette patch, gum, resoriblet, inhaler or nasal spray at least daily with no upper limit for use) until 24hours before surgery. Model: None reported	Maintenance of daily smoking habits, where smoking was allowed in single room studies	Self-reported continuous abstinence data at 15 days (pre-operative period) indicate a significant intervention effect compared to control (89% vs 13% abstinent; $p<0.05$). In the post-operative period 92% vs 50% were abstinent respectively ($p<0.05$)	Pre and post-operative smoking cessation advice with NRT can improve smoking cessation rates short-term

Stockings et al. 2012 Stockings et al. 2014	Mental health inpatients in a smoke free ward • Intervention $n=104$ • Control $n=101$	single-site: psychiatric ward; Australia	Standard care (see control column) as well as written self-help resources, a 10-15 minute motivational interview, 2 week supply of NRT on discharge, bi-weekly telephone follow-up for 4 months, additional 12 week supply of NRT, referral to Quitline, referral to community run cessation groups	Standard care(should have included):assessment of smoking status and nicotine dependence on admission, brief quit advice, NRT during admission and 3 days post-discharge, post-discharge smoking care plan	At end of follow-up (6 months) there was no difference between intervention and control, 7.7% versus 5.9%, but significantly more patients in the intervention (11.5%) versus the control (2%) group had 7-day point prevalence abstinence	Lack of strong evidence to support sustained smoking cessation in psychiatric inpatients using a multicomponent intervention.
Taylor et al. 1990	Patients hospitalised with myocardial • Intervention $n=86$ • Control $n=87$	Multi-site: 4 Kaiser Foundation hospital; USA	Nurse-managed intervention consisting out of an educational counselling session, written educational resource, audiotapes (assisted with progressive muscle relaxation), counselling on how to avoid high-risk relapse situations. If unable to quit follow-up outpatient appointment with nurse and if strong withdrawal symptoms free NRT was provided. Included telephone follow-up calls at 2 and 3 weeks and then monthly for 4 months following discharge	usual care: no specific quit instructions	At 12 month follow-up carbon monoxide validated smoking cessation rates significantly favoured intervention compared to control (61.6% versus 32%, $p=0.001$)	Nurse led intervention initiated in patients hospitalised for myocardial infarction improves 12 month cessation rates
Taylor et al. 1996	General hospital inpatients • Intervention, $n=315$ • Control $n=313$	Multi-site: 4 Kaiser Foundation hospital; USA	Multicomponent intervention including a standardised message from physician, one hour meeting with nurse during inpatient stay, 16 minute video, workbook, audiotape, counselling on high-risk relapse situations and offer of NRT if significant withdrawal symptoms or high nicotine dependence was established. Telephone follow-up was provided at 2 days, 1 week, 3 weeks 90 days post-discharge	Usual care: standardised message from physician + written self-help resource	Self-reported 7 day point prevalent cessation significantly favoured intervention compared to control at all time-points including 12 month follow-up (36% versus 28%, $p=0.022$). Following either cotinine or proxy confirmation, 12 months 7 day abstinence remained significantly in favour of intervention compared to control (31% vs 21%, $p=0.006$)	A nurse coordinated intervention can improve smoking cessation for hospitalised patients
Thomas et al. 2016	All adult smokers were eligible regardless of the ward they were admitted to • Intervention $n=300$ • Control $n=300$	multi-site: three tertiary hospitals; Australia	System change approach: pharmacist led behavioural counselling based on 5A's, pharmacotherapy was encouraged and offered free during hospital admission and at least 1 week after, access to educational resources and referral to a specialised cessation services. If interested patients were referred to Quitline and provided ongoing support post-discharge (communication with GP and community pharmacy)	Usual care: pharmacotherapy was available to all patients during hospital stay (not always offered systematically)+ brief counselling variably offered + NRT patches available to those eligible and interested	No difference in carbon monoxide verified sustained abstinence at 6 months between intervention (11.6%) and control (12.6%), OR 0.91, 95%CI 0.55-1.50) nor at 12 months, 11.6% versus 11.2%	Multicomponent intervention led by pharmacists did not appear effective in improving smoking cessation rates

Vial et al. 2002	Adult smokers admitted to medical or surgical wards • Hospital-based program $n=35$ • Community pharmacy-based program $n=34$ • Minimal intervention $n=33$	One hospital; Australia	All intervention participants received a 30-45 minute consultation with the hospital pharmacist and were commenced on nicotine patches (half price) following counselling for appropriate use. And referred to either a Hospital-based program or Community pharmacy-based program one week later. Weekly counselling sessions post-discharge and provision of discounted patches continued for 16 weeks.	Minimal intervention: provided with commercially available quit resources and cessation advice including strategies and behavioural approach	Self-reported continuous abstinence was not different between the three groups at 3, 6 and 12 months. This was the same for self-reported 7-day point prevalence at 3 and 6 months, at 12 months there was a significant difference between hospital (38%), community pharmacy (24%) and minimal intervention arms (4.6%) ($p=0.031$)	Counselling in addition to nicotine patches was equally as effective when provided in the hospital or community pharmacy setting and superior to minimal intervention
Warner et al. 2011	Pre-operative patients undergoing elective surgery • Intervention $n=149$ • Control $n=151$	One hospital; USA	Intervention: clinician-delivered intervention to facilitate Quitline use provided by the Mayo Clinic Tobacco Quitline using a dedicated toll-free number with an initial session post-recruitment with a Quitline counsellor for approximately 45-minutes and up to eight subsequent proactive sessions combined with four weeks of free NRT with optional four more weeks of NRT if patient still engaged in quitting Model: 5A approach (Ask, Assess, Advise, Assist and Arrange)	Brief (approximately 5 minute) intervention based on the 5A approach including a brochure with the number for Quitline	Self-reported 7-day point-prevalence data at 3 months showed no difference between groups with 25.8% compared to 26.8% abstinent in the control and Quitline groups respectively; Continuous abstinence was also not significant and neither were 7-day point prevalence of continuous abstinence rates at 1 month	No difference was observed between the Quitline facilitated group and the group receiving the information brochure that included the Quitline number
Warner et al. 2016	Hospitalised smokers • Quitline assistance $n=300$ • Brief advice only $n=300$	Two hospitals; USA	Quitline facilitation intervention including cessation advice and Quitline information to facilitate use of the service. An information brochure and wallet sized card were also provided. At the participant's discretion a call to Quitline was made for them to arrange for an initial counselling call and enrol them in relevant services. NRT was also offered during inpatient stay and for two weeks following discharge Model: Social Cognitive Therapy	Brief intervention including brief assistance and advice in using a brochure targeting cessation and including the Quitline number, though use of the number was not actively encouraged. NRT was also offered during inpatient stay and two weeks following discharge	7-day point-prevalence abstinence were not statistically difference between intervention and control groups at 7 days (33% vs 36%, $p=0.49$), 30 days (31% vs 31%, $p=1.0$) or 6 months (24% vs 24%, $p=1.0$)	Facilitating Quitline utilisation did not improve self-reported smoking abstinence compared to providing brief general advice and resourced

Wolfenden et al. 2005	Pre-operative patients undergoing surgery • Intervention $n=124$ • Control $n=86$	One hospital; Australia	Intervention: tailored counselling on cessation delivered by computer (17 minutes), print material to prompt advice by cessation nurse and anaesthetic staff, computer assisted technology to deliver counselling following attendance at the clinic and before admission (telephone counselling), patients smoking >10 cigarettes per day received free NRT (1-2 weeks) with NRT available during post-operative admission Model: None reported	Usual care consisted of clinic staff who had the opportunity to provide advice on quitting and to prescribe pre- and post-operative NRT at their discretion	Self-reported continuous abstinence at 3 months showed that intervention subjects, when compared with usual care participants, were more likely to report abstinence before surgery (73% vs 56%; OR2.2) and 3 months after attendance (18% vs 5% OR=3.9) respectively	Tailored counselling sessions delivered in person, over telephone and via a computer provided superior treatment efficacy compared to usual care for pre- and post-operative surgical patients

Abbreviations: nicotine replacement therapy=NRT, Odds Ratio=OR

Chapter 7.

Inhaled anticholinergics for chronic obstructive pulmonary disease in the elderly

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Name of principal author (candidate)	Zoe A Kopsaftis		
Contribution to the paper	Invited to write the review, conceived and designed the manuscript, extracted data, interpreted results, analysed the data, wrote the first draft, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions and approved final version.		
Signature		Date	22/02/2019
Name of co-author	Kristin V Carson-Chahhoud		
Contribution to the paper	Conceived study design, interpreted results, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions and supervised the process.		
Signature		Date	10/01/2019

An invitation to write a short commentary was extended from the journal *Gerontology & Geriatrics Research*. This was used as an opportunity to highlight a point for discussion and reflection around current clinical practice. COPD prevalence increases with age as does multi-morbidity and subsequent issues with polypharmacy. Anticholinergic agents are recommended for the management of stable and AECOPD. They are one of two types of inhaled bronchodilators given as mono or combination therapy for respiratory management, although their anticholinergic effects are not localised to the lungs and may cause adverse effects.

Elderly patients are particularly susceptible to these adverse effects as morbidity is considered to increase with age and further enhanced by associated comorbid conditions including cardiovascular disease and diabetes. Furthermore, elderly patients are likely to be taking one or more medications that may produce anticholinergic side effects such as anti-arrhythmic, antihistamines, muscle relaxants, antidepressants and psychotics as well as anti-ulcer and diarrhoea drugs. Considering the burden of anticholinergic drugs likely to be consumed by elderly people on a daily basis, the necessity of adding inhaled anticholinergics to their treatment plans for the management of COPD should be further assessed as it may be desirable to eliminate their use where possible.

Inhaled Anticholinergics for Chronic Obstructive Pulmonary Disease in the Elderly

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Chronic obstructive pulmonary disease (COPD) has an estimated prevalence of 15% among people aged above 65 years [1]. While morbidity is considered to increase with age, it is also hypothesised that this could be further enhanced by associated comorbid conditions including cardiovascular disease and diabetes [2-4]. COPD usually occurs as a result of exposure to smoking or other noxious particles in combination with genetic predisposition [3]. Subsequent chronic inflammatory processes in the lungs result in loss of elasticity and plugging of the small airways as well as parenchymal destruction [5]. People with COPD often experience respiratory symptoms including: breathlessness, chronic cough, increased sputum production and purulence, wheezing and tightness of the chest; these are often compounded by fatigue, anxiety and depression [3]. Stable COPD is punctuated by periods of exacerbation, whereby the above symptoms are acutely worsened in response to either an infective or non-infective trigger [6]. Underlying mechanisms for these episodes include; increased mucosal oedema, thickened sputum and additional constriction of the airways [7]. A novel treatment which would slow the progression of lung function decline associated with age and COPD is desirable and of increasing interest [8]. Hence, currently inhaled bronchodilators are, a staple of management of the occurrence and prevention of COPD [3]. These are separated into long and short acting depending on their time to, and duration of, effectiveness. Within these groups are beta-2 agonist and anticholinergic agents, which may be given either as mono or combination therapy.

Anticholinergic agents work by binding to muscarinic receptors in the lung to inhibit the constriction initiated by acetylcholine expressed via the cholinergic nerves [9]. However, muscarinic receptors are not localised to the lungs and anticholinergic effects may result in adverse effects, with increased risk to elderly and frail patients. Anticholinergic drugs have wider applications than simply inhaled forms for respiratory management, they are present in: anti-Parkinson, antispasmodic, mydriatic and antiemetic medications. Furthermore, it is likely that elderly patients are taking one or more of the following medications, which may produce anticholinergic side effects: anti-arrhythmic, antihistamines, muscle relaxants, antidepressants and psychotics as

well as anti-ulcer and diarrhoea drugs [10]. Figure 1 demonstrates potential anticholinergic adverse effects and how they may manifest in severity.

Anticholinergic agents are recommended for management of stable and exacerbations of COPD [3,8]. However, considering their association with adverse events which may have heightened risk to elderly and frail patients, the necessity of their addition to treatment plans should be further assessed. Given the burden of anticholinergic drugs likely to be consumed by elderly people on a daily basis, it may be desirable to eliminate their use where possible, thus, the necessity of inhaled anticholinergics for the management of COPD in the elderly should be further investigated.

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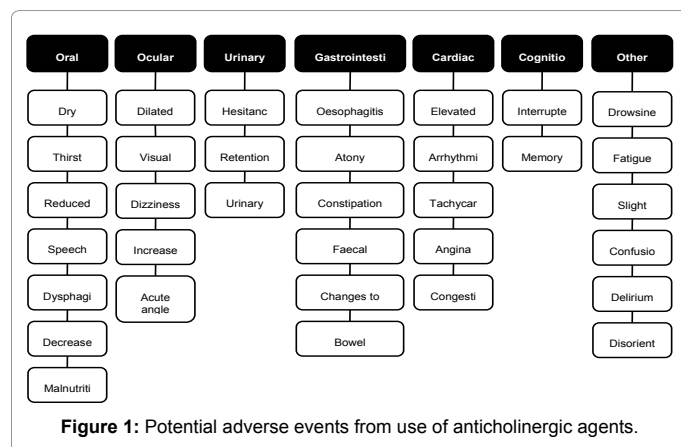


Figure 1: Potential adverse events from use of anticholinergic agents.

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Chapter 8.

Barriers and facilitators to best practice care for people with chronic obstructive pulmonary disease: A qualitative study

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Contribution to the paper	Conceived and designed the methods and manuscript, collected and analysed the data, wrote the first draft, contributed to writing the manuscript, agree with manuscript results and conclusions, jointly developed the arguments and structure for the paper, made critical revisions and approved final version.		
Signature		Date	05/03/2019
Name of co-author	Karen Royals		
Contribution to the paper	Assisted with development of the methods and some data collection. Transcribed the interviews. Agree with manuscript results and conclusions. Approved final version.		
Signature		Date	12/05/2019
Name of co-author	Kristin Carson-Chahhoud		
Contribution to the paper	Supervision of research conduct. Assisted with development of the methods and some data collection. Agree with manuscript results and conclusions. Approved final version.		

Signature		Date	12/02/2019

The evidence presented in Chapters 3-7 is an example of the thousands of papers published online every day. While evidence-based practice is the goal, keeping abreast of the sheer volume of available information in addition to the heavy demands of clinical workload can be a challenge for health professionals. Clinical practice guidelines are an appraisal and synthesis of the evidence base for a particular condition that aim to assist health professionals in making evidence-based decisions. Provision of guideline concordant care is associated with a reduction in exacerbation rate, yet the number of patients who do not receive best-practice care remains high. Interventions to improve provision of best practice are desirable, however, it is important to first explore the current barriers and facilitators from the perspective of the health professionals on the front line in order to best understand the underlying problem.

Qualitative research is an important aspect of health service research, enabling researchers to understand a phenomenon as it occurs in its natural setting by enquiring into the lived experience. In the case of the study presented in this chapter, the aim was not only to understand barriers to provision of best practice care but also to identify potential facilitators and innovation strategy. The overarching goal of this was to provide a basis for the development of an intervention that would be more successful than previously published efforts in improving uptake and adherence to guideline recommendations for the management of COPD in practice.

Data saturation was achieved after interviewing nineteen health professionals. Several barriers were identified to provision of guideline concordant care, including difficulties finding relevant information, lack of time to consult the guidelines, confusion around whose role it is to implement the latest guideline evidence and concerns over stepping on the toes of more senior staff. However, smartphone technology and engagement of specialist nurses were viewed positively as potential facilitators to overcome these issues. Results suggest that a multi-faceted, cross-disciplinary and technology-based intervention that improves awareness of guidelines and addresses organisation-level barriers is required to improve COPD management.

Barriers and facilitators to best practice care for people with chronic obstructive pulmonary disease: A qualitative study

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Keywords: COPD; chronic obstructive pulmonary disease; chronic disease; qualitative research; interviews; health professionals; doctors; nurses; guidelines; best-practice; respiratory; Australia

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Abstract

Uptake and adherence to best-practice guidelines for the management of chronic obstructive pulmonary disease (COPD) is variable in practice. This study aimed to identify perceived and actual barriers and facilitators to provision of guideline-concordant care for people with COPD. Nineteen semi-structured interviews with health professionals managing COPD patients across South Australia enabled data saturation. Questionnaires and Likert-scales facilitated data triangulation. Thematic analysis was undertaken by multiple coders using the Theoretical Domains Framework. Participants highlighted several organisational factors as barriers including: time, lack of standardised care and ineffective communication between multidisciplinary professionals and departments. Moreover, health professionals reportedly lack awareness of current guidelines and how to access/use them. However, smartphone technology and engagement of specialist nurses were viewed positively as potential facilitators to overcome these issues. Results suggest that a multi-faceted, cross-disciplinary and technology-based intervention that improves awareness of guidelines and addresses organisation-level barriers is required to improve COPD management.

Background

In 2012, 38 million deaths worldwide were attributed to non-communicable diseases with almost 11% the result of chronic respiratory illnesses such as chronic obstructive pulmonary disease (COPD) (Mendis. et al., 2014). COPD is a preventable chronic condition indicated by progressive limitations of airflow through the lungs. The two mechanisms contributing to this airflow limitation are an irreversible narrowing of small airways of the lung caused by ongoing inflammation and fibrosis, and degeneration of structures that facilitate expansion and compression of the lung as well as oxygenation of blood (Global Initiative for Chronic Obstructive Pulmonary Disease, 2019). People with COPD experience a number of symptoms and manifestations of the disease that negatively impact their quality of life. On any given day they may experience one or multiple symptoms including: breathlessness, cough, sputum production, wheezing, chest tightness, fatigue, anxiety, depression and weight loss (Global Initiative for Chronic Obstructive Pulmonary Disease, 2019; Yang et al., 2018).

COPD is responsible for 1.3% of all hospital admissions and 4% of deaths in patients aged 55 years or older (Australian Centre for Asthma Monitoring, 2011). At a rate of 282.6 per 100,000 people, COPD is ranked second for avoidable hospital admissions in Australia with the median length of stay being five to six days for people 55 years and older (Australian Institute of Health and Welfare, 2014; Page, Ambrose, Glover, & Hetzel, 2007). The rate of hospitalisations increases with age and given Australia's ageing population, with the number of older people projected to increase by approximately 10% by 2061 (Australian Bureau of Statistics, 2013; Australian Centre for Asthma Monitoring, 2011), the socioeconomic burden of COPD will be a long-term problem. The economic impact of this disease is significant, with estimated national expenditure for COPD in 2008/09 totalling \$929 million, 57% of which was attributable to inpatient costs (Australian Institute of Health and Welfare, 2014). Hence, addressing adequate and appropriate inpatient management of COPD to help reduce this burden is a priority.

Current management of people with COPD is heavily invested in the traditional physician outpatient model, where these appointments are time-fixed, inflexible

and typically occur when the patient is stable (Berkhof et al., 2014). Clinics are often booked months in advance creating difficulty in obtaining an urgent review. Delay in treatment or management advice for a COPD exacerbation often leads to a hospital presentation causing a deterioration in overall health status (Berkhof et al., 2014). Unfortunately, it is well recognised that many patients receive limited follow-up or COPD education and therefore are at risk of suboptimal management, despite recommendations for follow-up in COPD guidelines (Fromer, 2011; Golmohammadi, Jacobs, & Sin, 2004; Papala, Kerenidi, & Gourgoulisanis, 2013; Sundh et al., 2013).

It is estimated that there are 2,228 publications indexed on MEDLINE alone online every day (U.S. National Library of Medicine, 2016), with the number of new clinical trials registered increasing exponentially over the past 15 years (ClinicalTrials.gov, 2016). Clinical practice guidelines (CPGs) are one way of helping to navigate and utilize this vast amount of evidence. The Institute of Medicine defines them as follows:

“... statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.”(Institute of Medicine, 2011)

Despite the constantly developing evidence base for COPD management and development of high quality CPGs to assist integration of this knowledge into practice (Global Initiative for Chronic Obstructive Pulmonary Disease, 2019; Yang et al., 2018), studies highlight that up to 40% of patients do not receive guideline concordant care (Boulet, Bourbeau, Skomro, & Gupta, 2013; Grol & Grimshaw, 2003; Overington et al., 2014; Perez, Wisnivesky, Lurslurchachai, Kleinman, & Kronish, 2012; Pronovost, 2013). This issue with poor guideline uptake in practice is concerning given that CPGs improve quality of care by standardizing practice according to high level available evidence (Grimshaw & Russell, 1993; Haines & Jones, 1994).

To address this underutilization of CPGs it is important to explore themes relating to barriers and facilitators for guideline concordant care from the perspective of both health professionals and patients. Hence, the aims of this qualitative study were to: 1) identify perceived and actual barriers and facilitators to the provision of

guideline-concordant care for people with COPD, and 2) assist in identifying potential optimal approaches to guide clinical care towards evidence-based COPD management in both the inpatient and outpatient setting.

Methods

This research was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (REF: HREC/18/CALHN/150), the Human Research Ethics Committee of The University of Adelaide and The Human Research Ethics Committee of the University of South Australia. The study protocol was also registered prospectively on the Australian New Zealand Clinical Trial Registry (REF: ACTRN12618000641291) for transparency.

Five cross-disciplinary groups of participants were identified that routinely provide COPD treatment, management and education in their clinical practice (Table 1). To ensure a representative amount of qualitative data was obtained, 3-5 participants were recruited into each category, as a minimum of 12 participants overall was estimated to be necessary to represent the perceptions and experiences within the sample population about the same topic (Guest, Bunce, & Johnson, 2006). However, recruitment continued until data saturation was achieved. Participant inclusion and exclusion criteria are presented in Table 1.

Table 1: Participant inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria
Ward Nurses	Is currently working on a hospital ward admitting COPD patients (e.g. general or respiratory)	- Unable to consent - Aged < 18 years old - Non-English speaking
Specialist Respiratory Nurses	- Is currently working as a specialist respiratory nurse managing people with COPD - Has treated COPD patients regularly for >12 months in the last 5 years	
General Medicine Physicians	Has worked as a doctor in the general medicine specialty	

	Inclusion Criteria	Exclusion Criteria
Thoracic Medicine Physicians	Has worked as a doctor in the thoracic medicine specialty	
Trainee Medical Officers	Has worked as a trainee medical officer with at least one rotation through a general medical (dealing with people with COPD) or respiratory ward	

Key: COPD = chronic obstructive pulmonary disease.

Participants were purposively sampled from two large teaching hospitals in South Australia. Each participant completed a demographic questionnaire and to assist with data triangulation, agreed or disagreed with nine statements on a seven-point Likert scale broadly summarising some of the main topics discussed in the interview, including: beliefs about capabilities, knowledge/skills, role, social influences, and opinions on current COPD practices.

A moderator-guide based on 18 domains of the Theoretical Domains Framework (TDF) was used to direct semi-structured interviews with participating health professionals. The TDF is a framework that has been validated for use in implementation research (Cane, O'Connor, & Michie, 2012; Huijg et al., 2014). Questions asked to participants were open-ended and related to their perceptions and experiences around best-practice and guideline concordant care for COPD. These personal experiential accounts were encouraged through use of prompts by the interviewer (Pietkiewicz & Smith, 2014). After four interviews, [Author 2 (A2)] precluded herself from interview conduct, all with remaining interviews completed by [Author 1 (A1)] as the study team believed her role as a specialist respiratory nurse may have influenced participant responses. Interviews were audio recorded and transcribed verbatim by a member of the study team. Transcripts were returned to the individual participants for validation. Upon review of the transcripts, the four interviews attended by A2 were not significantly impacted her presence and were therefore included in the results of this study.

Analysis

Deductive thematic analysis was undertaken for qualitative data, under the 18 domains of the TDF: knowledge, skills, role, beliefs about capabilities, consequences, optimism, intentions, goals, innovation, innovation strategy, socio-political context, organisation, patient, social influences, positive and negative emotions, behaviour regulation and the nature of behaviours (Cane et al., 2012). Analysis was conducted according to the TDF to identify key ideas that may help to inform a practical future intervention to address the problem of variable guideline uptake seen in practice. Themes were synthesised and elaborated upon narratively and supported by direct quotes from participants.

Qualitative analysis was undertaken in NVivo version 12. Comparison of quantitative data collected via the questionnaire was completed using the Mann-Whitney test in SPSS.

Results

Data saturation was reached with recruitment of 19 health professionals. Interviews were between 30 to 90 minutes in duration and took place between May and August 2018. Figure 1 displays distribution across categories for participants recruited and interviewed in this study. The median number of years treating people with COPD was 9 for Medical Officers and 13 for Nurses; see Table 2 for further participant characteristics split by either Medical Officer or Nurse profession. Overall, health professionals were predominantly female, of median 44 years of age with 13 years treating and managing people with COPD.

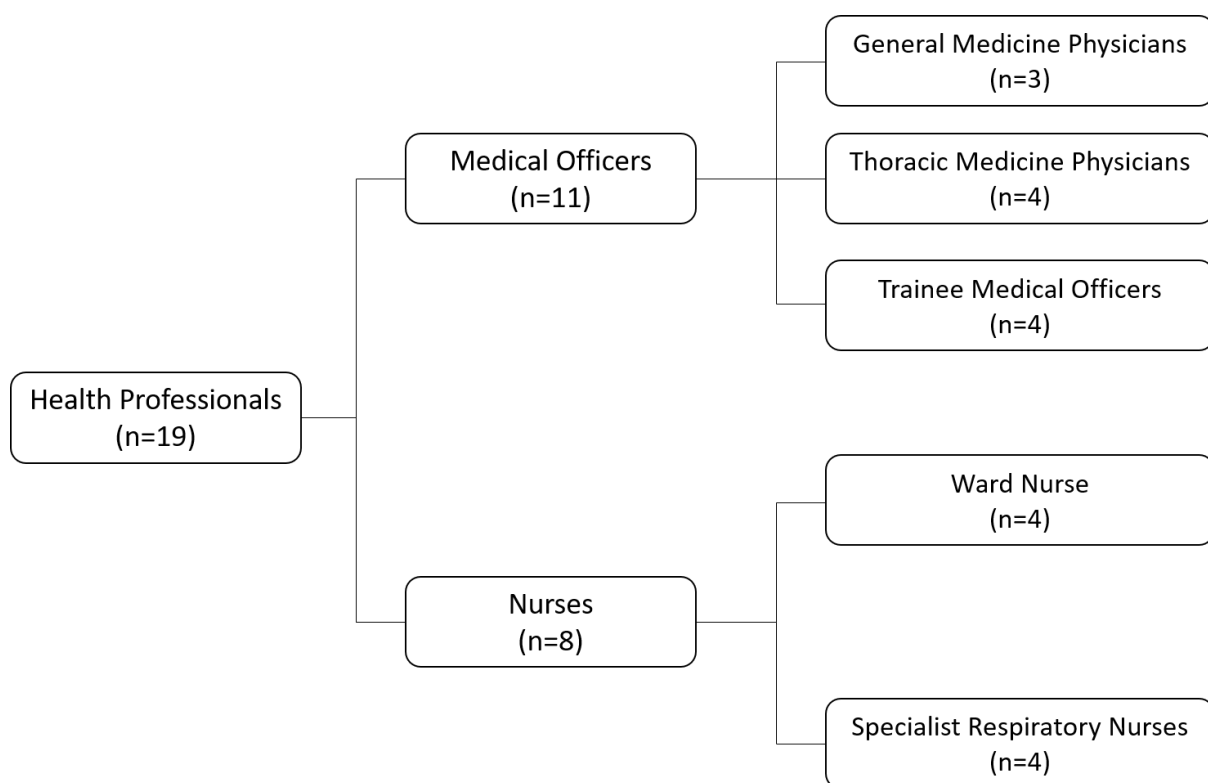


Figure 1: Participants recruited and interviewed

Key: n= number.

Table 2: Participant characteristics

Medical Officers (n=11)	Median (range)	Nurses (n=8)	Median (range)
Gender (n; male)	7	Gender (male)	1
Age (years)	39 (25-77)	Age (years)	46 (26-52)
Years treating COPD (years)	9 (2-50)	Years treating COPD (years)	13 (2-33)
Treats COPD in the inpatient setting (n (%))	19 (100)	Treats COPD in the inpatient setting (n (%))	7 (87.5)
Treats COPD in the outpatient setting (n (%))	16 (84.2)	Treats COPD in the outpatient setting (n (%))	3 (37.5)

Key: n = number.

Analysis of qualitative data from the 19 health professional interviews is presented below with representative quotes in Table 3.

Knowledge and Skills

Clinicians were familiar with the existence, format and contents of best practice guidelines for COPD and possessed the skills to locate and access them. While clinicians agreed that guidelines were helpful and well written, there was a general apathy toward actually accessing them in day-to-day practice. This was particularly apparent in more senior groups of clinicians with greater years of experience. Amongst Medical Officers and Nurses with more years of experience there was a strong preference to rely on personal experience and knowledge accrued over years of clinical practice and medical training.

“...I don’t personally check off on a guideline ever, well I feel confident that I know what the critical issues are in COPD management.” (Thoracic Medicine Physician)

Ward Nurses and Specialist Respiratory Nurses with less years of experience in their role expressed that they commonly consulted guidelines away from the patient bedside to further their knowledge development and support practice.

General Medicine Physicians (GMPs) felt confident in their knowledge and skills in treating average COPD patients but acknowledged there were gaps and room for improvement in managing more complex cases, particularly around escalation of pharmacotherapy. Despite this, there was a somewhat guilty lack of intention to consult guidelines with GMPs expressing their need to have sound knowledge of many conditions as a limitation to spending extra time on COPD.

As with GMPs, Trainee Medical Officers (TMOs) were confident treating average COPD patients and freely acknowledged a need to develop knowledge and skills around more complex cases; particularly with respect to patients with multiple comorbid conditions, those requiring escalation of pharmacotherapy and interventional approaches to COPD management. TMOs felt that guidelines were useful in supporting their ability to assess and treat their COPD patients and are

most likely to refer to them following a ward round or during an outpatient clinic. In the case of a ward round, TMOs would prefer to consult a more experienced Medical Officer for guidance than access a guideline.

While more experienced Medical Officers were confident in the knowledge and skills of their Trainee counterparts, experienced Nurses expressed doubts about the knowledge and skills possessed by more inexperienced Nurses. This was corroborated by an inexperienced ward nurse, who willingly acknowledged knowledge gaps around oxygen and inhaler requirements. This interviewee was also unaware of the existence of guidelines for the management of COPD but wished that they had known about them and described their clinical decision-making thusly:

“I think we just do what the doctors want to do, like we just follow doctors’ orders, like give patients the meds that are ordered, things like that.”

Role

Clinicians across the board confidently discussed their role in the management of patients with COPD. The way Medical Officers and Nurses perceived the nature of their roles in relation to COPD management resembled a treat and teach pattern. Medical Officers overall felt that their role centred on assessing their patient’s COPD, formulating and prescribing a treatment plan and ensuring it is executed by themselves and other required health professionals. Specifically, TMOs perceived their role to be a “first line of defence” and felt that responsibility for coordination of the overall patient care journey rested with them.

“I think a lot does revolve around me for better or worse...” (Trainee Medical Officer)

While Medical Officers highlighted the importance of educating patients on key topics including inhaler technique, they were comfortable that Nurses and Pharmacists were capable of taking on this task. Nurses agreed that the nature of their role in COPD management centred on teaching the patient; particularly

focussing on correct inhaler technique and non-pharmacological approaches. Specialist Respiratory Nurses believed their role to be critical in the management of COPD due to their ability to offer ongoing case management services. The value of the role was supported by Ward Nurses and Medical Officers who respectively deferred to, and trusted, in the depth of knowledge of Specialist Respiratory Nurses and the flexibility afforded to them in terms of being able to follow up in the community setting.

“...their ability to reach the patient, that's critical.” (Trainee Medical Officer)

Clinicians overall agreed that it is the responsibility of all health professionals involved in the care of patients with COPD to ensure that guideline recommendations are adhered to in practice. However, there was a tendency amongst Medical Officers, regardless of experience level, to attribute more responsibility for this to themselves, perceiving themselves to be the leaders of the care team who should set an example.

“I think it would be the definitely the...medical staff's responsibility.” (Trainee Medical Officer)

Amongst Nurses there was an inclination, once again regardless of experience level, to attribute higher responsibility for ensuring adherence to guideline recommendations in practice to those in senior leadership positions, e.g. Nurse Unit Manager.

Beliefs about capabilities & Consequences

Medical Officers had a strong belief that they were capable of delivering best practice COPD care. While Respiratory Specialists felt that this translated to actual provision of best practice care in the majority of cases, GMPs acknowledged key aspects of best practice (e.g. checking inhaler technique) were often skipped primarily owing to a split focus on multiple conditions.

Perceived barriers identified by clinicians about their ability to deliver best practice care were: lack of resources, time and heavy patient load both in the inpatient and outpatient setting. Conversely, admission to a respiratory unit to be cared for by specialist Respiratory Physicians, Advanced Trainees and Nurses was perceived to be a facilitating factor.

“Time precious without a doubt, at the moment I’ve got 30 inpatients, I’ve got an intern, my usual advanced trainee is on stress leave, my usual RMO is not here today ‘cause admin said they’ve worked too many days, the relieving RMO called in sick. So I started my ward round of 30 patients with 2 interns so there’s certainly pressures: time pressures, a lot of patients, they’ll be the big ones.” (General Medicine Physician)

The primary consequence of failure to provide quality care appeared obvious to all; their patients had the most to lose. Clinicians unanimously agreed that suboptimal care results in poor patient outcomes and burden on the health system. The outcome being not only increased expenditure but higher demands on already stretched resources, which compounds pre-existing time and workload constraints. The latter was particularly apparent amongst all participants.

“Everyone really, you name it, obviously the patient, healthcare providers...I would have less patients obviously if it was managed better, the GP’s, it’s a vicious cycle, the tax-payers, employers people being off sick for COPD exacerbations, the kids, I think everyone!” (General Medicine Physician)

Optimism, Intentions & Goals

Irrespective of years of experience or profession, there was an initial expression of optimism that best practice care was being provided to people with COPD, however, this waned with reflection.

“I think the ingredients are there for it to be performed correctly but I think sometimes if things get a bit busy that yeah some things might get missed or put by the wayside.” (Trainee Medical Officer)

Furthermore, clinicians predominantly expressed a lack of optimism when reflecting on whether improved quality of care in the future may reduce COPD-related hospital usage. Barriers to this were identified to be the nature of the disease itself, being chronic and progressive. As well as, an observed lack of intention on both the individual and organisational level to action change. Some clinicians expressed optimism contingent on the continued availability of novel pharmacotherapy, refined models of care, continued research and improved access to resources.

Innovation & Innovation Strategy

Clinicians seemed unaware of innovations in the field of COPD management in development. Despite this, they acknowledged that past pharmacological and interventional innovations had improved their ability to manage patients and that guidelines had kept well apace of these developments.

“I know they’ve just released a whole flood of new inhalers onto the market, pharmacological things but [other than that] no.” (Ward Nurse)

Further, they believed that there would be continued advancement in this area which would translate to clinical benefit. All participants acknowledged there had been advancements in the accessibility and format of best practice guidelines over the years, however, length and presentation format were still perceived to be a barrier to use in practice.

Smartphone technology was believed to be a potential facilitator to provision of best practice care but while clinicians viewed its potential use favourably on a personal level, they agreed that it may not be the most feasible intervention option for the typical demographic of people with COPD. The perceived advantage of smartphone technology was the ability to facilitate reminders, interactivity and convenience. Younger Medical Officers in particular relied on smartphones for information access frequently in practice.

“Yeah I think if there was an app it would be...I would use it. There’s always an app for everything, no I think if there’s anything on the smartphone that can help

with management I think that trumps anything else on a piece of paper or on even the computer.” (Trainee Medical Officer)

Older Medical Officers and Nurses regarded innovation around models of care and education for both clinicians and patients to be future facilitators to best practice. However, COPD was not perceived to be an appealing disease and this was thought to be a barrier to interest and subsequent innovation in the area compared to other respiratory conditions including cystic fibrosis and asthma.

Socio-political Context

Collectively, clinicians did not believe that COPD management was a priority in the eyes of society or the government. There was a perception that wider societal awareness was low and that a COPD diagnosis was still stigmatised.

“Ah I think people tend to assign a moral judgement to the diagnosis of COPD and you know the moral judgement is you brought this on yourself because you smoked.” (Trainee Medical Officer)

Once again, clinicians unanimously believed government attitude toward health care to be reactionary and financially motivated. Despite this, they believed improved COPD management failed to attract enough attention or support from the government. High profile advocacy and the submission of impactful business cases with continued pressure by motivated clinicians were perceived to be facilitators to change in this area; that would in turn result in increased support and resources desperately needed by health professionals.

Organisation

Medical Officers believed the greatest organisational barrier to provision of best practice care was time. There was an inherent pressure perceived by the volume of patients requiring care both in the inpatient and outpatient setting.

“So a normal clinic, not a busy clinic, would be four patients an hour, 15 minutes per patient that’s all I’m given. Often my slots are double booked so... you know it’s difficult.” (Trainee Medical Officer)

This was a belief somewhat shared by Nursing staff, in particular Ward Nurses; while Specialist Respiratory Nurses felt that this pressure was slightly mitigated by the nature of their role, i.e. the ability to self-determine time allocation and see patients in a variety of settings.

Access to a quality multidisciplinary team was believed to be a strong facilitating factor to best practice care. In particular, Specialist Respiratory Nurses were highly regarded for their ability to provide high level education, case management and community outreach services. Ready access to physiotherapists, pulmonary function testing and psychological services were perceived as a theoretical facilitator (available to some but not all hospitals). However, reality appears to be that absence of resources in this area can be a barrier.

Compounding the above is the perception from more experienced Medical and Nursing staff alike that there is a lack of support at the executive level to support necessary changes and increase resources. Medical Officers and Nurses with less experience felt that the support they received from more experienced clinicians within their own department to be a facilitator to provision of best practice.

"I think we're working really hard to make...to let government and hospital bureaucracy understand how we manage COPD patients I think it's always difficult for them to fully comprehend that I suspect sometimes they don't listen." (Ward Nurse)

While the less experienced clinicians appeared to exude a confidence in their ability to suggest and effect change for the betterment of practice though communication with their managers, clinical journeymen appeared jaded from the repeated lack of support from above.

Patient

The COPD patient was identified as both a major barrier and facilitator to best practice care by all participants, depending on the individual. Clinicians believe motivated patients help them provide best practice care through high compliance

and engagement. However, they held the belief that a large proportion of people with COPD possess attributes that are barriers to care. Patient-based barriers identified included: lack of motivation to attend appointments and listen to advice, low socioeconomic status, depression and anxiety and low health literacy.

“So I think socioeconomics, education and peers do have a role in it.” (Thoracic Medicine Physician)

Social Influences

Clinicians across the board believed they shared similar management approaches with their colleagues. There appeared to be a team loyalty and unwillingness to deviate from this message verbally though physical cues indicated otherwise. Particularly amongst the Medical Officers, most of whom broke eye contact and pulled faces which implied their answer was not entirely honest. However, one TMO highlighted that there was often differing opinions amongst more experienced Medical Officers, which leads to some confusion about the best approach to take.

“...there’s differing opinion between different consultants even within the same unit and I think that’s when it starts getting tricky...” (Trainee Medical Officer)

Amongst the Medical Officers a hierarchical culture was evident with Trainees feeling averse to questioning a consultant’s judgement even if they believed the decision to be out of line with best practice recommendations.

Positive & Negative Emotions

For all clinicians, positive emotions were centred on their patients. They valued the opportunity to build relationships with their patients and celebrated the good clinical outcomes that were associated with patient compliance.

“Well I think the positive things are when everything goes well, patients give up smoking, take the medications regularly and do what they’re supposed to do it can make a real difference to their quality of life so that’s good.” (Thoracic Medicine Physician)

Patients were also a source of negative emotions for clinicians where their recalcitrance resulted in treatment failure and repeated admissions to hospital.

Behaviour Regulation & Nature of Behaviours

More experienced clinicians universally relied on a mental checklist developed over their years of experience managing people with COPD. While merits of a physical checklist were acknowledged, there was a perception that they were not practical and had failed to be used in practice in the past. Conversely, TMOs believed that use of a standardised checklist for best practice management of COPD improved ability to provide quality and standardised care. Further, the use of computers in daily practice facilitated consistent use of the checklist.

“...I go vaccinations, exacerbations, exercise tolerance, cough, haemo, I have like a checklist that I go through...and then in the clinic I go through the same questions with everyone.” (Trainee Medical Officer)

Personal motivation was also perceived to be either a barrier or facilitator to best practice management. Thoracic Medicine Physicians and Specialist Respiratory Nurses believed they were more likely to refer and adhere to guidelines because of their special interest.

Table 3: Interview themes categorised into the theoretical domains framework with supporting participant quotes

TDF Domain	Example Quote
Knowledge & Skills	“...they do to some degree have a stepwise escalation sort of protocol or outline but it’s not phrased or formatted in a way that’s very easy for someone who’s short of on time to quickly refer to.” (<i>Trainee Medical Officer</i>) “...I have been working in this area for a long time and I go to conferences and I attend unit meetings and I’m involved in research so as developments occur I have the opportunity to keep abreast of what’s happening in the field and I’m a bit allergic to guidelines that’s why I don’t use guidelines...” (<i>Thoracic Medicine Physician</i>) “...from an inpatient management I don’t really use much guidelines I’m a lacuna I think in how we treat COPD patients is that we are very quick to admit them and not great at turning them around at the door, I don’t think we’re good at enabling them to deal with exacerbations themselves...” (<i>General Medicine Physician</i>) “Yeah I do and I’d say it’s because I specifically manage exacerbations I’m quite bad on escalation of treatment and I’m quite bad on you know if they’re on one agent what’s the second agent to add or if they’re already on two you know do I add a steroid and there was for a long time a very limited number of inhalers and there’s

	been a little explosion recently and I'm quite bad at it..." (<i>General Medicine Physician</i>) "Yeah I do I use COPDX and I use GOLD and NICE and they are the key broader ones and then I use local guidelines to and more at an intervention level" (<i>Specialist Respiratory Nurse</i>)
Role	"...seeing patients on a daily basis on the wards so we sort of act as the first line of defence I guess and so a lot of that comes down to simple prescribing practices and doing the basics so puffers and steroids and sort of assessing and examining and working out the degrees of severity..." (<i>Trainee Medical Officer</i>) "I think a lot does revolve around me for better or worse in the sense that I'm the person expected to coordinate the outpatient care, ensure the GP is kept up to date, manage the inpatients most of the time yeah." (<i>Trainee Medical Officer</i>) "I think physicians; respiratory physician should be the leader. Should take the lead in that management and then closely liaise with the GP and the Respiratory Nurses." (<i>Thoracic Medicine Physician</i>) "I think given the health economic climate in which we operate in I think it's very difficult to expect that of the medical staff as well. So...I would expect at the very least respiratory ward nurses and...the respiratory capital

	R nurses as well. Pharmacist certainly can help out as well.” (<i>Trainee Medical Officer</i>) [on Specialist Respiratory Nursing] “I think the community outreach is important, that’s very important because you know it’s not always feasible to get someone who may be on a pension or poor or you know otherwise physically disabled to get to come in for a clinic, so their ability to reach the patient that’s critical.” (<i>Trainee Medical Officer</i>)
Beliefs about capabilities & Consequences	“... I think there are probably things we could probably do better like inhaler technique, vaccines and pulmonary rehab which I’ll bet if they were taken care by our respiratory specialists would tick those boxes and there’s evidence to show that, it’s not my gut instinct, they would probably do better than we are.” (<i>General Medicine Physician</i>) “...yeah but just I think it’s the nature of being a generalist rather than a specialist, probably don’t cross the t’s and dot the i’s as well as a Specialist would in any given arena. However, as a you know we tend to do well when people have lots of things wrong and need everything kinda okay. Whereas, a Specialist might manage what’s in front of them pretty good but then may have to call in five other specialists for five other diseases; and so the model for General Medicine is taking care of lots of things that are going wrong. As I said, I think we’re probably underserving the patients who have only one thing going wrong, they should probably be under specialists.” (<i>General Medicine Physician</i>)

	“I think in the Respiratory Unit yes we do, I mean most of the times, obviously it’s never perfect but I think, yeah, 80% of the times we are doing it.” <i>(Thoracic Medicine Physician)</i> “...We're very spoilt here, you know we've got a lung function unit attached to us so that allows me to stage it” <i>(Trainee Medical Officer)</i> “Oh well, everybody. Everybody from the funders to the providers to the users to the families to their employers the whole of society” <i>(Thoracic Medicine Physician)</i> “Well I think that’s lots of people I think that the patient because cause they’re not going to get better if they’re on suboptimal management I think that the hospital they’re gonna have increased length of stay and maybe more frequent presentations I suppose outpatients because they’re probably gonna be more frequent flying to outpatient visits and things like that GP’s cause gonna attend GP’s more cause they not being properly managed yeah so it’s really gonna impact the health service as a whole because they are not being properly managed plus the patient plus probably their families too because their loved one is always sick” <i>(Specialist Respiratory Nurse)</i>
Optimism, Intentions &	“No! ...I think you know every now and then a spotlight is shown...’where are our biggest wins here?’ so COPD always comes up, it does actually come up, so like what are we gonna do? What are we doing about that? Wow it’s gonna require some pretty deep philosophical change in this place and it’s always sort of put as a like

Goals

worthwhile but hard ...'let's not do it'..." (*General Medicine Physician*)

"Nothing's changed in the last 10 years, except there's been, I mean the reduction in length of stay, modest as it is, infers that there has been some change. But in terms of the broad system aspects nothing's changed ..."
(*Thoracic Medicine Physician*)

"Yeah I think COPD management is always improving, there's always new medications that are coming out and I think there's been sort of big emphasis on anti-smoking campaign for some time now so I think over time and the number of people that are smoking will reduce." (*Trainee Medical Officer*)

"I am optimistic that it will continue to get better but like I said earlier with the caveat that you know there will be a group of patients who will always continue to exacerbate maybe a bit pessimistic but you know I suspect there's always a group of patients who will exacerbate frequently and because we don't have the full palette of outpatient therapies available to us in Australia...it's a bit difficult comment to whether that can get better."
(*Trainee Medical Officer*)

"Well some of the recent changes have; well I was at the [hospital name] five years ago, there was COPD nurses, pulmonary rehab back then so, it's probably not that new an intervention but that certainly made me

	more optimistic that things are going the right way. Surveys like this, knowing that there's research in the area is making me pretty optimistic too, so yes optimistic!" (<i>General Medicine Physician</i>) "Today, no!...I think we've got a long way to go yet, sort of like we still have this gap between tertiary care and primary care; we don't have that real good intermediary model we're you know patients can get everything that they need..." (<i>Specialist Respiratory Nurse</i>)
Innovation & Innovation Strategy	"Yeah I think if there was an app it would be... I would use it. There's always an app for everything, no I think if there's anything on the smartphone that can help with management I think that's, that trumps anything else on a piece of paper or on even the computer." (<i>Trainee Medical Officer</i>) "I think education to clinicians so on what is best practice management making sure they're all over the guidelines and what is best practice and what should they be doing..." (<i>Specialist Respiratory Nurse</i>) "It's not! I think that is the biggest problem, like there is no interest, there's no one person; elsewhere you may have like an asthma clinic or but here it's not, it's just sort of something we do on top of everything else. We do [interstitial lung disease] which we love, we do interventions but oh we have to see COPD. It's not the sexy one, it's not it the one like oh here's a puffer come back and see me." (<i>Trainee Medical Officer</i>)

**Socio-political
context**

“Ah I think people tend to assign a moral judgement to the diagnosis of COPD and you know the moral judgement is you brought this on yourself because you smoked. It also tends to disproportionately affect the lower SES class groups, so...as with many other issues this particular group doesn't have a united voice or a media presence or...any of the other things that would enable wide access to funding for example. The comparison would be to say cystic fibrosis. Everyone knows what cystic fibrosis is, not many people know what COPD is yet the prevalence of COPD WAY outstrips that of cystic fibrosis, yep.” (*Trainee Medical Officer*)

“No! They should be spending more money, Education, Nursing staff and also for patients out in the community, what causes it you know to prevent it from occurring, yeah in a basic sort of way so that they'd understand what's causing it and what it could lead to and things like that.” (*Ward Nurse*)

“Well it certainly doesn't seem to be a, second most common avoidable medical condition for hospitalisation because if it was then we would be being supported and encouraged to make a difference that we know we can, so, what is the problem that would make it, well, you know the usual things you either have to have a single incident where somebody in prominence or be it visible suddenly becomes you know an issue for instance the Bali burns area was a very powerful trigger to the burns needs of the community, the, sometimes an epidemic or something or other like HIV makes a big difference. For the less acute type of situations one then has to really work on it over a period of time as cancer has so in the absence of if you like leadership in that area it's not going to happen.” (*Thoracic Medicine Physician*)

	“The government has to provide more financial support to the community for to the community, because if it is not controlled in the community then the patients keep coming to hospital that impacts the health and finance so its prevention is better than cure.” (<i>Specialist Respiratory Nurse</i>)
Organisation	“A time restriction is always there depending on the patient load... I, can spend so much more time with one patient if my ward round consists of five people as opposed to if I've got 20 people; so I don't think it's an imposed time restriction, I think it's just a time restriction that's circumstantial in the sense of what other things you have to do on that day.” (<i>Trainee Medical Officer</i>) “Definitely yeah, the unit I've just come off of it, everyone is very supportive never felt like I couldn't voice any concerns.” (<i>Trainee Medical Officer</i>) “Look, there's a difference between listening and doing and following through and I think they occasionally listen but they will not have been shown any evidence that they've followed through.” (<i>Thoracic Medicine Physician</i>)
Patient	“I don't think so ... I feel like we tend to get more older patients in the ward whose got it and I think the more older patients are the more, they just don't care.” (<i>Ward Nurse</i>)

	“So I think education is the basic thing that I have noticed. so if they are not really well educated or if... with all due respect I have got a significant difference in patients from the northern suburbs versus western suburbs their approach...I see patients in the north as well and even if they have severe COPD they are still not keen to give up because they're, everyone there is smoking they're not much educated they're not really working they're on disability pension they're getting money for free and they spend it on cigarettes, they don't want to pay the doctors but they want spend on the cigarettes. in western suburbs we have a different population we have you know working class who have works, I'm sorry I'm not sort of saying anything [offensive] it's just my general thinking form the patients perspective ... whereas when i see patients at the western hospital they are much more open towards stopping smoking and then interventions.” <i>(Thoracic Medicine Physician)</i> “I try...I think it is a bit more tricky as an outpatient but for me personally it's mostly to do with patients not turning up and for clinics...10, on a bad week 15% 20%” <i>(Trainee Medical Officer)</i> “I find that most patients don't tend to see an immediate benefit from the preventer and so go on to not use it and the preventers the one that keeps them out of trouble however, despite verbal explanations in clinic often it just doesn't stick because patients may not have the tools necessary even to understand you know or retain the explanations that they've been given...” <i>(Trainee Medical Officer)</i>
Social influences	“I would of thought fairly, fairly similar we discuss management a lot in meetings so” <i>(Thoracic Medicine Physician)</i>

	“How many people go to the consultants and ask them have you done an action plan for this patient? I can't, I wouldn't...they're my seniors they do my evaluation.” (<i>Trainee Medical Officer</i>)
Positive emotions & Negative emotions	“Positive aspects of COPD management, well I mean it's a chronic disease so you develop relationships with patients yeah so that's a big plus for me, yeah that would be the main big plus for me.” (<i>Trainee Medical Officer</i>) “Positive aspects of COPD management I think it's wonderful to see a patient who is engaged and does all the right things and manages to stay out of hospital, you never see them again or they tap in every now and then to ask advice but are managing their disease.” (<i>Specialist Respiratory Nurse</i>) “So I think the down-side with COPD management is that there's nothing new, there's nothing exciting at the moment and that's why it's just sort of one of those onerous laborious things ...” (<i>Trainee Medical Officer</i>) “The frustrating thing I think sometimes is when you have the patient that just isn't engaged and they are the tricky ones that sort of like represent to hospital but there isn't a lot you can do while they are not in the mindset to change anything.” (<i>Specialist Respiratory Nurse</i>)
Behaviour	“It's all up here baby...yes years of practice but for a long time I used to use a checklist but you know it just

**regulation &
Nature of
Behaviours**

became ingrained in the brain.” (*Specialist Respiratory Nurse*)

“In terms of other people, find that they don’t look at guidelines so the general population that aren’t specialists in respiratory and then my nursing colleagues not in a specialist role they’re not familiar with looking at guidelines and they say that to me... because it’s my sole role to do it, I apply the evidence to practice, I do certain assessments I’m looking for certain things, I’m looking to get you know certain things ticked off for all the patients that I’m looking after. However that goes with me as an individual.” (*Specialist Respiratory Nurse*)

Quantitative data comparing Medical Officer and Nurse responses, identified that both groups had a similar level of agreement on all statements relating to best-practice COPD management (Table 4). However, Nurses believed that improving COPD care should be a higher priority in South Australia compared to their medical colleagues.

Table 4: Quantitative data analysis from Likert scale responses

	Medical Officers		Nurses		
	Median	Range	Median	Range	p-value*
I feel confident in my ability to adequately manage COPD patients.	6	5-7	6	4-7	NS
I feel confident in my ability to provide training and/or education to patients to assist with their COPD management.	6	4-7	6	4-7	NS
I have the support and resources to adequately manage COPD patients.	5	5-7	5.5	5-7	NS
I understand what my role is within a multi-disciplinary team in the care and treatment of COPD patients.	6	5-7	6.5	5-7	NS
My colleagues and I share similar approaches to COPD	6	5-7	6	4-7	NS

management.					
I actively seek more information about new advances in COPD care and treatment (e.g. journals, conferences, colleagues etc...)	6	4-7	6	4-7	NS
In my experience, the standard of care for COPD patients in South Australia is poor.	3	1-5	5	2-6	NS
Improving COPD care should be a higher priority in South Australia.	5	4-7	7	6-7	<0.05
I believe COPD patients are well equipped to manage their COPD independently.	3	2-6	4.5	2-6	NS

Key: SD = standard deviation; NS = not significant; < = less than.

* Where $p > 0.05$ using Mann-Whitney test.

Discussion

This study used deductive thematic analyses to understand health professionals' views on current best practice management of COPD in South Australia. Overall several barriers were identified to provision of guideline concordant care, including difficulties finding relevant information, lack of time to consult the guidelines, confusion around whose role it is to implement the latest guideline evidence and concerns over stepping on the toes of more senior staff. These findings are consistent with other qualitative investigations and literature reviews, both specific to COPD and in general (Cabana et al., 1999; Overington et al., 2014; B. Smith et al., 2005). The majority of participants in this study felt they had sound knowledge

of guidelines for COPD, however, they were reluctant to explore intrinsic factors relating to provision, or not, of best practice care in depth. This is an interesting observation given that other studies have identified lack of familiarity and awareness of guidelines as a barrier to adherence (Cabana et al., 1999; Overington et al., 2014; B. Smith et al., 2005).

Health professionals participating in this study demonstrated a strong connection to their professional identity when discussing their role in the management of COPD. Psychologists exploring the phenomenon of a Medical Officers' professional identity have proposed that this is developed in stages over time resulting in the internalisation of characteristics, values and norms that result in the individual behaving like a doctor (Cruess, Cruess, Boudreau, Snell, & Steinert, 2014). It has been proposed that socialisation is the primary process through which professional identity forms and matures (Burford, 2012; Hafferty, 2008). It is the idea that an individual learns to function within an environment or group by internalising its norms and values (Ofcom, 2013). This notion is supported by results of this study, in which clinicians overall demonstrated loyalty to their colleagues and held the belief that they shared similar management approaches. This speaks to the strength of social influence in determining behaviour in the clinical setting. Further, Medical Officers were generally perceived to be leaders of the clinical team. It is therefore likely that any behavioural change effected in this group would trickle down throughout other members of the wider multidisciplinary team.

Organisational barriers (e.g. lack of time, resources and executive support) to provision of best practice care for COPD have been outlined in previous research (Cabana et al., 1999; Overington et al., 2014; B. Smith et al., 2005) and are confirmed by results of the current study. However, there is a gap in the literature relating to clinicians' beliefs about the influence of socio-political context on provision of best practice care for COPD. In the current study it was identified that clinicians believed COPD was stigmatised by the wider public as a self-inflicted disease and that awareness amongst the general public was low. Both ideas are supported by limited literature that demonstrates societal awareness of COPD has

increased in the last decade, though it remains low at about 20% of the population in some countries (Grouse & Nonikov, 2014). Interestingly, the clinicians' perspective that COPD is stigmatised as self-inflicted by society is not only probable but likely a brand that people with COPD assign to themselves (Halding, Heggdal, & Wahl, 2011). It may then be inferred that this self-condemnation leads to patient-related barriers to provision of best practice care such as lack of motivation and compliance with advice, as identified in this and other studies (Cabana et al., 1999; Overington et al., 2014). Another stigma identified in this study, but not described elsewhere, is one held by the clinicians themselves - that COPD is an unpopular unsexy condition to treat. Attempting to reframe this thought may be beneficial when considering the best ways to change behaviour and engage clinicians in improving provision of guideline concordant care.

The way clinicians expressed their beliefs in this study naturally lead to the interpretation and understanding of many barriers to best practice as described above. Though this appears reflective of the general lack of enthusiasm and optimism surrounding COPD management amongst clinicians, some positive aspects of care and facilitators to best practice were also identified. The primary facilitating factors perceived by clinicians were past and future innovations. Past innovations in inhaled medications were thought to be imperative to their ability to best manage COPD. Though none of the clinicians were aware of any upcoming innovations in this space, there was a strong belief that there would be further developments in the future. Moreover, clinicians believed that smartphone technology was a potential facilitator to provision of guideline concordant care. This is unsurprising given the technology boom in recent years and rapid proliferation of personal mobile devices (Ofcom, 2013, 2015; A. Smith, 2013; World Health Organization, 2014). Participants in this study highlighted that smartphones possessed attributes that could counteract known and re-identified barriers to knowledge translation (e.g. lack of interactivity, inaccessibility, inconvenience, length and format) (Cabana et al., 1999; Overington et al., 2014; B. Smith et al., 2005). However, there is presently a paucity of studies to identify if this is a commonly held belief amongst other health professionals.

Access to a multidisciplinary team, particularly Specialist Respiratory Nurses, was another facilitating factor identified by clinicians. They were valued for their COPD knowledge and ability to case manage patients in the community. Clinicians also believed that flexibility in time available to spend with patients by Specialist Respiratory Nurses is a major benefit to provision of best practice care. The Specialist Respiratory Nursing role, which includes outreach services and case management within its scope, is relatively new in practice and constantly evolving (Preston & Kelly, 2016). As such there is a lack of information on their effectiveness in appropriately managing people with COPD. A systematic review of only eight studies demonstrated that the present evidence base for this type of nursing service is conflicting but shows some improvement in quality of life (Wong, Carson, & Smith, 2012). The lack of current evidence for both respiratory nursing and smartphone technology is likely attributable to the researchers' inability to keep pace with rapid developments occurring in clinical practice and information technology.

Overall, this study contributed to the existing literature by corroborating and expanding what was known about barriers and facilitators to best practice care for COPD. Further, through deductive thematic analysis using the TDF, it is possible to use these results to inform a future intervention to improve provision of guideline concordant care.

Strengths and limitations

There were some limitations to this study that should be considered. During the conduct of data collection, interviews were conducted by both [Author 1 (A1)] and [Author 2 (A2)]. After four interviews, investigators became concerned that the presence of A2, a specialist respiratory nurse, may be influencing participant responses. Therefore, A2 was excluded from conducting further interviews unless the participant was unfamiliar with A2's clinical role. Upon review of the transcripts there appeared to be minimal influence on participant responses following A2's abstention from the data collection process, therefore, all interviews were included in the analysis.

Generalisability of results from this study is limited. Participants were Medical Officers and Nurses sampled from two large teaching hospitals in metropolitan South Australia. Hospital-based clinicians were the target population as this study aimed to inform an intervention to improve guideline adherence in the acute setting, though interviewing a more diverse group of multidisciplinary clinicians may have been beneficial.

Despite its limitations, the beliefs and experiences of participants in this study appear well reflected in the existing literature. Moreover, the use of the TDF proved beneficial in allowing investigators to explore all facets of the problem ranging from personal to socio-political, as well as gaining insight into potential innovative strategies that could be of value to the target population in future research.

Future directions

There would be merit in replicating the current study to address limitations discussed above. In particular, the composition of the investigator team should have a balance among the interviewers that engenders collegial openness of expression without biasing the participants' responses. Improving the generalisability of results is also desirable, hence it would be ideal to expand the sampling frame to include a wider range of health professionals involved in the management of COPD, for example physiotherapists and social workers. The problem of variable uptake and adherence to guidelines for the management of COPD in practice remains an area for improvement, which could translate to improved outcomes for both patients and health services. Hence, a true understanding of the landscape is necessary, as the success and/or failure of any future efforts to implement guideline-related interventions in practice centre on beliefs and behaviours of front-line clinicians.

While further qualitative investigations into this area are warranted, the findings of this study corroborate other accounts in the literature and as such provide a solid basis for future interventional research (Cabana et al., 1999; B. Smith et al., 2005). Future interventions aimed at improving provision of best-practice management for COPD may consider investigating the effectiveness of the Specialist Respiratory Nurse. According to the results of this study Specialist Respiratory Nurses are highly knowledgeable and in the optimal position of being able to provide integrated, patient centred chronic care overcoming the major perceived barriers of time and patient load. There is a small pool of evidence to suggest that intervention by a Specialist Nurse may translate to improved patient quality of life (Wong et al., 2012) . Despite this, a paucity of information currently exists to clearly define nursing best practice in COPD. Hence, an intermediate step should be taken to quantitatively evaluate how current nursing practice compares to best-practice guidelines in order to confirm the beliefs expressed by the clinicians in this study.

Results of this study indicate that a technological intervention (specifically involving smartphones) to improve guideline concordant management for COPD would be well received by clinicians. Their ready availability makes them a potentially cost-effective means of improving efficiency, safety and end user satisfaction (Gawande & Bates, 2000; MacDonald, 2003; Medicine, 2002; Walker et al., 2005). As a result, there has been great interest in developing ways to implement and adopt information technology in health service organisations (Bates & Gawande, 2003; Bush, 2004; Connecting for Health, 2004; Health & Services, 2001; Thompson & Brailer, 2004). To date, most studies focus on use of smartphones to bridge the knowledge translation gap for patients in order to assist with improved self-management (Johnston, Maxwell, Boyle, Maguire, & Alison, 2013; Juen, Cheng, & Schatz, 2015; Wang et al., 2014). Subsequently, a reasonable opportunity exists to use this technology to facilitate similar interventions for health professionals.

Technological interventions to address the issue of variable adherence to best practice recommendations in clinical care may overcome some established

barriers and present an exciting prospect in their relative novelty in health research and clinical practice. However, it is important for researchers to consider the complexity of this problem. There is a significant behavioural component at its core that may not be overcome solely through the use of technology. Therefore, future research endeavours should be multifaceted, capitalising on the novelty and convenience of technology whilst also attempting to change the engrained behaviours which contribute to this persistent problem in COPD management. A potential avenue for this is capitalising on the strong role-related professional identity reported by clinicians and using a multi-pronged approach tailored to both the individual and group level to create change in engrained learned behaviours.

Conclusion

This study identified several barriers to provision of best-practice care by health professionals including difficulties finding relevant information, lack of time to consult the guidelines, confusion around whose role it is to implement the latest guideline evidence and concerns over stepping on the toes of health professionals with more years of experience. Potential facilitators were also identified, including the increased use of Specialist Respiratory Nursing services and potential for technological innovations to improve accessibility and implementation of best-practice guidelines. Future studies should consider multifaceted interventions that take into account the barriers and facilitators highlighted in this study whilst addressing behavioural barriers which have made previous efforts unsuccessful.

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Chapter 9. Discussion

10.1 Significance and contribution to knowledge

This thesis presents a methodologically rigorous evidence base systematically assembled to inform the next phase of research, which can be used to improve provision of clinical care for people with COPD. These published studies [196-200] have consolidated the latest evidence to inform management of clinical care for various aspects of COPD treatment previously lacking in current practice. As such, these studies can and have been used to inform and update recommendations in best-practice COPD management guidelines, such as COPD-X [201]. Moreover, the qualitative study, prepared as a manuscript for journal submission, has produced new evidence identifying barriers and facilitators to provision of existing best-practice management of COPD in the hospital setting [202]. Based on these collective findings, an intervention has been developed for investigation as the next step needed to address the various barriers identified in each study and capitalise on newly identified strengths in COPD patient care (presented in Appendices 4 and 5). In addition, an intervention mapping process is currently in progress that provides a theory-based framework to underpin successful development and implementation of this intervention as a potential new model of care. Steps one to three of this six-step process are also described here in relation to how this newly developed intervention has been informed by both evidence produced within this thesis combined with theoretical approaches from the wider behavioural change discipline. Ensuing sections report the significance and contribution to knowledge for each of these individual studies and the subsequently developed intervention, which is ready for implementation and evaluation within clinical practice.

10.1.1 Cochrane and other systematic/literature reviews:

Five reviews of the literature were undertaken as part of this thesis. Each focused on a topic area of clinical priority relating to best-practice management of COPD. MEDLINE indexes over 800,000 new articles annually, translating to more than 2,000 per day [203]. The sheer volume and frequency within which new literature is produced makes it difficult for health professionals to keep abreast of the latest information among the heavy demands of their clinical load and associated responsibilities [201]. Literature reviews are a means by which health professionals can access expertly assembled syntheses of the latest evidence to answer their clinical questions [203, 204]. Systematic reviews in particular are

preferred for their more robust and reproducible approach to evidence synthesis [203, 204]. The Cochrane Collaboration has become synonymous with the preparation, maintenance and promotion of these systematic reviews to inform clinical and policy decision making in health. Cochrane reviews adhere to transparent pre-published protocols in order to minimise bias and improve the quality and reliability of results whilst also ensuring that the evidence does not become out of date [205].

In an attempt to update and fill literature gaps related to key areas of COPD management impacting clinical decision making in the acute setting, two Cochrane reviews (Chapters 4 and 5), two systematic reviews (Chapters 6 and 7) and one literature review (Chapter 8) have been produced. These studies have highlighted the paucity of evidence used to underpin routine interventions in current COPD management. Firstly, Chapter 4 presented results of an updated Cochrane review assessing efficacy of influenza vaccination for people with COPD [199]. The review found that while inactivated vaccine reduced the number of exacerbations, the evidence base was small and out-dated. It appeared that the acceptance of influenza vaccine as best-practice for management for COPD by the clinical community and its existing integration into best-practice guidelines had deterred researchers from investigating the area further. Despite the obvious satisfaction with evidence for influenza vaccine relating to clinical outcomes, there is a need to further explore economic outcomes which are highly relevant to influence policy change but under-evaluated in clinical trials. This review found only two studies investigating the impact of influenza vaccine on hospitalisations for AECOPD and one assessing cost-effectiveness in Thailand, hence, further enquiry into this area is warranted in order to best tailor recommendations to the current Australian context and underpin policies to support consistent adherence to this recommendation in practice. Despite the small body of relatively old evidence on the topic, influenza vaccine is a staple guideline recommendation and it has been shown that without prompt to clinicians to check, only 50% of people hospitalised with AECOPD have their vaccination status assessed [116, 163]. The conferral of potentially high benefit to patient outcomes and hospital utilisation outweighs the resources and time required to meet this recommendation in practice and as such effort should be made to bring this item of best practice to the forefront of the clinician's mind as they manage their patient.

In Chapter 5 the updated Cochrane review of oxygen therapy in the pre-hospital setting for AECOPD highlighted the importance of caution during administration [197]. Use of a titrated approach to oxygen administration significantly reduced mortality compared to usual high-flow administration. There was a real paucity of evidence suitable for inclusion in this review with only one study identified that met the criteria. While further randomised controlled trials would be ideal to confirm the findings, there is some concern about whether it would be ethical to re-evaluate this following the findings from this review. In particular, the process of randomising people to an intervention known to have higher mortality rates based on current evidence may not be considered appropriate, despite the fact that this approach is still used in current care (i.e., people with AECOPD are not always provided with titrated oxygen during transport to hospital). In order to ensure increased safety when administering oxygen therapy, it is important to more widely disseminate the findings of this review and bring it to the attention of frontline health professionals who are delivering it in their everyday practice. This could be achieved through multidisciplinary consultations with emergency services at both executive and frontline level as well as presentations. The latter was achieved when the results of this review were disseminated via an oral presentation at a national conference. This presentation received the award for best oral presentation in the Evidence Based Medicine special interest group (see link: <https://www.thoracic.org.au/researchawards/2016-award-winners>). Furthermore, the principle of titrated oxygen as a safety measure for people with COPD can be extrapolated from the pre-hospital setting to the hospital setting itself and is an opportune area to provide decision support in order to standardise care.

The published systematic review presented in Chapter 6 again identified a paucity of methodologically rigorous evidence evaluating the use of short acting bronchodilators for AECOPD in the hospital setting [198]. Previously published systematic reviews [92, 206] have identified that these relievers improve symptoms in people with stable COPD and this is now supported by findings from this review for AECOPD in the hospital setting. However, there remained a lack of standardisation for a minimum effective treatment protocol that should be used to produce a clinical benefit without conferring any extra risk of adverse events. The evidence available for review did not identify any additional benefits for participants receiving higher doses of short-acting β_2 -agonists than 2.5mg, or by

addition of ipratropium β 2-agonists, or based on type of delivery method. However, there was a small increase in cardiac adverse events for participants using higher doses of β 2-agonists. The findings of this review challenge the current clinical mindset that more is better, and this is certainly the feedback received upon dissemination of these results at both national and international conferences. If people with AECOPD continue to be prescribed superfluous short acting bronchodilators in the hospital setting there is a risk of unnecessarily high treatment costs attributed to medication waste and compounded by potentially prompting adverse events resulting in increased health service utilisation. This systematic review has identified an area of clinical practice that can be easily modified to improve patient outcomes and reduce health care costs and service utilisation. Therefore, it is important to ensure dissemination of the evidence beyond academic conferences potentially through policy and practice protocol change as well as engagement of relevant departments and clinicians. Without consolidation of this evidence, which has been done here for the first time, this information may not have been known and potentially unsafe clinical practices would continue in the hospital setting. The lack of evidence in this area is reflective of the majority of existing literature surrounding COPD management, which is based on research largely conducted in the community and then extrapolated into the hospital setting. This provides an interesting point for reflection, given that people with AECOPD are heavy users of the hospital system and acute management remains based on evidence produced in the community setting. Hence, re-evaluation of basic, standard practice for management in the hospital setting is warranted in order to underpin acute management guidelines.

An Australian government commissioned policy document published in Evidence Base (Chapter 7) highlighted the importance of considering the individual when determining the type of smoking cessation intervention to provide to patients admitted to hospital [196]. Given the link between smoking and progression of COPD, it is important to capitalise on the 'teachable moment' that hospitalisation presents [207]. However, the delivery of such interventions by health professionals in practice is variable and improvement in this area is important [208-210]. Hence, it is vital to improve dissemination of evidence such as that presented in Chapter 7 of this thesis in order to see real change in the clinical setting. Thus far translation has been attempted through the policy document itself, created not only to

systematically evaluate the existing literature to identify effective interventions that may be used in the hospital setting, but to do so in a format that can assist in wider dissemination of evidence to policymakers who are considering implementation of a smoking cessation program within hospitals. Its publication in the online policy repository of the Australia and New Zealand School of Government *Evidence Base*, was intended to extend the reach of this dissemination beyond the local setting. In addition, the results of this publication were also disseminated internationally through presentation at a conference.

The published commentary presented in Chapter 8 highlights a need for clinicians to stop and think when making decisions about prescription of pharmacotherapy for AECOPD, particularly the addition of muscarinic agents [211]. Multi-morbidity is common in older adults and prevalence of COPD increases with age [212, 213]. Subsequently, polypharmacy is prevalent in this population with these patients often prescribed unnecessary medications [214]. The commentary underlines the potential side effects of muscarinic agents and the many varied medications they are present in, calling for further investigation into the need for their use in COPD exacerbation management. Though the evidence base was limited, results presented in Chapter 6 indicated that addition of short acting muscarinic agents to β agonists conferred no additional benefit when treating AECOPD in the hospital setting [198]. Hence, it may be possible for clinicians to consider leaving this out of their treatment plan, reducing the burden of unnecessary and potentially harmful muscarinic use particularly among the elderly.

The topic areas covered by the literature reviews included in this thesis are fundamental aspects of routine best-practice care for COPD that potentially impact acute management of AECOPD or that should be undertaken or considered as part of hospital based exacerbation management. While there were some interesting findings with the potential to change practice, perhaps the most concerning to come from these syntheses of the literature is the lack of evidence specific to the hospital setting. This raises questions about the efficacy and safety of current inpatient management for COPD and calls for research to provide an evidence-based foundation for minimum standard practice. Producing the evidence to underpin clinical practice in the hospital setting is important not only to ensure that inpatient management of COPD translates to improved patient related outcomes, but also to optimise hospital utilisation, whilst minimising waste and

unnecessary treatment. Although identification of these gaps is alarming, it cannot be presumed that all patients are receiving poor clinical treatment within the hospital setting. Further intervention specific and large scale hospital data analyses are required to answer these needs. Another facet of the problem surrounding provision of evidence based care is the lack of adherence or uptake of disease specific guidelines in practice. Hence a barriers analysis was necessary to understand how evidence is being applied in the real-world setting with the view to informing future intervention design.

10.1.2 Qualitative study:

Despite the constantly developing evidence base for COPD management and the development of high quality CPGs to assist integration of this knowledge into practice, studies highlight that up to 40% of patients do not receive guideline concordant care [7, 11, 116, 154-157]. In order to address this issue, it was important to explore themes relating to barriers and facilitators of best-practice COPD care from the perspective of currently practicing health professionals in the field, with the view to also identify optimal approaches that can guide clinical care towards evidence-based COPD management.

A deductive thematic analysis guided by the Theoretical Domains Framework added methodological rigour to the qualitative process. This structure facilitated identification of many previously unknown or unexplored barriers and facilitators and confirmed others noted in existing literature [6, 116, 215]. The study highlighted barriers including difficulties finding relevant information, lack of time to consult the guidelines, confusion around whose role it is to implement the latest guideline evidence and concerns over “stepping on the toes of more senior staff”.

Further, results of this study indicated that a technological intervention (specifically involving a smartphone) to improve guideline concordant management of COPD would be well received by clinicians. To date, most studies focus on use of smartphones to bridge the knowledge translation gap for patients in order to assist with improved self-management [182, 183, 186]. Hence, a reasonable opportunity exists to use this readily available and cost-effective technology to facilitate similar interventions for health professionals [172-175]. This study also highlighted the complexity of issues surrounding provision of consistent best-practice COPD care. A significant behavioural component exists at its core that may not be overcome

solely through the use of technology. Moreover, COPD was associated with a lack of interest and innovation in recent times both on an individual level among health professionals and on a societal level.

Subsequently, the outcomes of this qualitative study, in addition to synthesis of available literature, have been used to underpin development of a multifaceted intervention. This is intended to capitalise on the novelty and convenience of technology, whilst also attempting to change the engrained behaviours that contribute to these persistent problems in COPD management.

10.1.3 Intervention development

There are a number of reasons why previous interventions for improving guideline adherence underperform. They, like other complex health interventions, often lack careful planning and theoretical underpinning [216] or start by providing a solution to the problem without proven evaluating practical implementation aspects (pilot work), applicability (feasibility studies), appropriate evidence-based underpinning (systematic reviews) or planning (approach already shown to be ineffective in the global literature) [217, 218]. While most theories of behavioural change can provide some guidance in intervention development, they often do not provide intervention developers with the tools to operationalise theory into intervention components [19-21]. There is an abundance of psychological theories available, yet trying to determine which theory (or preferably theories) to use can cause confusion or implementation of inappropriate approaches.

Rather than basing the intervention on a behavioural change theory, intervention designers should choose to use intervention development frameworks such as the Intervention Mapping (IM) Approach [219, 220] or the Behavioural Change Wheel (BCW) [221] to guide intervention development. While both approaches differ (IM is multi-theoretical, whereas BCW relies on the capability, opportunity, motivation and behaviour (COM-B) model/Theoretical Domains Framework [222]), they share a similar method in guiding the development of an intervention. Both frameworks provide a step-by-step approach that guides intervention developers from needs assessment to implementation and process evaluation, and both frameworks provide designers with a large number of theory and evidence-based behavioural change methods to choose from. In IM, these methods can be found in chapter three of *Planning health promotion programs: an Intervention Mapping approach*

[219] and the BCW refers to the behavioural change taxonomy as developed by Michie and colleagues [223].

Designing a health intervention or resource is an iterative process, which often involves adjusting, tweaking and improving components on which the intervention relies, both during the design process and during or after the outcome and process evaluation. This is much similar to practices in fields such as engineering in which there is continuous quality improvement [224].

Results presented in this thesis were used to assist in the development of resources (using the IM approach; see Appendices 4 and 5) based on best-practice guidelines to improve guideline concordant management of inpatients with COPD. These will be used as intervention materials in future research studies (see Section 10.3) with a view of integration into everyday clinical practice.

IM is an intervention development framework that guides construction of a health promotion program/product in six-steps [219, 225]:

1. **Needs assessment:** mapping of the problem behaviour and its related determinants to create a full understanding of the problem. The result is an extensive logic model of the problem and all the areas of influence.
2. **Matrices of change:** transforming the logic model of the problem into specific change objectives separated per actor or stakeholder. The change objectives allow for a detailed description of all elements that should be addressed to achieve the desired change.
3. **Theory-based methods and practical strategies:** selecting appropriate theories of change and evidence-based practical strategies derived from the scientific literature.
4. **Develop program plan:** operationalise the results from step 1-3, via extensive design documents, and turn them into the intervention products. Product trialing and consultation with stakeholders.
5. **Adoption and implementation plan:** develop an adoption and implementation plan to ensure that the intervention gets operationalised and adopted appropriately.

6. **Evaluation plan:** develop evaluation plan, including outcome evaluation via the proposed study as well as impact and process evaluation to ensure adaptation for real-world use.

Steps 1 to 4 are described here whilst plans for steps 5 and 6 are explained in section 10.3.

The needs assessment (Step 1) was informed by the barriers and facilitators identified in the qualitative study presented in Chapter 8 and additional consultation with key stakeholders. This was simplified into a logic model of the problem, which identified personal determinants of the behaviour leading to variable uptake and adherence to COPD guidelines in practice. These determinants are knowledge, attitude, self-efficacy, skills, and intention. The needs assessment also identified external determinants of the problem (e.g. patient and organisational factors). However, these were thought to be outside the scope of the current project and were not carried forward into Step 2. This logic model was then translated into 46 specific change objectives (matrices of change; Step 2), which were then matched to evidence-based techniques used in general behavioural change research [223]. These theory based techniques were then translated into practical applications that could be used to form intervention resources (Step 4).

The work from Steps 1-3 culminated in the development of the following intervention resources:

COPD order set (Appendix 4)

An order set embedded within the South Australian electronic medical record (EMR) was developed as part of the intervention package. An order set is a group of common orders collated into a single location for a single clinical situation, process or condition (e.g., AECOPD) [226-229]. The order set functionality was identified as a potentially useful resource for this intervention package for its ability to possibly overcome barriers to delivery of best practice identified in Chapter 9, including lack of time, by integration into daily workflow [226-233]. Further, this functionality would allow integration of guideline recommendations and has the potential to improve standardisation of care [60, 227, 229, 231-235]. The ability to easily keep up with guideline updates by amending recommendations and orders via an electronic medium compared to a paper-based medium was also a

desirable feature when aiming to design an intervention that has longevity [232, 236]. These functions have been identified in the literature as features of clinical decision support systems which result in successful outcomes [237].

Hence, the order set (Appendix 4) is a compilation of commonly used orders for the in-hospital management of COPD from pathology and imaging orders through to appropriate medication and dosing orders, whilst also encouraging referral to relevant multi-disciplinary clinicians. This component of the intervention package aimed to overcome barriers identified in Chapter 8 of this thesis [202], including health professionals reporting a lack of time and that access to computers facilitated use of checklists, which was believed to improve provision of best-practice care. It was developed based on the current Australian best-practice guideline [18] and required 18 months of consultation with key stakeholders. Given that the order set is a living, breathing part of clinical care and has the potential to greatly impact patient care, the consultation and development process was extensive. It encompassed not only several rounds of local consultation with relevant clinicians from the Central Adelaide region but also agreement and buy-in from other Local Health Networks in the North and South. This order set was assigned its own adoption manager to ensure that the clinicians' and researchers' suggestions were within the system's capabilities and built accordingly. Every step was subject to rigorous front and back end testing and approvals by executives and governing bodies relating to medication safety. The experience of developing an order set was resource intensive, iterative in nature and will require ongoing commitment to maintenance not unlike the experience of others who have undertaken similar feats [238]. It was further complicated by the fact that the state-wide EMR was newly commissioned and beginning roll out at the time, meaning that this process was subject to the teething problems being worked out system wide including a twelve-month activity freeze, which halted all progress. It is an illustrative example of the types of challenges that are faced in real-world clinical practice and translating research in the eHealth era. With this in mind, it was a considerable achievement to have this product designed and functioning in everyday practice during the time of this thesis and is evidence that this body of work has contributed to direct translation informing improvements for clinical practice.

To improve patient safety and avoid wasteful use of medication, evidence from Chapter 6 of this thesis [198] was used to justify the pre-specification of a low dose of short acting bronchodilator administered through metered dose inhaler as the preferred treatment option within the order set. Other safety precautions embedded into the order set were the use of warnings and mandatory fields. An example of this is the oxygen therapy order. Following the findings presented in Chapter 5 [197] regarding the potential for increased mortality with use of high-flow oxygen therapy, discussion in clinical meetings revealed that whilst this is generally well done by respiratory specialists within the hospital, it had been observed that there were areas of the hospital admitting AECOPD patients that are not as compliant. Hence, flow rate was made a mandatory field within the order set. This means that if the clinician wishes to complete their order set, they must specify the flow rate with a saturation guideline of 88-92% via a titrated approach provided. Any prescription outside of these parameters would require explicit reasoning and documentation. Text was placed within this order to explain the reason for caution in prescribing oxygen to people with AECOPD. The choice to use an electronic medical record integrated order set as part of the intervention package is underpinned by the theory based behavioural change techniques of facilitation, cues, nudging and repeated exposure that were identified through the IM process and balanced by lessons learned from other attempts in AECOPD documented in the literature [190, 191, 239]. While the order set is bound by some potentially limiting factors identified in the literature, namely the rigidity of the system, care was taken to balance other potential impediments to success such as alert fatigue [240]. This was achieved by restricting the number of mandatory fields to those most critical to patient safety (i.e. oxygen therapy titration).

Flip-chart embedded with augmented reality technology (Appendix 5)

The novel COPD inpatient management flip-chart, incorporates results from the systematic reviews produced in this thesis with the latest evidence from national COPD guidelines [18] and locally developed algorithms for acute management of COPD. The flip-chart may be mounted at the patient bedside, in clinic rooms or kept at the clinicians' workstation for reference. Its pages cover all aspects of inpatient management from admission through to discharge with a focus on evidence-based recommendations that are often overlooked, for example identifying and addressing comorbid anxiety and depression. Given that use of

smartphone technology was identified to be a facilitator for delivering best-practice care in the qualitative study (Chapter 9) [202], certain pages of the flip-chart are embedded with novel augmented reality (AR) technology.

AR delivered via a free smartphone application, superimposes virtual components (e.g. audio-visual content) over real-world objects (e.g. the paper-based flip-chart), so that they appear to coexist [241, 242]. A popular example is the recent Pokémon Go [243] phenomenon where local landmarks and locations were overlayed with AR. This meant that using a free app 'players' could scan the landmark and on their smartphone the Pokémon character would appear to be playing and ready for capture in that location (Figure 2). AR is now widely used for educational purposes and no longer requires any more specialised equipment than a smartphone to use [241].



Figure 2: Pokémon Go game played on a smartphone using augmented reality [244].

The increasing popularity of AR as a clinical education tool is due to its ability for personalisation, placing the viewer at the centre of the knowledge process, thus increasing their motivation to learn. AR can also address issues of poor health literacy [245] among patients with delivery of easy to digest video, audio and digital information. It also improves geographic reach and accessibility of health information and allows for real-time updates of content as new information

becomes available, providing a cost-effective means to disseminate information to clinicians and patients.

Moreover, AR is a new technology that is gaining momentum and investment. In particular, the augmented reality market was valued at USD11.14 billion in 2018 and is projected to reach USD60.55 billion by 2023 [246]. This suggests that augmented reality technology is likely to soon become part of our daily lives. Thus, application of this technology into emerging health interventions in the context of COPD may pave the way for respiratory patients to be early adopters of a technology that can improve the way we communicate.

In order to ensure that the evidence is at the clinicians' fingertips AR technology was used to provide direct links from the flip-chart recommendations to the relevant evidence in the national guidelines. In addition, an instructional video was developed with clinical experts to demonstrate the appropriate setup of a non-invasive ventilation circuit and appropriate mask fit techniques, which is overlaid on the third page of the flip-chart. Finally, in collaboration with the Lung Foundation of Australia (LFA), instructional videos for correct inhaler technique were overlaid on the last page of the flip-chart. The latter was a particularly interesting opportunity as studies suggest that anywhere between 4% to 94% of people with asthma or COPD use their inhalers incorrectly [247]. Furthermore, a study specifically in hospitalised people with COPD identified that critical errors in inhaler technique were made by 60% of participants [248]. Only 60% of these individuals had received education from a health professional regarding appropriate technique, just over half having had it in the preceding six months [248]. This was seen to be a good opportunity to take advantage of the AR functionality to potentially improve provision of inhaler technique education at the bedside.

The LFA were approached for a collaboration which would allow use of their existing suite of inhaler technique videos covering all types of inhaler devices available for the management of COPD. These preliminary discussions lead to collaboration on a trial of the technology which was subsequently used on the last page of the flip-chart presented in this thesis (see Appendix 4) and disseminated nationally by the LFA as part of their clinical resource package to support best-practice. The benefits of this were two-fold for the intervention. It reduced the cost by working with an established suite of resources and was instantly recognisable

by clinicians having been a regularly used resource in its purely paper-based form for years prior to the addition of AR. The LFA have since decided to continue to incorporate the augmented reality content as part of this resource on an ongoing basis, owing to the excellent user feedback they have received on it and have very recently updated the chart to reflect the latest evidence updates and pharmaceutical developments [249]. The last page of the flip-chart is currently undergoing an update to reflect this change. Informed by the IM approach, the use of a paper-based flip-chart format in addition to the previously described order set is underpinned by the theory based behavioural change techniques of facilitation and repeated exposure.

The development of this flipchart and associated AR content spanned a twelve month period. It involved several consultations with multidisciplinary teams involved in the management of people with COPD in the major hospitals in the Central Adelaide region. The primary benefit of engagement of the end user at this stage was the ability to tailor AR content to suit their needs. Furthermore, it was crucial in providing the local adaptation to the national guideline recommendations which is often lacking upon dissemination. Volunteer health professionals were also engaged in filming some of the video content used as part of the AR, providing a sense of ownership over the end product, with the view to ultimately improving engagement with the resource. Further, other clinicians may find interacting with videos featuring their peers, novel and engaging.

Education and user support program

Through the IM process it was identified that an education and user support program would be needed to run alongside the order set and flip-chart in order to address the problem of variable provision of best-practice management of AECOPD in practice. The education and user support program were completely underpinned by theory based behavioural change techniques to target determinants of variable guideline use. The result is a multi-session program that is both didactic and interactive in nature. Planned content includes workshops to improve clinicians' knowledge, attitudes, self-efficacy, motivation and skills around benefits of consistent provision of best-practice care and use of intervention resources. The content is underpinned by theory based behavioural change techniques including, but not limited to, active learning, framing, individualisation,

guided practice, modelling and direct experience. An example of a planned session is a guided workshop where clinicians are stepped through use of resources by a respected member of their clinical team. This clinician will be one of several early adopters who will be engaged by the study team as 'champions' to lead by example in the field and present a behaviour model for their colleagues. Once again, representatives from the end user group were engaged at this stage of the intervention development. Several respiratory specialists, nurses and medical advanced trainees were part of the IM process workshopping sessions to provide clinical perspective to the construct of the program design.

The IM Framework provided a comprehensive approach for development of a rigorous theory and evidence-based intervention, which specifically targets behaviours that have been historically difficult to change around uptake and adherence to COPD guidelines in the hospital setting. The result is a technology-based intervention package designed to be relevant and feasible in current clinical practice supplemented with an education and user support program. This intervention is intended to be assessed for feasibility prior to being rolled-out in practice and evaluated as part of a post-graduate fellowship application.

10.2 Limitations and problems encountered

10.2.1 Systematic reviews, Cochrane meta-analyses and policy publications:

For the Cochrane meta-analyses [197, 199], literature reviews [198, 200] and policy document [196] there is a possibility that potentially relevant information will not have been included. Although all attempts were made to ensure that the search strategies were as comprehensive as possible with inclusion of grey literature via screening of bibliographies for included studies, review of online clinical trial registries and author contact, there is still a possibility that relevant citations were missed.

Moreover, for the Cochrane reviews in particular, only randomised controlled studies meeting the pre-specified and pre-published eligibility criteria were included. This means that many potentially relevant, though lower quality, studies were excluded in order to maximise the quality of the review and level of evidence being produced.

10.2.2 Qualitative study:

The qualitative study undertaken as part of this thesis [202] encountered several limitations described in detail in Chapter 9. In summary, there is a possibility that the presence of a co-investigator, known by the participants to be a respiratory nurse, may have influenced participant responses to interview questions. However, after only four interviews this co-investigator abstained from the interview process, and, upon review of the transcripts, there appeared to be minimal influence on participant responses. In addition, generalisability of results are potentially limited. Participants were medical officers and nurses sampled from two large teaching hospitals in the Central Adelaide Local Health Network in South Australia. Hospital-based clinicians were the target population as this study aimed to inform an intervention to improve guideline adherence in the acute setting, though interviewing a more diverse group of multidisciplinary clinicians may have been beneficial. However, despite these limitations the methodology used and data obtained from this study still provide useful information that can direct patient care and future investigations in addition to providing an evidence base for future, similar research projects.

An additional limitation relates to the intervention developed (section 10.1.3). While the qualitative study identified data relating to patient and system level barriers and facilitators to best practice care, these domains were deemed to be outside the scope of possibility for a single intervention. Given the available resources and existing resources, targeting the health professionals in the acute setting was most feasible in the short term.

10.3 Future directions

Future research is planned as a continuation of the findings and outcomes of this thesis. This will be, in the first instance, an iterative co-design process using a feasibility study for the implementation of the complex package intervention (e.g. order set, flipchart, user support program) described in 10.1.3. This study will aim to identify and address potential problems with methodology and implementation strategy prior to applying for funding to conduct a rigorous multi-centre randomised controlled clinical trial to evaluate intervention effectiveness.

10.3.1 Evaluation of practicality using qualitative research:

Version one of the intervention content has been developed (see 10.1.3) and will have its practicality, usability and feasibility assessed prior to being included in a post-doctoral fellowship application. The research in this application will ultimately aim to evaluate its effectiveness in improving provision of best-practice management for AECOPD. As a first step, an iterative co-design process will be undertaken whereby the intervention package will be demonstrated to four interview participants (health professionals) who will be encouraged to interact with the resources. Following their feedback, the resources will be improved before being shown to the next group of interview participants until by the end of this iterative process, an improved version of the order set, flip-chart and education program are ready for testing in a feasibility study. One-on-one interview participants will be health professionals from multiple disciplines including medical professionals (senior and junior), nurses and pharmacists. These participant groups were chosen to gain a good representation of end users who will ultimately be expected to interact with the intervention when it is implemented into practice.

10.3.2 Evaluation of feasibility:

According to the Medical Research Council, assessing feasibility of a complex intervention study prior to roll out of the full scale evaluation is important [250]. As such, a feasibility study is planned in order to avoid issues with acceptability, recruitment and intervention delivery, which often undermine the success of full scale studies [251]. This study will aim to 1) estimate recruitment and retention rate, 2) assess feasibility and acceptability of the intervention, and 3) assess feasibility and acceptability of the data collection methods. The latter is especially important given that the order set is embedded within the electronic medical record, which is constantly undergoing refinement and accessing data from this source may present some process issues or delays.

The findings presented in this thesis have provided an evidence base that has acted as the foundation for the next phase of research essential to improve provision of clinical care for people with COPD. The work has underpinned the development of a theory based multi-component intervention and the clinical

practice recommendations within it. Within this, there have already been important changes made to current clinical practice and education. First with the roll-out of an evidence-based order set embedded into the local EMR and integrated into daily workflow. Then with the national dissemination of the LFA inhaler wallchart which augments an existing paper-based resource with audio-visual content to facilitate improved education around correct inhaler technique. Moreover, the feasibility and evaluation of this intervention is being planned, with the view to conducting a full scale randomised controlled trial in the future. In addition, an acknowledgement as a contributor to the national COPD-X guidelines has just been received and published in the latest document update [11].

Chapter 10. Conclusions

The literature reviews presented in this thesis identified that key areas of best-practice management for COPD in the hospital setting is currently underpinned by limited and outdated research. Despite this there are some recommendations that can be made from the available literature. In order to reduce exacerbations vaccination status should be checked and where lacking, inactivated influenza vaccine should be recommended for people with COPD. In addition, though underpinned by only a single study with important implications, oxygen therapy should be delivered in a titrated approach to those being transported to hospital for treatment of AECOPD as there is increased risk of mortality when using a high-flow rate.

In addition, current prescription and administration of mainline pharmacotherapy, namely short acting bronchodilators, may be excessive. The available evidence indicates a low dose is sufficient to relieve symptoms without conferring additional risk of cardiac adverse events. Given its prominence as the single most important and modifiable factor in COPD disease progression, provision of smoking cessation advice is paramount. It is important for clinicians to capitalise on the 'teachable moment' afforded by the enforced abstinence of a hospital admission. Evidence presented as part of this thesis indicates that this approach should be tailored to the individual needs and circumstances of the patient using an appropriate combination of behavioural and pharmacotherapeutic treatments for the best chances at a successful quit attempt.

The evidence produced as part of this thesis not only contributed to underpinning real-world clinical practice recommendations, but through a qualitative study identified perceived barriers and facilitators to provision of best-practice care by health professionals to people with COPD. Some key barriers included difficulties finding relevant information, lack of time to consult the guidelines, confusion around whose role it is to implement the latest guideline evidence and reluctance to challenge the decision-making of more experienced clinicians. These, along with facilitators identified through this research, such as use of smartphone technology, have provided the basis for the development of a theory based intervention which aims to improve the longstanding problem of variable adherence to best-practice guidelines.

The developed resources, including a decision support tool (order set) embedded within the EMR and a paper-based flip-chart embedded with AR technology, along with the tailored and theoretically underpinned education and user support program, will be further refined through an iterative co-design process. Following refinement feasibility of the intervention will be tested before the intervention is fully rolled-out in practice and its effectiveness evaluated as part of a future planned post-doctoral fellowship application.

Studies like these, and the real-world application and dissemination of results through mechanisms like peer reviewed publications in influential journals, EMR decision support and/ or AR will help to reduce the significant burden of cost and suffering from diseases such as COPD.

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Appendices

Appendix 1 Evidence for smoking Quitlines (Publication)

Appendix 2 COPD EPAS Order Set

Appendix 3 COPD Flip Chart

Appendix 4 Ethics approval letter: Qualitative study

Appendix 5 Ethics approval letter: Intervention development process

Appendix 1 Evidence for smoking Quitlines (Publication undertaken during PhD period but not part of the assessed thesis demonstrating contribution to policy)

Evidence Check

Evidence for smoking quitlines

An **Evidence Check** rapid review brokered by the Sax Institute for Cancer Council Victoria.
April 2019.

This report was prepared by:

Kristin Carson-Chahhoud, Zoe Kopsaftis, Kelsey Sharrad, Adrian Esterman

April 2019.

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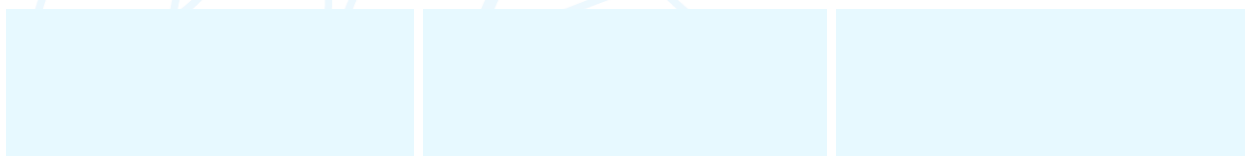
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Evidence for smoking quitlines

An **Evidence Check** rapid review brokered by the Sax Institute for Cancer Council Victoria
April 2019

This report was prepared by Kristin Carson-Chahhoud, Zoe Kopsaftis, Kelsey Sharrad and Adrian Esterman



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Abbreviations

ACT	Acceptance and Commitment Therapy
AI/AN	American Indian/Alaskan Native
ASQ	Asian Smokers Quitline
ATC	Alcohol Tobacco Counselling
CA	Continuous Abstinence
CALD	Culturally And Linguistically Diverse
CBT	Cognitive Behavioural Therapy
CDC	Centre for Disease Control
CI	Confidence Interval
CO	Carbon Monoxide
df	Degrees of Freedom
ENDS	Electronic Nicotine Delivery Systems
GPs	General Practitioners
ITT	Intent-to-treat
MAC	Medication Adherence Counselling
MI	Motivational Interviewing
MM	Massed Mailings
n	Number
N/A	Not applicable
NAQC	North American Quitline Consortium
NHMRC	National Health and Medical Research Council
NC SCT	National Centre for Smoking Cessation and Training
NIH	National Institute of Health
NRT	Nicotine Replacement Therapy
NYSSQ	New York State Smokers Quitline
NZ	New Zealand
OR	Odds Ratio
PORTSSS	Proactive Or Reactive Telephone Smoking ceSsation Support
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses

QFL	Quit For Life
QoL	Quality of Life
RCT	Randomised Controlled Trial
RM	Repeated Mailings
RR	Risk Ratio
SC	Standard Care
SD	Standard Deviation
SH	Self-help Group
SMS	Short Messaging Service
SNTQ	Swedish National Tobacco Quitline
TEQ	Technology Enhanced Quitline
TOC	Tobacco Only Counselling
UK	United Kingdom
US	United States
Vs	Versus
WHO	World Health Organization

1 Executive summary

Background and review questions

Quitlines are telephone-based services providing behavioural support for people considering or seeking to stop smoking, and advice to family, friends and professionals seeking to help others to stop smoking. In Australia, each state and territory government funds a Quitline. There is no central body that oversees quitlines in Australia. On the contrary, six different organisations deliver the eight different Quitline™ services around the country.

Although there are World Health Organization (WHO) guidelines on delivery of a quitline for smoking cessation, there are no national minimum standards for Quitline™ in Australia. This means the clinical offerings (types of counselling offered), data collection and reporting, functionalities (i.e. technological capabilities), clinical supervision processes, and evaluation differ from jurisdiction to jurisdiction.

To ensure that Quitline™ provides consistent, high quality, effective behavioural support, this rapid review of evidence commissioned by the Cancer Council Victoria provides evidence that can be used to underpin development of evidence-based Quitline™ national minimum standards to implement across Australia. Two questions have been formulated around which the evidence has been synthesised:

Question 1: What are the key components of dedicated telephone counselling services (quitlines) that have been shown to be effective for smoking cessation?

Question 2: What are the enablers of, or barriers to, the delivery of effective service components identified in Question 1?

Summary of methods:

The search included studies from 2009 onwards in English, and undertaken in Australia, New Zealand (NZ), the United Kingdom (UK), the United States (US) and Europe. Databases searched included the Cochrane Database of Systematic Reviews, PubMed/Medline, Embase and PsycInfo as well as multiple sources of grey literature. Due to the expectation of wide variability across studies, no attempt was made to undertake meta-analysis. Instead a narrative synthesis of evidence has been provided. The National Health and Medical Research Council (NHMRC) Level of Evidence table was used to appraise the quality of evidence found.

Key findings:

A total of 51 records were identified for inclusion in the narrative synthesis of evidence in this rapid review. An additional 31 records with relevant information pertaining to the key components under review were identified from grey literature. These did not meet the criteria for inclusion in the primary evidence synthesis. They have been discussed, however, within the detailed analysis of evidence (section 8 below). Level 1 evidence was available to support some key component recommendations, and this was supplemented by lower quality evidence for other areas as detailed below. Conflicting studies were common and have been discussed in detail within the analysis of evidence. Recommendations need to be assessed with consideration of limitations and contextual factors associated with each individual research study, as detailed in the synthesis of relevant papers, quality assessment and analysis of evidence below.

Question 1: Key components of quitlines shown to be effective:

Counselling competencies

Assessment of the fidelity of counselling compared to treatment protocols is reportedly undertaken as part of standard practice across many quitline services. However, studies evaluating impact of specific counselling competencies and levels of adherence to treatment protocols were lacking. A minimum set of qualifications and experience in a related discipline is typically required for counsellors. In addition, specific quitline counselling skills-based training is required with ongoing training and feedback provided from within most organisations.

Behavioural change counselling approaches

Cognitive behavioural therapy (CBT) is the standard behavioural change technique used to underpin quitline counselling. The addition of other theoretical models, including acceptance and commitment therapy (ACT)¹ and motivational interviewing (MI)^{2, 3} have demonstrated the potential for increased quitting benefits. However, other techniques, such as the addition of gain-framed messaging, have not shown benefits in long-term quitting outcomes.^{4, 5}

Quality assessment of service and counsellors

Among studies reporting participant satisfaction with the service and/or counsellors, satisfaction is rated as high and the service reported to be helpful. Assessment is by self-report among follow-up participants, which typically only represents half of the initial enrolling population. Therefore, these responses need to be considered in the context of the larger study population of non-responders, where non-responders are typically relapsed smokers. Of the two included studies reporting on assessment of fidelity of counselling, neither reported results related to this assessment.

Counsellor or participant-initiated follow-up calls

There is strong Level 1 evidence to support the provision of quitline initiated follow-up counselling support compared to client-initiated follow-up calls.^{6, 7}

Among five individual studies evaluating quitline-initiated or client-initiated counselling sessions, four studies showed no evidence of effect on quit smoking outcomes by final follow-up. The one study showing a significant benefit on quitting outcomes by 12 months⁸ was undertaken in a military population with differing levels of nicotine replacement therapy (NRT) provision between the intervention and control groups (four- to eight-week supply compared to two-week supply). The potential additive benefit of more NRT was not evaluated. Moreover, the quitline-initiated group received substantially more counselling calls at all follow-up periods, with high retention rates across the six counselling sessions. However, another study⁹⁻¹¹ did evaluate the additive benefit of a six-week supply of free NRT, identifying no evidence of any effect above that of standard counselling.

Counselling protocols

Level 1 evidence identified that quitline-initiated first calls increased quit attempts (51 studies), with effect estimates being slightly larger if more calls were offered and in trials specifically targeting smokers motivated to try to quit.⁶ Another systematic review identified that quitline-initiated first calls are less effective than client-initiated first calls, likely related to the initial level of motivation to quit and readiness to quit.⁷ However, this evidence only comes from one included study within the systematic review, therefore should be interpreted with caution.⁷

Evidence from lower quality studies around the impact of different counselling protocols was also mixed. Some studies showed no additive benefit for quitline-initiated versus client-initiated follow-up counselling¹¹

or the use of NRT^{11, 12} compared to standard counselling without NRT. Others, however, did show that quitline-initiated follow-up counselling⁸ and the addition of pharmacotherapy^{13, 14} do have greater efficacy on quitting outcomes. No dose-response correlation was observed for the duration of NRT provision, indicating that giving quitline callers higher quantities of pharmacotherapy like NRT above that of a starter-pack does not result in better smoking cessation outcomes.¹⁵⁻¹⁷ A dose response was observed between the number of counselling sessions and likelihood of successful quitting outcomes regardless of NRT provision, with completion of more counselling sessions more likely to result in successful quitting outcomes.¹⁴

Frequency and length of calls/counselling sessions

While there is Level 1 evidence to support provision of quitline-initiated follow-up calls, there is mixed evidence about the optimal number of quitline calls/counselling sessions (with most using more than two calls) and little discussion of optimal length of calls to be provided.⁶ Some studies suggest no evidence of significant increased benefit with an increased number of quitline calls^{18, 19}, while others report that a higher number of calls is significantly associated with better quitting outcomes.²⁰ For studies where there is an interaction between frequency of calls and quitting outcomes, the association is likely bi-directional, meaning better quit smoking outcomes lead to better treatment compliance and vice versa. This is because quitline participants who relapse and return to smoking are more likely to drop out of the counselling service. A paucity of evidence was available to enable any recommendation about the length of calls.

Hours of operation:

No studies evaluated the impact of differing or extended operating hours for quitline services. Therefore, it was not possible to make any recommendations about this key component of quitline counselling service provision.

Question 2: Enablers of or barriers to delivery of effective service components identified in Question 1

- The most important factor that determined compliance with the full quitline program of five calls was the provision of NRT. Smokers who received NRT were more likely to be adherent to the counselling program compared to those who did not receive NRT. Face-to-face skills-based training of counsellors was more effective than online training at improving smoking cessation outcomes among clients who quit smoking, through increased compliance to best-practice protocols.

According to multiple studies, smokers with lower levels of adherence to the quitline service are typically:

- Females
- Younger people
- Those with only high school education (as opposed to less or more education than this)
- Those with children at home
- Those who smoked less than 20 cigarettes a day
- Those living with a smoker
- Those with a failed quit attempt in the past.

Facilitators and barriers were often intertwined and related across services. For example, while access to resources/budgets was identified as a barrier in some organisations resulting in poor uptake of recommended guidelines, it was identified as an enabler among organisations which did have good uptake of guidelines. Key inter-related barriers and enablers included:

- State quitline budgets to facilitate uptake of best practice recommendations

- Technical capacity and capabilities of quitline service providers (particularly in relation to technical capacity and capability to implement recommendations related to technology in new or innovative ways)
- Priorities of individual state funders/organisation directors (particularly in relation to reach of target populations)

Recommendations

Inconsistent data was identified in this rapid review for most of the key components to underpin Quitline™ services. Certainly, this rapid review did not identify any strong evidence to deviate from the current Victorian Quitline™ protocol consisting of two pre-quitline quitline-initiated follow-up calls, plus four post-quitline calls (based on recommendations in the seminal paper by Zhu and Pierce²¹), underpinned by CBT using trained counsellors.

Based on the available evidence, authors of this review recommend that state/territory and federal policy makers as well as senior managers of Quitlines™ consider implementing the following as a national set of minimum standards:

- A generic approach to counselling with a standardised core protocol can be considered for the majority of tobacco users, as extensive tailoring of services based on characteristics of individual participants contacting the Quitline™ do not appear to be associated with successful quitting. However, there may be merit in considering a tailored approach for some populations of Quitline™ callers, such as young callers, pregnant women, culturally and linguistically diverse (CALD) populations, Indigenous populations and those with mental health conditions
- Providing a two-week starter pack of free NRT to eligible Quitline callers is likely to increase smoking cessation outcomes
- All counsellors should be trained health professionals
- Counselling sessions should be monitored intermittently to measure compliance with best practice protocols, enabling identification of additional training requirements
- Face-to-face booster training should be provided to counsellors to supplement online training, and easy access provided to treatment manuals within each service, to reinforce compliance with best-practice guidelines
- The most commonly used behavioural approach is CBT, however, ACT and MI have also shown benefits in smoking cessation outcomes. Therefore, consultation with an appropriate organisation could be made for advice on the best approach or combination of approaches, including the optimal number of sessions for the specific technique/s taken
- In the situation where a service needs to be scaled down due to limited resources, the focus should be on providing counselling to clients who initiate the first quitline contact, or to those known to be highly motivated to make a quit attempt, rather than quitline counsellors making the initial call to smokers who are less motivated to quit.

As detailed in the report below, these recommendations should be considered as a package approach to increase the likelihood of successful increases in smoking abstinence among Quitline™ callers. The authors also strongly suggest that key stakeholders are engaged to help to build the evidence base that is currently lacking for several key components including: the ideal number and duration of contacts, addition of ACT and/or MI as an adjunct to CBT, ideal hours of operation and minimum counselling competencies required.

2 Background and introduction

Cigarette smoking is a major risk factor for the development of many diseases, including cancers, cardiovascular and respiratory diseases, stroke, peripheral vascular disease, abdominal aortic aneurysm, type 2 diabetes, peptic ulcers, macular degeneration and infertility²² Many well-conducted epidemiological studies over the past 40 years have established a clear link between tobacco smoking and many different types of cancer. These include cancers of the lung, oral cavity, pharynx, oesophagus, stomach, bowel, liver, pancreas, nasal cavity and paranasal sinuses, larynx, uterine cervix, ovary, urinary bladder, kidney, ureter and bone marrow (myeloid leukaemia).²³

Approximately 12% of Australians aged 14 years and over are currently daily smokers²⁴, however, by worldwide standards, this smoking rate is comparatively low. For example, current estimates for smoking prevalence in adults are: 15% in the US²⁵, 15% in the UK²⁶ and 16% in NZ²⁷, 26% in the Netherlands²⁸, 34% in Japan²⁸, 36% in France²⁹, 37% in Greece²⁹ and 59% in the Russian Federation.³⁰

Smoking rates in Australia have declined from approximately 36% in 1977, to 26% in 1998 and 14% in 2014–15.³¹ This decline to our current smoking rate is likely the result of tobacco control activities undertaken by federal, state and territory governments, and non-governmental organisations such as the Cancer Council of Australia, the Australian Council on Smoking and Health, and Action on Smoking and Health. Activities have included mass media quit smoking campaigns, legislation to ban smoking in public areas, plain packaging legislation, and increases in the tobacco excise.³¹ In particular, the Australian Government established and funded the National Tobacco Campaign in 1997, which is ongoing. However, the trend in decreasing smoking rates has plateaued recently, with daily smoking prevalence remaining relatively stable between 2013 (12.8%) and 2016 (12.2%).³² Furthermore, smoking contributes to 9% of the national Australian disease burden and is the single most important reversible risk factor for premature death, putting two million smokers at risk unless they quit.^{33, 34} Smoking is also a major contributor to health disparity. Smoking prevalence remains as high as 45% (2014–15) in the Indigenous population and prevalence has actually increased by 7% between 2013 and 2016 in those with mental health conditions.³⁵ This pattern is also apparent outside the Australian context with smoking prevalence at 40–45% in Indigenous New Zealanders and Americans and up to 30% of all cigarettes smoked by adult Americans consumed by people with a mental health condition.^{36–38} Hence, a redoubling of efforts to further reduce smoking rates is warranted.

Internationally, several different interventions have been used to help people quit smoking. These include brief advice from General Practitioners (GPs), self-help materials, medications such as nicotine replacement therapy (NRT), bupropion hydrochloride and varenicline tartrate³⁹, as well as psychological therapies including Cognitive Behavioural Therapy (CBT) and Acceptance and Commitment Therapy (ACT).⁴⁰ Recent evidence suggests that a combination of these strategies is most effective. Supplementation of pharmacotherapy with behavioural therapy improves the odds of a successful quit attempt three-fold.⁴¹ There is a wide spectrum of behavioural interventions available to support quit attempts including: brief advice from a health professional, intensive multi-session interventions delivered either in person or via telephone; and technology-based programs. In hospitalised patients, intensive behavioural therapy programs have been identified as effective for smoking cessation.⁴²

Many countries around the world also make use of telephone helplines to assist smokers to quit (quitlines). This is because quitlines provide a valuable service to smokers in the community, being sources of

knowledge about cessation strategies and providing structured counselling.⁴³⁻⁴⁵ They are easy to access and appeal to a broad cross-section of tobacco users.³¹ Quitlines provide confidential advice to people wishing to cease smoking and are staffed by trained counsellors. The support offered by quitlines may include mailed materials, recorded messages, counselling at the time of the call, call-back from a counsellor and combinations of these elements.⁴⁶ Quitlines can also provide access to subsidised NRT for certain populations, send written materials in the post and work with the client to establish an individualised quit plan.⁴⁷ While the telephone service remains the core of quitline businesses, they have also ventured into alternative means of information dissemination including short message service (SMS) and online service channels such as websites and e-mails.⁴⁷ Although the perception of quitlines is largely that they only provide call-back counselling—which may be a deterrent to individuals uninterested in this type of intervention—the operators are also able to match the smoker to other more preferred treatments.

Quitline interventions are therefore complex and the quality of their counselling content can vary from service to service, as can aspects of their delivery (e.g. the number, timing and length of calls and who initiates them; whether NRT is also provided etc.). In order to maximise the likelihood that quitlines are providing the cessation benefits demonstrated in trials, a standardised approach to service provision across Australia based on best-practice evidence is needed. This is especially important given that resource limitations in some jurisdictions preclude quitline outcome evaluation.

A 2013 Cochrane review concluded that telephone counselling is effective, and that quitline-initiated follow-up calls (call-back counselling) enhances their usefulness both for those who self-refer to quitline, as well as when quitline makes the initial contact. Telephone quitlines provide an important route of access to support for smokers. However, the review found little evidence about what aspects of the quitline service were most beneficial to assist smokers to quit.⁶ Variability in quitline services can occur across several areas including: content provision⁴⁸, theoretical practices underpinning service provision¹, training⁴⁹, and assessing and reporting reach of the service.⁵⁰

In Australia, there is no central body that oversees quitlines. Instead, six different organisations deliver the eight different Quitline™ services around Australia, one for each state and territory.³¹ Guidelines for service delivery and training of counsellors are available from the World Health Organisation (WHO)^{51, 52} and currently recommend combining a behavioural intervention (such as quitline) with NRT or cessation medications. There have been efforts to establish local practice protocols within Australia before^{31, 53}, however, this has not resulted in a standardised nation-wide protocol.

As yet no formal, evidence-based, national minimum standards are available to underpin and standardise Quitline™ services in Australia. This means the clinical offerings (types of counselling offered), data collection and reporting, functionalities (i.e. technological capabilities), clinical supervision processes and evaluation differ from jurisdiction to jurisdiction.

To ensure that quitlines provide consistent, high quality, effective behavioural support, this rapid review of evidence commissioned by the Cancer Council Victoria provides evidence that can be used to underpin development of evidence-based Quitline™ national minimum standards that are implemented across Australia. Two questions have been formulated around which the evidence has been synthesised:

Question 1: What are the key components of dedicated telephone counselling services (quitlines) that have been shown to be effective for smoking cessation?

Question 2: What are the enablers of or barriers to the delivery of effective service components identified in Question 1?

3 Methodology

Criteria for study inclusion

Study types: Included studies were eligible if they could be classified according to the NHMRC level of evidence, including: systematic reviews of randomised controlled trials, randomised controlled trials, pseudo-randomised controlled trials, comparative studies with concurrent controls, comparative studies without concurrent controls, case series with either post-test or pre-test/post-test outcomes.

Participants and interventions: Studies were included if they were conducted with any participants recruited from within a quitline service, used data from quitline participants or collected data from funders/counsellors of quitlines.

Outcomes: Studies had to evaluate a key component of quitline service delivery, including at least one of the following:

- Counselling competencies required
- Behaviour change counselling approaches and adherence to these
- Quality assessment of service and/or counsellors
- Counsellor or participant-initiated follow-up calls
- Counselling protocols and adherence to these
- Frequency and length of calls/counselling sessions
- Hours that service is open.

Additional outcomes and analysis methodology

Additional outcomes: Additional outcomes related to referral pathways and efficacy were also evaluated in studies identified for inclusion based on the above criteria.

Referral pathways refer to the means by which participants within studies were recruited.

Efficacy assessment refers to outcome measures as defined by individual study authors including:

- Quit attempts
- Reduced numbers of cigarettes smoked
- Smoking cessation at 3, 6, or 12 months (or other time period)

Barriers and enablers of effective service components identified in Question 1 were also evaluated to answer review Question 2. These were defined by the Cancer Council as:

‘Enablers’ are system and other supports that have been identified by individual study authors and may have included (but were not limited to): workforce requirements e.g. qualifications, training, skills, supervision; awareness campaigns; and appropriate resourcing.

‘Barriers’ were identified by individual study authors and may have included (but were not limited to): service, resource or skill-related issues impeding optimal service delivery.

Sub-group analyses: Where data was available, sub-group analyses were conducted for tailoring to the following priority populations:

- Culturally and linguistically diverse (CALD) populations
- Indigenous populations
- Mental health
- Pregnant women
- Substance use disorders
- Young people.

Tailoring of services to meet priority population needs may have included (but were not limited to) tools/resources, staff training, designated staff, translation services, cultural competence and counselling methods.

Information pertaining specifically to age, gender and rural/remote locations has been discussed where available within the narrative synthesis of individual studies.

Analysis of evidence: Data was analysed through narrative synthesis with characteristic and outcome evidence also documented within tables based on the NHMRC evidence hierarchy (Table 1). Where no or limited evidence was available from studies meeting the inclusion criteria for the rapid review to address a specific outcome, this is stated and a summary of available (lower quality) evidence from observational studies, surveys and/or qualitative investigations is provided.

Strength of the evidence to be included: This review included strong evidence in relation to the review questions as well as evidence which is medium or weak in relation to the review questions (e.g. a study which suggests an intervention is promising but requires more rigorous research). Equivocal/conflicting evidence in relation to the review questions were noted.

NHMRC levels of evidence:

Included studies were categorised according to the NHMRC evidence hierarchy, as outlined in Table 1.

Table 1: NHMRC evidence hierarchy

Level of evidence	Study design
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternative allocation or some other method)
III-2	A comparative study with concurrent controls (i.e. non-randomised experimental trials, cohort studies, case-control studies, interrupted time series studies with a control group)
III-3	A comparative study without concurrent controls (i.e. historical control study, two or more single arm studies, interrupted time series studies without a parallel control group)
IV	Case series with either post-test or pre-test/post-test outcomes

Evidence was then summarised according to the NHMRC matrix grading system for recommendation (Table 2). Components evaluated included the evidence base, consistency, clinical impact, generalisability and applicability.

Table 2: NHMRC matrix of evidence quality

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a systematic review or multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population in question	Population/s studied in the body of evidence are similar to the target population in question	Population/s studied in body of evidence differ to target population in question, but it is clinically sensible to apply this evidence to the target population	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian context	Applicable to Australian context with few caveats	Probably applicable to Australian context with some caveats	Not applicable to Australian context

Search strategy

Countries included: The review evaluated and summarised evidence from Australia, Europe, NZ, UK and US.

Search terms: The review included evidence searched from:

- The peer-reviewed literature including searches of the Cochrane Database of Systematic Reviews, PubMed/Medline, Embase and PsycInfo (see Appendix 1 for search details and results).
- Grey literature (i.e. agency reports from the Cancer Council, international organisation reports including Australian Institute of Health and Welfare and the World Health Organization (WHO), and guidelines including Smoking Cessation Guidelines for Australian General Practice, Royal Australian College of General Practitioners Support Smoking Cessation: A guide for health professionals, the WHO Guidelines for Smoking Cessation Telephone Counselling and North American Quitline Consortium Guidelines (see Appendix for search details and results).

Limitations to the search strategy: Studies were included only in English and the review was limited to studies published from 2009. However, seminal papers prior to this which were considered important for Cancer Council Victoria were also included.

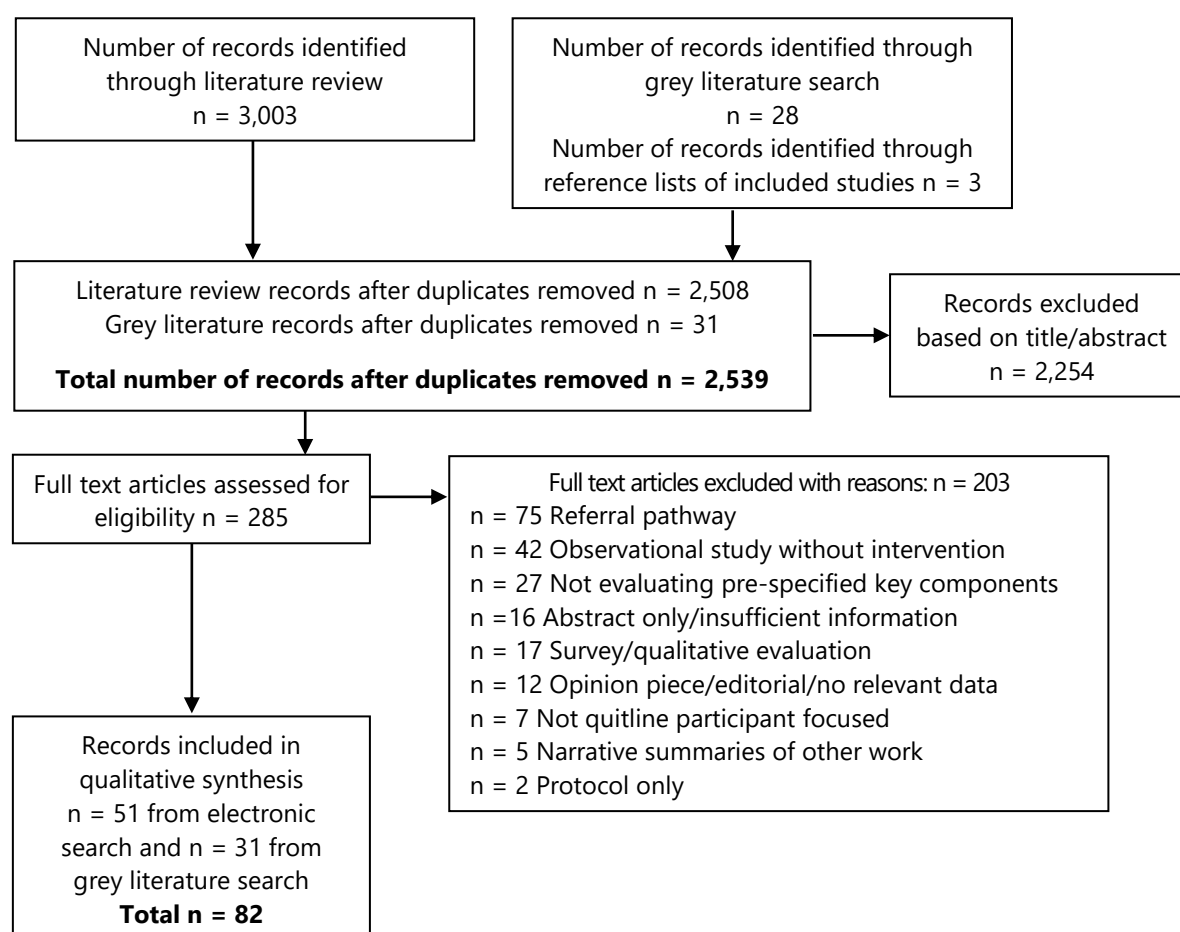
Search terms: All searches were limited to English, were published since 1 January 2009 and were conducted in human subjects. A full list of the search terms and results are included in the appendix.

A search of electronic database was conducted on 29 October 2018.

4 PRISMA flow diagram

In total 3,034 records were identified from the database and grey literature search. Once duplicates were removed a total of 2,539 records were screened for inclusion eligibility. Based on title/abstract screening, 2,254 records were excluded and considered not relevant, leaving 285 records requiring full text review. Of these, 203 records were excluded resulting in inclusion of 82 records representing 80 studies and/or guidelines for this rapid review of evidence. Figure 1 summarises the search process and outlines reasons for study exclusion.

Figure 1: PRISMA flow diagram of studies identified for inclusion in this rapid review of quitline services



5 Synthesis of relevant papers

Overview of findings of the comprehensive search strategy:

In total, 51 records were identified from the literature search for inclusion across the six NHMRC evidence categories. This was supplemented with guidelines, reports and key articles from the grey literature search, which are synthesised further in the section VII analysis of evidence. See section IV PRISMA diagram (Figure 1) for more details of the initial search. Four studies assessed level I evidence, 21 studies level II evidence, two studies level III-1 evidence, four studies level III-2 evidence, five studies level III-3 evidence and 15 studies level IV evidence. Of these 51 studies, all examined at least one key component of quitline counselling as per the pre-specified inclusion criteria.

Given the diverse reporting methods and inconsistent terminology used for smoking cessation studies, quitline interactions will be classified as either 'quitline-initiated' or 'client-initiated' depending on who initiated first contact and/or follow up calls.

NHMRC level I: Systematic reviews of level 2 studies

Four systematic reviews were identified providing level I evidence. One of these (Medical Advisory Secretariat 2010) only evaluated the evidence from a 2006 Cochrane review. Therefore, this systematic review will not be discussed further in favour of the most recent update of the Cochrane review by Stead et al. 2013.⁶

The systematic review by Stead et al. in 2013 identified 77 studies for inclusion that evaluated quitline-initiated or client-initiated follow-up telephone counselling to assist smoking cessation offered to smokers or recent quitters. These 77 studies included almost 85,000 individual participants with a median trial size of 820. Only six of the studies included less than 100 participants, while six other studies, all involving callers to quitlines, had more than 3000 participants. Sixty of these 77 studies were conducted in the US, eight in Australia, two in Spain, three in the UK, one in Hong Kong, one in Norway and two in Germany. Studies within this review were grouped into three broad categories: trials of interventions for smokers who contacted a helpline (n = 15 studies); trials assessing the effect of providing access to a helpline (referral pathways; n = 2 studies); and trials that offered support proactively in other settings, not initiated by calls to quitlines (n = 51 studies). There were eight additional studies that did not fit within any of these three categories with one included study unaccounted for by review authors. Of note, most of the studies included in the Stead et al. review did not meet the criteria for inclusion as individual randomised controlled trials (RCTs) within this rapid review for several reasons, including: studies from countries other than Australia, Europe, NZ, UK and US; conducted/published prior to 2009 and not primarily conducted in the quitline setting and/or with

quitline callers (e.g. quitline intervention was part of a community study in the general practice setting or quitline was only one component of an intervention in one arm).

The Tzelepis et al. 2011 systematic review included 24 randomised controlled trials evaluating recruitment channel (quitline initiated-treatment, smoker-initiated treatment or mixed) and methodological quality for follow-up telephone counselling calls initiated by quitline.⁷ A total of 37,339 participants were included across these 24 studies, all published prior to December 2008 (meaning all included studies in this systematic review did not meet the criteria as individual studies for inclusion in the rapid review). Most studies were from the US (n = 15), three from Australia, two from Spain, two from the UK, one from Canada and one from China.

Another systematic review by Schwindt et al. 2017 examined the impact of tobacco quitlines on persons with a mental illness, identifying four studies for inclusion with 1,412 participants.⁵⁴ The number of participants within individual studies ranged from 123 to 577, and the population characteristics, smoking status and recruitment strategies differed between studies. Three were randomised controlled trials and one a quasi-experimental prospective study. Two were conducted in the US, one in Australia and one in the Netherlands. Of note, none of the four studies identified in the Schwindt et al. 2017 review were included in the 77 studies identified in the Stead et al. 2013 review. Within the Stead et al. review, three of the Schwindt et al. studies were classified as excluded but relevant due to design components not meeting the criteria of the Cochrane review, while the fourth study was published in 2016, after publication of the Cochrane review.

Tabulation of included studies

Source	Setting	n-values		Description of Intervention and Comparator		Outcomes	Effect
		Study	Participant	Intervention	Comparison		
Medical Advisory Secretariat 2010 ⁵⁵	World-wide	n = 1 Cochrane review; n = 48 studies in the review	Over 36,000 participants	Evaluated one Cochrane systematic review published in 2006 <i>"Telephone counselling for smoking cessation"</i> intervention included quitline-initiated counselling calls with number of calls ranging from 1–12 over weeks or months; average 10–20 min duration	Standard advice; General information; Different intensity quitline service	- Statistically significant increase in smoking cessation at 6 months for quitline-initiated follow-up calls in addition to provision of materials, compared to brief counselling through a single counselling session (Risk Ratio (RR) = 1.63; 95% Confidence Interval (CI) 1.23–1.50) Quitline-initiated follow-up counselling on its own (i.e. without provision of additional materials) had a modest benefit on smoking cessation at 6 months compared to a single counselling session (RR = 1.29; 95% CI 1.19–1.40) 3/7 studies showed an increase in quit rates or sustained abstinence while remaining studies showed no significant effect - Statistically significant increase in smoking cessation at 6 months for additional quitline initiated calls vs provision of materials or brief counselling at a single call (RR = 1.63; 95% CI 1.23–1.50)	↑ ↑ ↔ ↑

Source	Setting	n-values		Description of Intervention and Comparator		Outcomes	Effect
		Study	Participant	Intervention	Comparison		
						Quitline-initiated follow-up counselling had a modest benefit on smoking cessation at 6 months (RR = 1.29; 95% CI 1.19–1.40)	↑
Stead 2013 ⁶	World-wide	n = 1 Cochrane review; n = 77 studies in the review	Almost 85,000 participants	Quitline- or client-initiated follow-up telephone counselling to assist smoking cessation offered to smokers or recent quitters	Lower intensity or brief counselling, self-help materials or different counselling interventions	- Groups randomised to receive multiple sessions of quitline-initiated follow-up counselling had higher quit rates compared to those receiving single counselling sessions initiated by the client (R = 1.37; 95% CI 1.26–1.50) - Evidence was mixed about whether increasing the number of calls altered quit rates, however most trials used more than two calls - Studies comparing different counselling approaches during a single quitline contact did not detect significant differences - Quitline-initiated follow-up counselling was associated with increased quitting observed through pooling of 51 studies (RR 1.27; 95% CI 1.20 – 1.36) - The relative extra benefit of counselling was smaller when the counselling protocol provided included counselling in addition to pharmacotherapy (usually nicotine replacement therapy) than when the control group only received self-help material or a brief intervention	↑ ↔ ≈ ↑ N/A
Schwindt 2017 ⁵⁴	World-wide	n = 4 studies with 1,412 participants	n = 1,412 participants	Studies that evaluated the efficacy or effectiveness of quitline interventions for adult participants (aged 18 years and over) diagnosed with a mental illness	Quitline with adjunctive treatments or another smoking cessation intervention	- Significantly higher smoking cessation rates were observed for two of the four included studies - Only one of the four studies identified an association between smoking abstinence and a significant improvement in depressive and psychotic symptoms as well as mental health functioning for all groups	↔ ↔
Tzelepis 2011 ⁷	World-wide	n = 24 studies	n = 37,339 participants	Quitline-initiated primary call and follow-up telephone counselling for smoking cessation for adults (>18 years) in the general community; i.e.	Quitline-initiated follow-up telephone counselling following client-initiated first call	Quitline-initiated follow-up telephone counselling significantly improved point prevalence abstinence at 6–9 months compared to printed materials or no intervention (RR = 1.26, 95% CI 1.11–1.43, p = <0.001). This was not sustained at 12–15 months Telephone counselling initiatives using both active recruitment (quitline-initiated treatment) (RR = 1.35, 95% CI 1.02–1.80, p = .04) and	↑ ↑

Source	Setting	n-values		Description of Intervention and Comparator		Outcomes	Effect
		Study	Participant	Intervention	Comparison		
				described as 'active recruitment'	for smoking cessation for adults (>18 years) in the general community; i.e. described as 'passive recruitment'	passive recruitment (smoker-initiated treatment) (RR = 1.22, 95% CI 1.08–1.38, p = .001) were superior to print materials or no intervention • Quitline-initiated follow-up telephone counselling significantly improved continuous abstinence at 6–9 months compared to printed materials or no intervention (RR = 1.58, 95% CI 1.26–1.98, p < .001), this was sustained at 12–18 month follow up (RR = 1.40, 95% CI 1.23–1.60, p < .001) • Both active recruitment (p = 0.02; first call initiated by quitline counsellors) and passive recruitment (p = 0.001; first call initiated by client) showed benefit for continuous abstinence at 12–18 months follow up	↑ ↑

Key: ↑ = increase; ↓ = decrease; ↔ = mixed; ≈ = no difference; N/A = Not applicable

NHMRC level II: Randomised controlled trials

Twenty-one randomised controlled trials were identified for inclusion, published between 2010 and 2016. Sample size ranged from 121 to 5,752. The majority (n = 16) were conducted in the US, two in the UK, and one each in Australia, the Netherlands and NZ.

Tabulation of included studies

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
Bricker 2014 ¹	Uninsured callers to the South Carolina State	n = 121 uninsured quitline callers	Acceptance and Commitment therapy (ACT) over five sessions plus two weeks of nicotine replacement therapy (NRT)	Cognitive and Behavioural therapy (CBT) over five sessions plus two weeks of NRT	• ACT participants completed significantly more calls (1.1 more calls on average) than CBT participants when comparing two different behavioural change techniques • More calls predicted higher 30-day point prevalence abstinence at 6-month follow-up for ACT (Odds Ratio (OR) = 1.6; 95% CI 1.1–2.6;	↑ ↑

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
	quitline, US				p = 0.03) but not for CBT (OR = 1.6; 95% CI 0.9–3.0; p = 0.10) • Quit rates of 30-day point prevalence abstinence at 6-month follow-up for ACT were 31% compared to 22% in the CBT group (OR 1.5; 95% CI 0.7–3.4; p = 0.32) • Among participants depressed at baseline (n = 47) quit rates were 33% in ACT and 13% in CBT groups (OR 1.2; 95%CI 1.0–1.6' p = 0.10) identifying an improvement in mental health outcomes	≈ ≈
Bullen 2010 ¹²	Dependent smokers who called the NZ quitline	n = 1,100 quitline callers	Two weeks of nicotine patches and/or gum prior to their target quit date followed by usual care (8 weeks of patches and/or gum plus support calls from quitline advisor)	Usual care alone (8 weeks of patches and/or gum plus support calls from Quitline advisor)	• Six months after quit day 7-day point prevalence abstinence was observed in 22.7% of participants in the pre-cessation group and 21.0% in the control group (n = 125 and n = 116 participants respectively), showing no additional increase in cessation rates for pre-cessation NRT • Self-reported continuous smoking abstinence was 18% in both the pre-cessation group (n = 99) and control group (n = 97) • Reduced daily cigarette consumption was observed in both groups by their quit date, going from 19 cigarettes per day to 7 in the intervention arm and 16 in the control arm • By six-month follow-up among those who relapsed, both groups reported smoking fewer cigarettes than at entry into the trial, with an average of approximately 11 cigarettes per day in both groups	≈ ≈ ≈ ≈
Burns 2016 ⁵⁶	Colorado quitline callers, US	n = 1,495 quitline callers	Eight-week supply of nicotine patches shipped in 4-week batches; dosing followed the normal Nicoderm package insert with patches distributed per normal protocol by mail from the quitline distribution centre; plus, usual quitline protocol	Single 4-week supply of nicotine patches – the amount available under state policy for smokers of ≤20 cigarettes per day at the time plus usual quitline protocol	• Smoking rates including 7-day and 30-day point prevalence and continuous abstinence did not differ between study groups by 6-month follow-up • Intervention participants who requested the full 8-week supply of NRT were significantly more likely to complete all counselling calls (33.5%) compared to the intervention participants who only received the 4-week supply of NRT (1.6%; p<0.0001) • Intervention participants who requested the full 8-week supply of NRT were significantly more likely to obtained 30-day point prevalence abstinence (29.3%) compared to intervention	≈ ↑ ↑

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
					participants receiving the 4-week supply of NRT (15.7%; p<0.001)	
Bush 2012a ¹⁹	Oklahoma Tobacco quitline callers, US	n = 2,000 quitline callers	CBT cessation-related weight concerns program integrated into usual quitline practices. The weight concerns program included three additional calls with a weight coach and specialised support material adapted from an in-person CBT weight concerns intervention	Usual quitline practices including a mailed quit guide, 5 counselling calls with a quit counsellor, free NRT (2 weeks for insured and 8 weeks for uninsured participants) and referral to community-based cessation resources	- Average number of counselling calls completed for the intervention was 4.1 compared to 3.0 in the control arm - The intervention arm reported a 3.5% increase in quit rate compared to the control arm by 6-month follow-up, however, these results were not significant; Likewise, intention to treat quit rates identified no differences between intervention and control groups (17.1% and 17.8% respectively) - In the intervention arm 30.0% reported perceived weight change compared to 50.8% in the control group (p = 0.0004) with a perceived change of -3.4 pounds in the intervention arm compared to +1.8 pounds in the control arm (p = 0.01)	↑ ≈ ↑
Carlini 2012 ⁵⁷	Indiana and Washington quitline callers, US	n = 2,985 previous quitline callers with a final sample of n = 521 smokers	Interactive voice response screening plus the interactive voice response intervention, consisting of automated questions to identify and address barriers to re-cycling in quitline support, followed by an offer to be transferred to the quitline and reinstate treatment	Interactive voice response providing a greeting and screening for current smoking, followed by a message thanking them for the information	Proactive calls (i.e. quitline-initiated first call) resulted in a re-enrolment rate of 28.2% in the intervention arm and 3.3% in the control arm	↑
Carlin-Menter 2011 ¹⁸	New York quitline callers, US	n = 4893 quitline callers in 2-month period; n = 1,923 eligible participants	Offer of 2 callbacks from the quitline. Callback counselling included setting a quit date on the intake call and provision of contact information and preferred times for callbacks. Client-centred cessation session strategies used, including checking smoking status, provision and use of nicotine patches, motivational	Standard care: offer of 4 callbacks from the quitline. Callback counselling included setting a quit date on the intake call and provision of contact information and preferred times for callbacks. Client-centred cessation session	Call duration averaged 8 minutes (range: 2.48–20.15 minutes), with no difference between intervention and control groups - Mean number of callbacks completed were similar for the intervention group 0.89 (0.87) compared to 1.04 (1.1) for the standard care group (P>0.05) - Reasons for not accepting callbacks were recorded overall; 39% reported being 'too busy', 30% believed the calls were unhelpful, 14% said they were not ready to quit - Of the 57% of all participants who accepted callbacks 89% said they were helpful in their quit effort	≈ ≈ N/A ↑

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
			interviewing and CBT	strategies used, including checking smoking status, provision and use of nicotine patches, motivational interviewing and CBT	- Mean number of nicotine patches did not differ between intervention 19.4 (14.1) and control 20.1 (13.9) ($P>0.05$) according to self-report - Overall 48% of all participants reduced their cigarette consumption by 50% or more 7-day non-smoking prevalence rate increased by 64% for every additional callback completed 30-day non-smoking prevalence rate increased by 73% for every additional callback completed - Cost per quitter in the intervention group was \$US442 for 131 quitters, cost per quitter in the control group was \$US445 for 135 quitters	N/A ≈ ↑ ↑ N/A
Danaher 2015 ⁵⁸	California and online, US	n = 1683 total, n = 421 web only users, n = 421 quitline only callers, n = 417 web+quitline callers, n = 424 control	Quitline+Web: See description of 'Quitline Only' and 'Web Only' below. Counsellors accessed the online dashboard enabling access to real-time metrics regarding the individual's web intervention use. Printed cessation self-help guide Quitline Only: proactive follow-up calls delivered by trained quitline counsellors. Calls followed a smokers' protocol adapted for smokeless tobacco users. Counsellors used computer assisted telephone interviewing to guide calls and schedule future calls. Motivational interviewing and CBT were also used. Four follow up calls offered. Printed	Mailed the printed cessation self-help guide only.	At 3- and 6-month follow-up repeated point prevalence of all tobacco abstinence was improved in the Web Only group vs. control (OR = 1.14, 95% CI 1.03,1.94, $p = 0.033$) as well as the 'Quitline Only' group vs. control (OR = 1.54, 95% CI 1.13,2.11, $p = 0.007$) - When comparing groups of individuals who were not offered any form of Quitline intervention vs. those who did receive quitline intervention, 3- and 6-month reported point prevalence of all tobacco abstinence was significantly greater in those who received the quitline intervention (OR = 1.26, 95% CI 1.01,1.56, $p = 0.038$) - Repeated point prevalence of all tobacco abstinence was more likely in older people ($\beta = 0.04$, $p = 0.012$; OR = 1.23, 95% CI 1.10,1.37) and males ($\beta = 2.46$, $p = 0.037$; OR 1.04, 95% CI 1.17,123.67) who received the quitline intervention 70% of all participants reported using the printed self-help guide, 93% of these individuals read some or all of the material, 12% read the material more than once. No difference in usage identified between groups - Web intervention access did not differ between Web Only (90.0%) and Quitline+Web (90.4%) groups, 65.4% of all web users made	↑ ↑ N/A ≈ ≈

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
			cessation self-help guide Web Only: Fully automated tailored and interactive web program using CBT themes and strategies as text, activities and videos. Emphasis on the phases: planning to quit, quit, staying quit. Printed cessation self-help guide		multiple visits to the content 41.4% of all participants allocated to a group involving quitline participated in at least one call. Of these individuals: 9.7% had one call, 10.1% had two calls, 6.7% had three calls, 8.0% had four calls, 6.9% had all 5 calls - Quitline-only group had significantly more individuals with at least one call ($\chi^2 = 6.14$, $p = 0.013$, OR = 0.71, 95% CI 0.54, 0.93); mean number of calls did not differ between groups: Quitline only mean = 3.13 calls; Quitline+Web mean = 3.10 calls - Participating in at least one call was significantly related to 6 months tobacco abstinence ($\chi^2 = 7.72$, $p = 0.005$, OR = 1.61, 95% CI 1.15, 2.26) - Reported 6-month tobacco abstinence was 11% higher in participants receiving quitline calls than those who did not 347 individuals received at least one quitline call, 85.6% of them found the calls helpful and 93.8% would recommend the service to others; compared to Quitline Only, the Quitline+Web group rated both helpfulness ($p < 0.05$) and future recommendation ($p < 0.05$) higher	N/A ≈ ↑
Docherty 2014 ¹⁰ *Second ary analysis of data from Ferguson 2012	Government-funded quitline, UK	n = 2,591, quitline callers	See Ferguson 2012 **Secondary analysis to investigate if use of 'non-trial' support confounded outcomes of Ferguson 2012. 'Non-trial' support included: Over the counter NRT, NRT from other health professionals, bupropion, varenicline, NHS stop smoking support, NHS one-on-one therapy, non-NHS quitline, any other support	See Ferguson 2012	- Participants seeking additional 'non-trial' support did not affect continuous cessation at 6-month follow-up (trial model OR 0.86, 95% CI 0.7–1.06, $p = 0.11$; secondary model OR 0.84, 95% CI 0.66–1.07, $p = 0.17$) - Adjusting for 'non-trial' support also had no effect on the following outcomes published in Ferguson 2012: self-reported cessation ≥ 7 days (OR 0.85, 95% CI 0.67–1.07; $p = 0.17$); reported cessation ≥ 3 months (OR 0.86, 95% CI 0.66–1.10; $p = 0.23$); reported quit attempts lasting more than 24 hours (OR 1.15, 95% CI 0.88–1.50; $p = 0.30$)	≈ ≈

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
Ferguson 2012 ¹¹	Government funded quitline, UK	n = 2,591, quitline callers	Quitline initiated follow-up telephone counselling: Usual care plus additional telephone counselling by a trained counsellor before, on and after their quit date (up to 4 follow-up calls post quit) Voucher for free NRT: 6 weeks free NRT via pharmacy with trained counsellor to advise on precautions of use	Usual Care: cessation support provided via telephone, email, print resource, text message and if appropriate advice to seek additional support. two follow-up calls provided at 2 days and 3 weeks after the first session	- Neither quitline initiated follow-up telephone counselling nor provision of free NRT resulted in any difference for any outcomes relevant to this review, compared to usual care - For quitline initiated follow-up telephone counselling compared to control: continuous cessation (OR 0.92, 95% CI 0.75–1.14, p = 0.46); self-reported cessation ≥ 7 days (OR 0.95, 95% CI 0.77–1.16, p = 0.60); reported cessation ≥ 3 months (OR 1.01, 95% CI 0.80–1.26, p = 0.95); reported quit attempts lasting more than 24 hours (OR 1.04, 95% CI 0.86–1.26, p = 0.68); continuous cessation since quit date (OR 0.95, 95% CI 0.80–1.12, p = 0.55) - For provision of NRT compared to control: continuous cessation (OR 0.86, 95% CI 0.70–1.06, p = 0.16); self-reported cessation ≥ 7 days (OR 0.85, 95% CI 0.70–1.04, p = 0.13); reported cessation ≥ 3 months (OR 0.84, 95% CI 0.67 to 1.05, p = 0.14); reported quit attempts lasting more than 24 hours (OR 1.05, 95% CI 0.87 to 1.27, p = 0.60); continuous cessation since quit date (OR 1.01, 95% CI 0.86–1.19, p = 0.88) 51.3% of participants who received any NRT used it every day, 23.9% used it most days, 8.1% once or twice a week, 6.7% less than once a week, 6.5% not at all since quit date - Individuals in the usual care group received an average of 2.44 calls while the quitline initiated follow-up counselling group received an average of 3.35 calls; 50 participants in the usual care group contacted quitline for support, while 53 did so in the quitline initiated follow-up counselling group; participants called an average of approximately one time regardless of their group	≈ ≈ ≈ N/A N/A
Fucito 2011 ⁴	Telephone specialists and their smoking clients who contact the	n = 28 telephone specialists n = 2,032 smoking clients (n =	Web-based structured interview and counselling using gain-framed messages (i.e. content emphasising quitting benefits)	Web-based structured interview and standard care counselling	- No significant interaction of nicotine dependence scores and message condition on the likelihood of achieving 7-day point prevalence smoking abstinence at the 3-month follow-up (Wald = 0.02, p = 0.90, OR = 1.10) - Among continuing smokers at 3 months, smokers who reported higher nicotine dependence scores were more likely to report	≈ N/A

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
	New York State Smokers' Quitline	810 assigned to gain-framed; n = 1,222 assigned to standard-care)			smoking more cigarettes per day and this effect was greater in response to standard-care messages ($b = 2.07$; $t = 10.01$, $p < 0.001$) than gain-framed messages ($b = 1.41$; $t = 5.82$, $p < 0.001$)	
Klesges 2015 ⁸	Quitline callers from Memphis, Tennessee, who were adult smokers and beneficiaries of the Department of Defence military health care (TRICARE)	n = 1,298 active duty military personnel, their dependents, reservists, and retirees (n = 649 assigned to quitline initiated follow-up calls (proactive quitline); n = 649 assigned to client-initiated follow-up calls (reactive quitline)	Participants assigned to the proactive condition were scheduled for six counselling sessions over eight weeks. Trained counsellors contacted participants to deliver a cognitive behavioural intervention, with an additional call attempt if there is no response. Eligible participants also received an 8-week supply of nicotine replacement therapy (NRT) patches	Participants assigned to the reactive condition were asked to call the Quitline up to six times over the same eight weeks. Participants making contact will receive the same intervention as the proactive condition and those eligible received a 2-week supply of NRT patches	- In the Proactive condition, 78.89% of participants received ≥ 3 intervention calls compared to 13.87% of those in the Reactive condition. In the Reactive condition, 46.84% did not complete a single call compared to 3.54% in the Proactive condition - The Proactive condition was associated with greater odds of both prolonged (44.22% vs 24.9%; OR = 2.4, $p < 0.0001$) and 7-day point prevalence (49.92% vs 28.20%; OR = 2.5, $p < 0.0001$) smoking abstinence, a difference that was maintained for prolonged smoking abstinence at 12 months (22.03% vs 13.41%; OR = 1.8, $p < 0.0001$) - Prolonged smoking abstinence at 12-months favoured the Proactive condition in the active duty subgroup (OR = 1.643, 95% CI 1.077–2.507) and in the non-active duty subgroup (OR = 2.027, 95% CI 1.349–3.045)	↑ ↑ ↑
Klesges 2015b ⁵⁹	Quitline callers from Memphis, Tennessee, who were	n = 214 assigned to quitline initiated follow-up	Participants assigned to the proactive condition were scheduled for 6 counselling sessions over 8 weeks. Trained counsellors contacted	Participants assigned to the reactive condition were asked to call the Quitline up to 6 times over the same 8 weeks.	At 12-month follow-up, abstinence was self-reported in 22% and 26%-point prevalence in Proactive and Reactive conditions, respectively. However, 48% of participants who were tested for cotinine failed biochemical verification, indicating a considerable falsification of self-reported cessation	↔

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
	adult cancer survivors and regularly smoked cigarettes	calls (proactive quitline); n = 213 assigned to client-initiated follow-up calls (reactive quitline)	participants to deliver a cognitive behavioural intervention, with up to three call attempts if there is no response. Eligible participants also received a supply of nicotine replacement therapy (NRT) patches	Participants making contact will receive the same intervention as the proactive condition and those eligible received a supply of NRT patches	- Among Proactive participants, 7 (4.1%) tested cotinine negative compared to 8 (4.6%) in Reactive participants (OR = 0.89, CI = 0.27–2.87) - At 8-week follow-up, there were no differences between Proactive and Reactive conditions in point prevalence abstinence (Proactive: 28%, Reactive: 25%) and continuous abstinence (Proactive: 17%, Reactive: 14%) - At 12-month follow-up, neither self-reported point prevalence (Proactive: 22%, Reactive: 26%) nor continuous abstinence (Proactive: 13%, Reactive: 14%) were significantly different by condition - Adjusted cessation rates were less than 5% in both intervention conditions	≈ ≈ ≈ ≈
Klesges 2015 ⁶⁰	Quitline callers from Memphis, Tennessee, who were adult survivors of childhood cancer and regularly smoked cigarettes	n = 260 assigned to quitline-initiated follow-up calls (proactive quitline; n = 259 assigned to client-initiated follow-up calls (reactive quitline)	Participants assigned to the proactive condition were scheduled for 6 counselling sessions over 8 weeks. Trained counsellors contacted participants to deliver a cognitive behavioural intervention, with up to three call attempts if there is no response. Eligible participants also received a 4-week supply of nicotine replacement therapy (NRT) patches	Participants assigned to the reactive condition were asked to call the Quitline up to 6 times over the same 8 weeks. Participants making contact will receive the same intervention as the proactive condition and those eligible received a 2-week supply of NRT patches	- The Proactive condition self-reported a higher rate of smoking cessation than those in the Reactive condition at 8 weeks (33.2% vs 17.0%, p < 0.001) but not 12 weeks (23.0% vs 18.7%, p = 0.29) - However, 80% of participants claiming abstinence failed biochemical verification, indicating marked falsification of self-reported smoking status - Adjusted cessation rates were less than 2% in both intervention conditions	↔ ≈
McDaniel 2015 ⁶¹	Quit for Life Program, US	n = 1,785 total; standard n = 592, TEQ-10 n = 602, TEQ-	QFL (described in the comparison column) plus interactive voice response – Technology Enhanced Quitline (TEQ) with:	Standard Quit for Life (QFL) includes 5 counselling calls (an initial assessment and planning call plus 4	30-day quit rates at 6 months were 59.4% (95% CI 53.7–63.8%) for QFL, 62.3% (95% CI 57.7–66.9%) for TEQ-10, 59.4% (95% CI 53.7–65.1%) for TEQ-20. This was not significant 30-day quit rates at 12 months were 61.2% (95% CI 55.6–66.8%) for QFL, 60.6% (95% CI 56.0–65.2%) for TEQ-10, 54.9% (95% CI	≈ ≈

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
		20 n = 591	10 risk assessments (TEQ-10) or 20 risk assessments (TEQ-20) Risk assessments were pre-programmed identify relapse risk on five factors: lapses, cravings, negative affect, self-efficacy and motivation to remain quit. An algorithm was used to flag participants as 'at risk'	additional quitline-initiated outbound calls from an educated Quit Coach). Call schedule and content tailored to individual. Total of 4 calls. Participant free to call in the interim for additional support. May also access additional cessation resources e.g. print and NRT	49.0%–60.9%) for TEQ-20. This was not significant • 73.3% of TEQ participants were identified as at-risk by the interactive voice response technology assessments • Positive risk assessments identified participants less likely (OR 0.56, 95% CI 0.42–0.76) to be abstinent at 6 months	N/A N/A
Segan 2011 ⁶²	Quitline callback service, Victoria Australia	Assessed for eligibility n = 2,307 Randomised at recruitment n = 1,444	Up to 10 post-quitline callbacks over a 3-month period to help ex-smokers integrate a smoke-free lifestyle. Topics included (i) lifestyle changes, (ii) high-risk situations and planning to confront new situations, (iii) motivation; warning signs and cessation fatigue, (iv) emotional issues and (v) weight management.	Standard callback service, including up to 4 post-quitline callbacks over 1 month	- The intervention group received calls over a longer period compared with the usual care group (60.9 days comprising 28.5 days for standard calls and 32.4 days for integration calls versus 42.0 days in usual care group, $t = 7.07$, $df = 652.7$, $P < 0.001$) - There was no difference between groups in the proportion of participants reporting reaching the point of less than daily cravings (81% in each group). - The treatment condition was not significantly associated with point prevalence abstinence or measures of continuous abstinence at either 4- or 12-month follow-up - In addition, mean time to relapse for the baseline quit attempt was not significantly associated with treatment condition - At 4-month follow-up, 97% of participants in both groups rated the callback service as helpful (83% very; 14% somewhat), and 87% agreed that receiving callbacks made a difference to the success of their quit attempt	↑ ≈ ≈ ≈ ↑
Sims 2013 ⁶³	Callers to the State of Wisconsin's tobacco	Total callers n = 2,257 Eligible callers n = 1,737	Self-help materials based on stage of change model, and up to 4 follow-up calls from quitline counsellors	No cessation counselling, only self-help materials based on stage of change model	CI group was significantly more likely to set a quit date (59.8%) than the SH group (43.3%; $p < 0.002$) at 1-month post enrolment in the ITT analysis as well as in the responder-only analysis ($p < 0.001$). This	↔

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
	quitline vendor Free & Clear	Randomised and consented young adults n = 462	(Counselling Intervention (CI) group)	(SH group)	effect was not found at the subsequent study end points - The groups did not differ in the percentage of participants that actually reported making a quit attempt at any of the study end points. Similarly, the groups did not differ in percentage abstinent at any of the study end points for either the ITT or responder-only analysis - Within the CI group, participants who had two or more counselling sessions were somewhat more likely to report making a quit attempt (44.4%) compared to participants who had zero or one session (31.1%; p = 0.06) - Similarly, the group of participants that had more counselling sessions also had a marginally significant higher 7-day point prevalence abstinence rate (14.1%) compared to participants with fewer counselling sessions (5.4%; p = 0.06); follow-up time period not specified	≈ ↑ ↑
Smith 2013 ¹⁷	Callers to the State of Wisconsin's tobacco quitline vendor Free & Clear	n = 987 Quitline callers	- NRT duration (2 vs 6 weeks) - NRT type (patch only vs patch + gum) - Standard 4-call counselling (SC) vs SC + medication adherence counselling (MAC)	This study was a 2 x 2 x 2 fully crossed factorial design, yielding 8 possible treatment combinations.	- Analysis which included all main effects and interaction effects in the 2 x 2 x 2 design, yielded a statistically significant effect only for the NRT type main effect (patch only vs. combination NRT); no other main effects or interactions were significant - A higher rate of abstinence was observed for combination NRT (49.9%) versus nicotine patch only (42.3%), odds ratio (OR) = 1.36 (95% CI: 1.06–1.75) - Contrary to prediction, there was no significant difference between groups for 6 weeks of NRT (48.9%) versus 2 weeks of NRT (43.3%), OR = 1.26 (95% CI: 0.98–1.61) - Similarly, there was no difference in abstinence rates between groups for the MAC treatment (44.6%) versus no MAC treatment (47.6%), OR = 0.89 (95% CI: 0.69–1.14)	↔ ↑ ≈ ≈
Toll 2015 ⁶⁴	Callers to the New York State	n = 1,948 randomised participants	Brief motivational counselling to limit or abstain from alcohol plus an alcohol reduction	Smoking cessation counselling plus a smoking cessation	Alcohol and Tobacco Counselling (ATC) was associated with a significantly higher rate of smoking abstinence at 7-month follow-up compared with TOC (p = 0.03)	↑

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
	Smokers' Quitline		booklet added to standard care (Alcohol + Tobacco Counselling; ATC)	booklet added to standard care (Tobacco-Only Counselling; TOC)	When controlling for the treatment condition, heavy-drinking status was a significant predictor of smoking abstinence, in that participants who did not report any heavy drinking were significantly more likely to quit smoking than those who reported any heavy drinking ($p = 0.001$).	N/A
Unrod 2016 ⁶⁵	Callers to the New York State Smokers' Quitline	n = 5,752 Quitline callers consented and randomised n = 3,458 enrolled	Repeated mailings (RM) – 8 booklets sent over 12 months OR Massed mailings (MM) – all 8 booklets sent at once, plus usual care (as described in the comparison column).	Usual care: standard quitline protocol including brief counselling, 2-week starter kit of NRT (choice of patch, gum or lozenge); A 'ready to quit' kit was mailed after the initial call including a congratulatory cover letter, stop smoking guide, medication chart and two single page fact sheets about dealing with nicotine withdrawal and maintaining abstinence	Abstinence rates were 61.0% at baseline (relapse-prevention study), and 41.9%, 42.7%, 44.0% and 45.9% at the 6-, 12-, 18- and 24-month follow-ups, respectively Repeated Mailings (RM) intervention consistently produced higher abstinence rates, however analysis comparing MM or RM against usual care did not find significant differences or group x time interactions - Analyses of smoking status at follow-up among the subset of participants (n = 2108) who had achieved abstinence at baseline also failed to reveal significant group differences in outcomes, with similar rates across conditions - With regard to receipt of intervention, among responders at the 12-, 18-, and 24-month follow-ups, 12.5% of the MM group and 8.0% of the RM group did not endorse receipt of a single booklet 90% of responders reported having read the intervention booklets. At the 6- and 12-month follow-ups, abstinence rates were 42.8% and 43.70%, respectively, among those who reportedly read the booklets, compared with 27% and 29% among those who did not read the booklets ($P_s < 0.03$)	N/A ↔ ≈ N/A N/A
van der Meer 2010 ⁶⁶	Callers to the Dutch national smoking cessation quitline	Randomised participants n = 485 daily smokers with past major depression	Eight sessions of quitline-initiated follow-up telephone counselling with a mood management component—consisting of a self-help manual, two extra telephone counselling sessions, and supplementary homework	Eight sessions of quitline-initiated follow-up telephone counselling. This control intervention consisted of strengthening stop-smoking skills, namely social support,	Mood management intervention resulted in significantly higher prolonged abstinence rates at 6- and 12-month follow-up (30.5% and 23.9% vs 22.3% and 14.0%) or both follow-ups 7-day point prevalence rates were also higher in the experimental group, though this was not statistically significant - Subgroup analysis identified that quitting was associated with improvements in depressive symptoms	↑ ≈ N/A

NHMRC level III-1: Pseudo-randomised controlled trials

Two pseudo-randomised controlled trials were identified for inclusion, published in 2014 and 2010. Sample sizes were 1,212 and 2,032 for each study respectively. One was conducted in Sweden and one in the US.

Tabulation of included studies

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
Nohlert 2014 ⁶⁸	Callers to the Swedish National Tobacco Quitline	Quitline calls n = 1,212 Randomised n = 1,129	Counsellor initiated follow-up (described as proactive service): those who called on even dates were offered a call back service with several callbacks.	Reactive service (client-initiated follow-up): those who called on odd dates were informed that they could themselves call back whenever they liked, with no counsellor-initiated callbacks.	- There were no statistically significant differences in outcome between proactive and reactive service at the 12-month follow-up, in either point prevalence or continuous abstinence, or in either intent-to-treat (ITT) or responder-only analyses. Of those who responded to the 12-month follow-up, 47% were point prevalent abstinent and 35% were continuously abstinent for responder only analyses, while 27% were point prevalent abstinent and 21% continuously abstinent for all participants, classifying non-responders as smokers - The predictive model from the multivariable logistic regression analyses, which included only the variables known at baseline, showed that not smoking the week before baseline was the strongest predictor for both point prevalence (OR 3.2) and continuous abstinence (OR 3.7) at the 12-month follow-up	≈ N/A
Toll 2010 ⁶⁹	Callers to the New York State Smokers' Quitline	n = 28 quitline specialists providing counselling and print materials to n = 2,032 smokers	Specialists working at the quitline received gain-framed counselling and materials to provide to their callers. Gain-framing refers to the theory that when gains are made prominent in a decision situation, people are averse to risk	Specialists received standard care messages and print materials to provide callers.	- Specialists who received gain-framed counselling used gain-framed statements statistically significantly more frequently than those providing standard-care counselling Gain-framed counselling was associated with a statistically significantly higher rate of abstinence at the 2-week follow-up (23.3% in gain-framed group vs 12.6% in standard care group, p<0.001), but not at the 3-month follow-up (28.4% vs 26.6%, p = 0.48) - Statistically significantly more callers in the gain-framed group than the standard-care group made an attempt to quit smoking (p<0.001)	↑ ↔ ↑

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
		survey (n = 243 Latinos)	messages about quitting through actors portraying key family members aired in the Spanish language only on predominantly Spanish-language television and radio and in Latino-attended movie theatres. The campaign urged audience members to call the Colorado Quitline, which offered free NRT and five counsellor-initiated follow-up counselling sessions		campaign (24.9% compared to 34.8%; $p < 0.05$) - An increase in quitline calls were observed among Latino quitline callers by 390 per month during the pre-campaign period (169 over three months) to an average of 614 per month during the campaign - During the campaign Latino participants were less likely to stop being coached after 1 call, more likely to complete the program and were more likely to receive 1 NRT package (4-week supply), compared to pre-campaign counterparts, however, these results were not statistically significant - Average number of counselling calls was marginally higher among Latinos than non-Latinos during the campaign (3.0 compared to 2.6 calls respectively; $p = 0.06$)	↑ ≈ ↑
Burns 2010b ⁷¹	Smokers calling the Colorado Quitline, US	n = 1,710 Quitline callers	Light to moderate smokers (≤ 20 cigarettes per day) when a state Quitline reduced NRT supply from 8 weeks to 4 weeks	Heavy smokers (> 20 cigarettes per day) who were consistently eligible for 8 weeks of NRT during the same time-period	Smoking abstinence declined by nearly a quarter among light to moderate smokers (29.9% compared to 39.3%; $p < 0.01$) under the reduced NRT protocol - Heavy smokers reported no difference in abstinence rates (28.6% compared to 28.4%)	↓ ≈
Lindqvist 2013 ²	National tobacco Quitline, Sweden	n = 772 Quitline callers	Motivational interviewing (MI) by counsellors trained in MI	Standard treatment by counsellors trained in CBT	At 12-month follow-up, reported 6-month continuous abstinence was greater in the Motivational Interviewing (MI) group than the standard group (OR 1.48, 95% CI 1.00–2.19; $p = 0.047$), likewise for point prevalence abstinence (OR 1.48, 95% CI 1.00–2.19; $p = 0.047$)	↑

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
Miller 2009b ¹⁴	Low-income callers to the Quitline service from Adelaide, Australia	n = 1,000 intervention; n = 366 comparison group	Usual service of multisession counselling from the Quitline plus access to one week's worth of heavily subsidised nicotine replacement therapy (NRT)	Usual Quitline service only	- The response rate in the NRT group was significantly higher than in the comparison group (0.67% vs 0.25%, $X^2 = 283$, $p < 0.001$) - The average number of cigarettes smoked per day among both groups who reported smoking at each follow-up remained significantly lower than at baseline - Those in the NRT intervention group were more likely than the comparison to have made an attempt to quit some time before the 12-month follow-up, with statistically higher quit rates observed among the NRT group at 3-month and 6-month but not at the 12-month follow-up - The NRT group received more callbacks on average compared to the comparison group (6.3 vs 5.5 calls, $p < 0.001$) - Within the NRT group, those who had quit at 6 months used a significantly larger number of NRT vouchers than those who did not quit (6.0 vs 4.2, $t = 7.6$, $df = 625$, $p < 0.001$)	↑ ≈ ↑ ↑ ↑

Key: ↑ = increase; ↓ = decrease; ↔ = mixed; ≈ = no difference; N/A = Not applicable

NHMRC level III-3: Comparative studies without concurrent controls

Five comparative studies without concurrent controls were identified for inclusion, published between 2010 and 2015. Sample size for individual participants ranged from 1,895 to 26,334. All five studies were undertaken in the United States.

Tabulation of included studies

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
Augustso	US	n = 50 states	Nationwide mass	Call and visitor data monitored before,	• 132% increase in client-initiated calls (207,519 additional	↑

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
n 2012 ⁷²	nationwide	and n = 3 districts	media campaign featuring former smokers talking about their experiences living with diseases caused by smoking; Intended to encourage smokers to call quitline portal or visit website	during and after campaign and compared to data from corresponding weeks in 2011 (previous year)	calls); 365,194 calls in total compared to 207,519 calls during the comparator period in 2011	
Carlini 2015 ⁷³	Relapsed tobacco quitline users in New York State, US	n = 3,510 past quitters invited for intervention and n = 22,824 in comparison group	Re-engaging past quitline participants using messages consecutively delivered through interactive voice response followed by postcard and email reminders, two short messaging services (SMS) texts and a final cycle of interactive voice responses	Registry participants not selected for the study	• Quitline-initiated interactive voice response (IVR) calls resulting in re-engagement with the quitline service were successful among 12.2% of the intervention sample (n = 859 people) compared to 1.9% of the comparison group re-engaging with the quitline service (p<0.001) • Just over half of participants were available for follow-up with 79.9% reporting a quit attempt lasting 24 hours or more in the last 90 days with 24.5% reporting 7-day point prevalence • In the intention to treat analysis quit attempts and quit rates were 42.6% and 13.1% respectively	↑ ↑ ↑
Cummins 2015 ⁷⁴	Asian-language speaking smokers calling the California Smoker's Helpline's	n = 1,339 California n = 70 Colorado n = 215 Hawaii n = 162 New	A multi-state smoking cessation program promoting quitline services to 3 Asian-language-speaking communities: Chinese, Korean and	Smoking status and quitting history 7 months after enrolment in the quitline service compared to earlier efficacy trial of single-state program in California	• Although the rate of receiving counselling was higher in the multi-state program (91.6%) than in the efficacy trial (87.2%; p<0.05), they received fewer counselling sessions (mean: 4.1 vs 4.9; P<0.05) and fewer minutes of counselling across all sessions (58.2 vs 72.0; p<0.05) than those in the efficacy trial • Those in the multi-state program reported higher rates of using nicotine patches (43%) and any quitting aid (53.1%) than those in the efficacy trial (9.1% and 12.9%, respectively;	↔ ↑

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
	Asian-language lines	York n = 87 Washington n = 22 Texas	Vietnamese. Smokers chose their level of service (counselling, self-help materials or both) and received free nicotine patches if medically eligible. Quitline counsellors were bilingual and bicultural		p<0.05) - There were significantly higher rates of quit attempts among participants in the multi-state program than among those in the efficacy trial (65.3% vs 54.9%, p<0.05) - There were no significant differences in 30-day abstinence rates (32.3% for both groups) - The 180-day abstinence rates were higher in the multistate than in the efficacy trial (18.8% vs 16.4%, respectively), but the difference was not significant	↑ ≈ ≈
Cummings 2010 ⁷⁵	Callers to the New York State Smokers' Quitline (NYSSQL)	n = 2442 adult daily smokers	Five groups of smokers were mailed 2-, 4-, 6-, or 8-week supplies of free nicotine patches, as well as instructions and a self-help smoking cessation guide. Group 1 received 2-weeks supply, Group 2 received 4-weeks supply, Group 3 consisted of Medicaid/uninsured smokers who received 6 weeks of nicotine patches contingent upon first 2 weeks of use, Group 4 received 6 weeks supply, and Group 5 consisted of		- The number of patches reportedly used was related to the number of free patches sent to subjects, with a significantly greater number of patches used by those receiving the 6- and 8-week supplies relative to those who only received a 2- or 4-week supply of free patches, though this was not the case for Group 3 - Quit rates at 12 months were higher for smokers in the groups who received either 2 (Group 1), 6 (Group 4), or 8 (Group 5) weeks of free patches. Quit rate for the 4-week supply did not differ significantly from the 6- or 8-week groups - There is no consistent dose response relationship between the number of free patches given to smokers and smoking status outcomes, adjusted for age, gender, race, education level and number of cigarettes smoked per day at time of enrolment	N/A ↔ ≈

Source	Setting	n-values	Description of Intervention and Comparator		Outcomes	Effect
			Intervention	Comparison		
			uninsured smokers and received 8 weeks supply			
Cummings 2011 ⁷⁶	Callers to the New York State Smokers' Quitline (NYSSQL)	n = 2806 adult smokers	Participants were sent either a 2-week supply of nicotine patches, a 4-week supply, or a 6-week supply. Additionally, participants received a free stop smoking guide and 1 counsellor-initiated follow-up call		85.4% reported using the nicotine patches sent to them—the amount used varied in direct proportion to the amount sent. Overall, participants used 51.8% of the patches sent out - The 7- and 30-day prevalence rates did not differ significantly between the 3 groups (p = 0.403) - The cost per quit was not significantly different between the 3 groups - Overall, 45.9% reduced their cigarette consumption by 50% or more, with no differences by study group	↑ ≈ N/A ≈

Key: ↑ = increase; ↓ = decrease; ↔ = mixed; ≈ = no difference; N/A = Not applicable

NHMRC level IV: Case series with post-test or pre-test/post-test outcomes

Fifteen studies using a case series design with post-test or pre-test/post-test outcomes were identified for inclusion, published between 2012 and 2018. Sample size ranged from 176 quitline funders/providers who responded to the invitation for one study (Saul 2014) up to 189,993 quitline callers in another study (Bush 2012b). The majority (n = 13) were conducted in the United States, one study was conducted in two countries (United States and Canada) and one study was conducted in Sweden.

Tabulation of included studies

Source	Setting	n-values	Study description	Outcomes	Effect
Bombard 2013 ⁷⁷	Quitline data from the American Cancer Society across 10 states in US	n = 1718 pregnant women n = 246 completed follow-up; n = 24,321 non-pregnant women n = 4,123 completed follow-up	Analysed telephone quitline data between January 2006 and December 2008 for women 18–44 years; Pregnant women were offered self-help materials only, self-help materials with counselling or counselling only; Pregnant women received pregnancy tailored coaching which included up to 8 counselling sessions, 3 of which could be booster sessions; Pregnant women were ineligible to receive NRT from quitline; Counselling protocol for non-pregnant women differed by state; In general all non-pregnant women were offered self-help materials and/or counselling and up to five counselling sessions with one to two booster sessions; Non-pregnant women automatically received self-help materials when they received counselling	- Average frequency of counselling sessions for pregnant women was 2.3 occasions and for non-pregnant women 2.5 occasions - Most common referral pathway for pregnant quitline callers was by a healthcare provider (54%), whereas non-pregnant callers most often heard of the quitline from mass media (59%) - By 7-month follow-up 26.4% of pregnant women and 22.6% of non-pregnant women reported quitting - Adjusting for non-responders (assumed to be smoking) and non-disclosers, the adjusted quit rates were 2.9% for pregnant women and 3.5% for non-pregnant women, meaning the adjusted quit rate was approximately twice as high for pregnant and non-pregnant women who received counselling versus those who received self-help material only (p<0.01 for both groups)	↓ N/A ≈ ↑
Bush 2012b ⁷⁸	16 state quitlines in US	n = 16 states with n = 85,541 calls pre-tax increase and n = 104,452 calls post tax-increase	Analysed telephone quitline data between December 2007 and May 2008, and between December 2008 and May 2009 with a 62-cent increase in the federal cigarette tax and increase in other tobacco taxes enacted in February 2009, resulting in a total tax increase of \$1.01 per pack on 1 April 2009	- A 23.5% increase in total call volume was observed comparing the pre-tax (85,541 calls) and post-tax periods (104,452 calls), with the largest percent increase being 94.1% occurring in March 2009 - The number of tobacco users per month who received at least one counselling call increased during March and April 2009 compared to the same time in the previous year - although fewer calls enrolled in the multi-call program (4–5 counselling calls) after tax, they completed slightly more	↑ ↑

Source	Setting	n-values	Study description	Outcomes	Effect
				counselling sessions compared with those who enrolled before tax (1.9 versus 2.2 sessions respectively; $p < 0.0001$) By seven-month follow-up participant quit rate for 7-day and 30-day point prevalence did not differ significantly before versus after tax (7-day rates were 30.7% before and 28.7% after)	↑ ≈
Davis 2015 ⁷⁹	National multimedia campaign and quitline, US	n = 14,775 average calls per week to quitline in the 4 weeks pre and post the media campaign n = 30,304 average calls per week during the campaign period	Nationwide multimedia campaign from 19 March to 10 June 2012. Primarily run via the television it also included radio and video ads on websites including YouTube. Graphic and emotional content was featured in the campaign and all television and radio (in limited markets) ads were tagged with the quitline number or a smoke-free web address. Ads usually ran prior to 8pm to correspond with quitline operating hours	- An increase of 100 television gross rating points had a strong positive correlation with calls to the quitline ($\beta = 89.3$, $p < 0.001$) where the ad was tagged with the quitline number - When the ad was tagged with the web address, there was still a positive correlation between an increase of 100 television gross rating points and calls to the quitline, though this was not as strong ($\beta = 29.4$, $p < 0.001$) - The difference in correlation coefficients was significant ($p < 0.001$) - Analysis predicted that had all ads been tagged with the quitline number rather than some with the web address, approximately 140,000 more calls would have been made during the campaign period	↑ ↑ N/A
DeLaughter 2014 ⁸⁰	Alabama and Mississippi quitline, US	n = 2522 participants; n = 1,735 completed 4 quitline counselling sessions	12-month community based, multi-element quitline-facilitated peer navigation intervention integrated into the social networks of smokers with low income. Existing ex-smoking clients of quitline who were participating in their final quitline call at 6-month post successful quit attempt were recruited to become peer-navigators. These individuals received a 25-minute telephone training session equipping them with the tools to: market the quitline using their personal success story and persuade other smokers to provide their contact details to the quitline. Once the potential client provided their contact details attempts were made by the quitline to contact them	- During a 4-month period 11 peer-navigators were recruited from the quitline's existing eligible client list and underwent training; they were predominantly female (79%) - Out of 11, 4 peer-navigators returned referral slips from smokers known to them for a total of 23 smokers referred to the quitline - Attempts to contact the current smokers resulted in 3 new clients, all female and over 45 years old - Future improvements to protocol include: recruiting peer-navigators at the beginning of their cessation journey rather than at the 6-month point; simplifying the consent form for new smoker referrals; text messaging suggested	N/A N/A N/A N/A

Source	Setting	n-values	Study description	Outcomes	Effect
			to begin services	facilitator	
Duke 2014 ⁸¹	Florida quitline, US	n =141,221 quitline callers registered n =53,513 web users registered	Examination of the effect of a sustained media campaign about smoking cessation on registrations to quitline and a web-based service over a 35-month period. Campaign materials contained graphic content and emotive personal testimony and ads featured the Florida based quitline number and web address. A national campaign ran concurrently, see Davis 2015	- Registrations for the quitline surpassed the web service - An increase in television ads in a given market was associated with an increase of 7 quitline registrants per week ($\beta = 6.8$, $P<0.001$) and two web-coach registrants ($\beta = 1.8$, $P<0.003$) Ads highlighting free NRT resulted in more weekly registrants than those with no mention of free NRT ($\beta = 31.8$, $P<0.001$)	N/A ↑ ↑
Fildes 2015 ⁸²	Quitline data from Nevada state, US	n =1471 Nevada residents who are current smokers	Analysed outcome data for Nevada residents who enrolled in the Nevada quitline program for free smoking cessation services between 1 August 2013 and 31 July 2014. At 7-months post enrolment, outcome data related to abstinence was collected using the North American Quitline Consortium (NAQC) Minimal Data Set questionnaire	- The 7-month post-intervention follow-up data was available for 25.4% of the sample Quit rates showed that 34.6% reported continuous abstinence at 7 months, whereas 35.1% were abstinent at the 7-day point prevalence and 31.9% were abstinent at the 30-day point prevalence Patient satisfaction with the program revealed 77.6% of participants reported being very or mostly satisfied	N/A ↑ ↑
Goesling 2012 ⁸³	Callers to the Free & Clear telephone quitline based in Seattle, Washington, US	Initial dataset n = 7,357 n = 5,291 participants included in final analysis	Three items (confidence, stress, and urges) were added to an existing telephone protocol to explore the effect of self-efficacy on cessation outcomes	- Nicotine dependence ($p<0.001$) and stress ($p<0.001$) were related to baseline self-efficacy, with higher dependence and higher stress associated with lower self-efficacy for being able to quit in the future - Gender was correlated with baseline self-efficacy, with men reporting more confidence at baseline. However, this result was only marginally significant after controlling for nicotine dependence and stress ($p<0.06$). - Higher baseline self-efficacy was associated with higher rates of quitting (OR = 1.12, $p<0.01$) - No evidence existed of overconfidence leading to diminished cessation success ($p = 0.69$) - Shorter duration of quit attempts, shorter time to relapse, and stronger urges were associated with lower self-efficacy	N/A N/A N/A N/A N/A

Source	Setting	n-values	Study description	Outcomes	Effect
Kerkvliet 2014 ¹³	Enrolees to the South Dakota quitline, US	n = 11,603 full data sets of n = 26,876 enrollees	This study described the types of services requested by South Dakota quitline participants and the associated cessation outcomes across service types	- Frequencies of cessation services requested were coaching/varenicline (64.6%), coaching/bupropion (5%), coaching/NRT (22.6%), and coaching only (5.4%) Abstinence rates for service types were the following: coaching/varenicline (49.8%), coaching/bupropion (47.3%), coaching/NRT (42.9%), and coaching only (40.3%) - Chi-square analysis and confidence interval comparisons identified significantly higher abstinence ($p < .05$) for varenicline/coaching in comparison to coaching only or coaching/NRT	N/A N/A ↑
Kerkvliet 2015 ⁸⁴	South Dakota quitline, US	n = 10,720 quitline callers registered n = 4,935 quitline callers followed up and included in analysis	Examination of the association between self-reported mental health conditions and use of a quitline. Toll-free service for tobacco users, those who request cessation services were offered 5 quitline initiated follow-up coaching sessions delivered by trained health coaches. Eight weeks of complimentary NRT also provided, delivered in staggered batches following designated quitline calls	Quit attempt rate was significantly higher in the mental health condition group (74.5%) compared to those with no mental health condition (70.0%, $p = 0.007$) Quit rate was significantly lower in the mental health condition group, compared to the no mental health condition group (ITT = 16.4% vs. 21.5%, $p < 0.001$) - Both the mental health conditions group (mean 1.35 (0.73)) and no mental health conditions (mean 1.36 (0.71)) group were overall highly satisfied with the service on a scale out of 4. There was no difference between groups ($p = 0.9$) - There was no difference in the extent to which the quitline met the participants needs regardless of group ($p = 0.06$) approximately 90% of participants in both groups believed their needs were mostly met - Approximately 96% of participants in both groups would use the quitline again ($p = 0.4$)	N/A N/A N/A N/A
Kuiper 2015 ⁸⁵	Callers to the Asian Smokers' quitline, US	n = 5,771 callers from 48 states	The objective of this study was to examine characteristics of Asian Smokers' Quitline (ASQ) callers, how they heard about the quitline, and their use of the service	31% of callers were Chinese (Cantonese or Mandarin), 38% were Korean, and 31% were Vietnamese - About 87% of ASQ callers were male, 57% were aged 45–64 years, 48% were uninsured, and educational attainment varied - Ninety-six percent of all tobacco users were daily cigarette	N/A N/A N/A

Source	Setting	n-values	Study description	Outcomes	Effect
				smokers • Most callers (54%) were referred by newspapers or magazines • Nearly all eligible callers (99%) received nicotine patches • About 85% of smokers enrolled in counselling; counselled smokers completed an average of 4 sessions	N/A N/A N/A
Nohlert 2018 ⁸⁶	Callers to the Swedish National Tobacco Quitline (SNTQ)	n = 612 callers who returned the baseline questionnaire	The aim was to assess if self-perceived abilities to cope measured at baseline would predict abstinence at the 12-month follow-up. This was measured by two questions—one relating to the likelihood of the participant being smoke-free in one year, and one relating to the likelihood of the participant being able to handle stress and depressive moods without smoking	• Both variables at baseline were significant predictors for abstinence, however, only the perceived ability to handle stress and depressive mood without smoking remained significant in the adjusted analyses • The strongest predictor for abstinence in the adjusted analyses was smoking status in the week before baseline with an OR = 3.30 for point prevalence, and OR = 3.97 for 6-month continuous abstinence	N/A N/A
Rabius 2012 ⁸⁷	Callers to quitlines in various states across US	n = 45,510 callers and n = 3,522 RCT participants	This study evaluated how effectively African Americans are served by telephone counselling on quitlines. Empirical data from quitline callers was used, and to investigate effectiveness of counselling and quitting success among African Americans, data from a previous study by the author was reanalysed	• In all locations, African Americans were significantly more likely than non-Hispanic Whites to request counselling; (74% versus 67% in Texas, $p < 0.01$; 79% versus 74% in Louisiana, $p < 0.01$; and 92% versus 85% in DC, $p < 0.05$) • African Americans tend to use a quitline in greater proportions than their proportional representation in smoking communities. • African American quit rates were equivalent to those of non-Hispanic 'whites' as were their levels of satisfaction with the service and the number of counselling sessions completed • The effect of counselling when compared to self-help materials was higher overall ($p < 0.05$ among African Americans; $p < 0.001$ among non-Hispanic Whites), however the trend towards lower quitting rates among African Americans in both treatment groups was not significant. • There were no significant differences between African Americans and non-Hispanic Whites in reported 30-day	N/A N/A ≈ ≈

Source	Setting	n-values	Study description	Outcomes	Effect
				point prevalence of abstinence from smoking among respondents	≈
Saul 2014 ⁸⁸	Quitline funders and providers in US and Canada	Potential participants n = 273, with n = 176 quitline funders and providers responding to initial, n = 83 'key responders'	The research team identified practices that increased either the reach or efficacy of quitlines, as well as identified practices that were considered future strategies – those under consideration or being discussed by quitlines without much evidence. These practices were categorised by efficacy and reach, and a rating scale was established. Researchers aimed to determine the extent to which different practice types were implemented within and across quitlines, the patterns of implementation grouped by research evidence level, and the relationship between implementation of practices and either spending levels for quitlines or actual treatment reach outcomes	- Implementation rates ranged from 3% (n = 2; text messaging) to 92% (n = 57; providing a multiple-call protocol). More than half of the quitlines implemented 13 practices - A higher proportion of quitlines implemented A-level practices than C-level practices for efficacy (p = 0.026), and a higher proportion of quitlines implemented A-level practices than D-level practices for efficacy (p = 0.033). - Implementation of practices showing higher levels of evidence (B level) for increasing reach showed a moderate, but significant, positive correlation with both treatment reach (r = 0.39; P = 0.007) and spending per smoker (r = 0.36; P = 0.006). - Only 1 practice, conducting mass media promotions for the mainstream population, was moderately but significantly positively correlated with treatment reach (r = 0.41; p = 0.004) - The strongest relationship was found between quitline spending per smoker and treatment reach (r = 0.80; p < 0.001).	N/A N/A ↑ ↑ N/A
Vickerman 2015b ⁸⁹	Quitline data from North Carolina and Texas state, US	n = 2 states n = 715 Quitline callers during a 2012 national tobacco education campaign	Analysed telephone quitline outcome data via a survey 7-month post enrolment during the Centres for Disease Control and Prevention's Tips from Former Smokers (Tips) campaign from 19 March to 10 June 2012. The 12-week Tips campaign for smoking cessation predominantly advertised on television as well as radio, online video and banners, print media, and out-of-home advertising. Resources offered included the national quitline number or the National Cancer Institute's website which promoted the quitline number. Callers indicating readiness to	- At 7 months post enrolment, 27.7% of participants reported tobacco abstinence for 7 or more days, and 24.5% reported abstinence for 30 or more days. - Callers with high nicotine dependency scores were less likely to quit (quit ≥ 7 days model, adjusted OR, 0.71 [95% CI, 0.57–0.89], p = 0.003; quit ≥ 30 days model, adjusted OR, 0.74 [95% CI, 0.58–0.93], p = 0.01) than those with lower scores - Callers who completed more counselling calls were more likely to quit (quit ≥ 7 days model, adjusted OR, 1.15 [95%	↑ N/A ↑

Source	Setting	n-values	Study description	Outcomes	Effect
			quit within 30 days were eligible for a multiple-call program in North Carolina and Texas. The program included an initial assessment and planning call plus 3–4 additional counselling calls, as well as nicotine replacement therapy (NRT) benefits	CI, 1.01–1.30], p = 0.03; quit ≥30 days model, adjusted OR, 1.15 [95% CI, 1.01–1.30], p = 0.03) than those who completed fewer calls	
Zhang 2014 ⁹⁰	Quitlines in 23 states, US	n = 91,911 callers	This study examined the effect of the Centre for Disease Control (CDC)'s National Tobacco Education Campaign: Tips from Former Smokers (Tips) on quitline callers' cessation outcomes.	• The number of quitline callers and callers who received counselling and/or NRTs increased by 88.6% and 70.8% respectively • The number of quit attempts increased by 24.7%, from 11,616 to 14,489 • The number of 7+ day quits increased by 22.1%, from 6,821 to 8,328 • Successful cessation outcomes increased with increasing number of counselling calls completed. No consistent relationship between the Tips campaign and cessation outcomes by number of calls completed was found • For multiple-call enrollees who completed at least one call, higher exposure to Tips campaign was associated with significantly more quit attempts and 7+ day quits	↑ ↑ ↑ ≈ ↑

Key: ↑ = increase; ↓ = decrease; ↔ = mixed; ≈ = no difference; N/A = not applicable

6 Quality assessment of evidence

Overall scoring of the included evidence according to the NHMRC body of evidence matrix components can be seen in Table 3 for Question 1, which relates to key components of a quitline service; and Table 4, for Question 2, relating to barriers and facilitators to use.

Review Question 1 – key components

Evidence Base [A rating]

The grade of evidence assessed in this review is rated as **excellent**. The studies included for review included multiple Level I studies (n = 4) and several Level II studies (n = 21). These high-level studies were supported by a number of less methodologically robust studies, including: Level III-1 (n = 2), Level III-2 (n = 4), Level III-3 (n = 5), Level IV (n = 15). The quantity of evidence as well as the lack of any major methodological issues in the Level I and II studies included for review were the reasons for grading the evidence base component as excellent (**A rating**).

Consistency [B rating]

The consistency of the evidence, i.e. the extent to which the studies presented consistent results, is deemed to be **good**. Individual study outcomes relating to key components of a quitline service demonstrated a mix of neutral and positive effectiveness. This was further reflected in the findings of the Level I studies. While there is some inconsistency in the presented results this can be explained by understanding the nature of smoking cessation interventions in research and the inherent variability in intervention protocol and population which may influence the final outcome. The majority of studies used self-reported data and reported their outcomes at commonly accepted follow-up intervals (e.g. 3, 6, 12 months) using appropriate odds or risk ratios and confidence intervals. As explained in Section VII of this review, evidence for the effectiveness of individual components of a quitline service is varied, again this is likely due to the lack of consistently reproduced interventions available in the published literature. Hence, the consistency of the evidence presented in this review is satisfactory, demonstrating explainable inconsistency (**B rating**).

Clinical impact [C rating]

The clinical impact of the results presented in this rapid review are **good**. There is currently not an accepted and endorsed definition of clinical significance for smoking cessation. However, a recent Cochrane Systematic Review found that at the individual level, behavioural interventions compared to minimal intervention improved smoking cessation with a risk ratio of 1.57; this was reduced to a risk ratio of 1.24 when compared to individuals who were offered pharmacotherapy.⁹¹ Many of the studies demonstrated effect sizes similar to these figures. However, this was noted in both intervention and control groups in most instances, indicating that any intervention is better than none when it comes to provision of quitline services to smokers. (**B rating**)

Generalisability [B rating]

The generalisability of the results presented in this review is rated as **good** overall. Outcomes may be generalised to the Caucasian Australian population; two included studies were conducted in Australia and the rest were performed in other developed Western nations, e.g. the US and the UK. Of note, there are generalisability issues for certain key components such as the content of counselling protocols. The US tend to offer follow up counselling calls from quitline only to people willing to set a quit date within a month, whereas Australia quitlines typically offer at least two pre-quitting callbacks to see if it is possible to increase a smoker's motivation to change. This allows quitline counsellors to help people cut down (primarily for financial and skill development benefits) with clients for whom the prospect of sudden cessation is overwhelming or frightening. This difference in approach means that quit rates for US services are often higher than for Australian-based studies as they work with more motivated clients. No studies were identified or included in this study that involved the Australian Indigenous population. Despite this, there was evidence supporting cultural tailoring for Asian-language, which may be transferrable for the benefit of the large population of Asian people in Australia who have English as a second language. Though numbers of included studies were small for the following demographics, they are represented in the evidence base in this review: young people, individuals with a mental health condition, those with alcohol dependency and pregnant women. Given the similarity of the populations represented in the included studies to the target population and in acknowledgment of the lack of studies including indigenous Australians, the generalisability of the evidence was rated as good (B rating).

Applicability [B rating]

The evidence included in this review is considered to be **good** and hence applicable to the Australian population. Two included studies were conducted in Australia (Victoria and South Australia) and as such are likely to be the most applicable to the Australian population. However, the great majority of the remainder of the studies were delivered in English speaking, developed Western countries and may be applicable to the Australian context providing there is similar resourcing and infrastructure. **(B rating)**

Table 3: NHMRC body of evidence matrix summarising the evidence base for key components of a quitline service. Review author rating decisions are highlighted in grey

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a systematic review or multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target	Population/s studied in the body of evidence are similar to the	Population/s studied in body of evidence differ to target population in	Population/s studied in body of evidence differ to target population

	population in question	target population in question	question, but it is clinically sensible to apply this evidence to the target population	and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian context	Applicable to Australian context with few caveats	Probably applicable to Australian context with some caveats	Not applicable to Australian context

Review question 2 – barriers and facilitators

Evidence Base [B rating]

Regarding barriers and enablers to quitline use, the evidence base was deemed to be **good**. The studies included for review included multiple Level II studies ($n = 4$) as well as some Level III-2 ($n = 1$) and Level IV ($n = 1$). The studies lacked any major methodological issues, however, a greater quantity of studies to answer question 2 would have been preferred; hence the good rating (**B rating**).

Consistency [C rating]

The consistency of the evidence, i.e. the extent to which the studies presented consistent results, is deemed to be **satisfactory** for question 2. Individual study outcomes relating to NRT as an enabler for success demonstrated inconsistent results, this is likely a result of heterogeneous intervention design and sample characteristics. It was not possible to establish consistency for enablers to quitline use as the identified enablers were supported by single studies. Given the inconsistent intervention design and small pool of studies the consistency of the evidence presented in this review is satisfactory, owing to explainable inconsistency (**C rating**).

Clinical impact [C rating]

The clinical impact of the results presented in this rapid review, for question 2, are **satisfactory**. While the clinical impact of the evidence for barriers and enablers to quitline use is deemed moderate, the factors uncovered in this review do form some direction for future interventions seeking to improve exiting efforts. (**C rating**)

Generalisability [B rating]

As with review question 1, for question 2 generalisability of the evidence was found to be **good**. Outcomes may be generalised to the Caucasian Australian population; studies addressing barriers and enablers to quitline use were performed in developed Western nations, e.g. US and NZ. There is currently a paucity of literature on barriers and enablers relating specifically to Australian people. Given the similarity of the populations represented in the included studies to the target population and in acknowledgment of the lack of studies generalisable to indigenous Australians, the generalisability of the evidence was rated as good (**B rating**).

Applicability [B rating]

Once again, applicability to the Australian population was deemed to be **good** overall for the evidence base pertaining to question 2. The studies were delivered in English speaking, developed Western countries and may be applicable to the Australian context providing there is similar resourcing and infrastructure. There is

however a need for further literature in this area specific to the Australian context and taking into account specific barriers and facilitators relating to high risk subgroups, including Indigenous Australians and those with mental health conditions **(B rating)**.

Table 4: NHMRC body of evidence matrix summarising the evidence base for barriers and facilitators to quitline use. Review author rating decisions are highlighted in grey

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a systematic review or multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population in question	Population/s studied in the body of evidence are similar to the target population in question	Population/s studied in body of evidence differ to target population in question, but it is clinically sensible to apply this evidence to the target population	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian context	Applicable to Australian context with few caveats	Probably applicable to Australian context with some caveats	Not applicable to Australian context

7 Analysis of evidence

Review Question 1

Key components of quitline services

Studies meeting the NHMRC inclusion criteria were available to assess six of the seven pre-specified key components for this rapid review of evidence. The exception was for 'hours that service is open'. Where appropriate, this has been supplemented with relevant data from studies not meeting criteria for inclusion based on the NHMRC evidence grading.

Counselling competencies required

Assessment of fidelity of counselling compared to treatment protocols is reportedly undertaken as part of standard practice across many quitline services. However, studies evaluating the impact of specific counselling competencies were lacking. A minimum set of qualifications and experience in a related discipline is typically required for counsellors. In addition, specific quitline counselling skills-based training is required, with ongoing training and feedback provided from within most organisations.

A study of the Swedish National Tobacco Quitline (SNTQ) by Lindqvist et al.² reported that counsellors are trained health professionals such as nurses, dentists, dental hygienists or psychologists who undergo six months of training in tobacco cessation methods to become SNTQ counsellors. In this controlled clinical trial, half of the counsellors also underwent a two-day training course in motivational interviewing to compare the addition of this approach to standard care on quitting outcomes. Counsellors allocated to the standard treatment arm also underwent additional training totalling approximately 40 hours over the study period. A significant benefit was observed by six-month follow-up for continuous abstinence, with motivational interviewing increasing quit rates by 5%.

A study by McDaniel et al.⁶¹ reported on a three-arm RCT centred around the Quit for Life program operating in US by Alere Wellbeing (formerly Free and Clear). Quit coaches were required to have a bachelor's degree in a related field and complete more than 200 hours of training as well as receive ongoing supervision and feedback. Randomly selected counselling recording sessions were rated for compliance with the study protocol for fidelity, with the primary criterion being whether the counsellor focused the call on identified relapse risk(s). The rating was undertaken by two independent reviewers (a staff member and a quit coach supervisor). Any protocol deviations were addressed with individual feedback from the quit coach supervisors and ongoing training for all quit coaches. No outcomes about fidelity were reported.

Additional relevant data from studies not meeting criteria for inclusion in the rapid review:

A study by Lorencatto et al. in 2014⁴⁸ that did not meet criteria for inclusion in this rapid review of evidence, did evaluate treatment fidelity by comparing counselling manuals to 75 audio-recorded transcripts from the UK national quitline service. Compliance varied substantially across the 45 different smoking cessation behavioural change techniques being evaluated, with less than half (41.8%) of the treatment manual successfully delivered on average. Lorencatto et al. report that identifying gaps in current practice by coding recorded interviews to treatment manuals can be used as a means to identify training needs. Moreover, the low fidelity identified in this study highlights the need to establish routine procedures for monitoring delivery of behavioural support.

The Michael et al.⁹² study assessing counsellor effects on quit rates for the Arizona Smoker's Helpline in the US identified that 2% of differences in quit rates and 4% of the Outcome Rating Scale variability, being a proxy measure for life satisfaction, can be attributed to variability in the service provided by individual counsellors ($p = 0.003$). This compares to provider variability of between 6% and 10% among psychotherapists.⁹² Michael et al. reports the use of treatment guidelines as a means to train staff based on key principles outlined in the US Public Health Guidelines for Treating Tobacco Use⁹³ and in the Tobacco Dependence Treatment Handbook.⁹⁴

Relevant results from grey literature search not meeting inclusion criteria for this rapid review:

In an audit by Brose, McEwen and West⁹⁵ evaluating 46,237 one-to-one treatment episodes in the UK, 7.6% of variance in carbon monoxide verified four-week quit rates could be attributed to differences between individual specialist practitioners and 6.4% due to differences between services. However, specialist practitioner and service factors contributing to these differences were not described. The number of one-to-one treatment episodes delivered by the practitioner was not associated with successful quit attempts, suggesting that busier practitioners were not necessarily more effective.

One study by Brose et al.⁹⁶ evaluating a training program for all stop smoking practitioners in the UK (not just those involved in quitline services) used 25 multiple-choice questions to evaluate the national online knowledge training program developed by the National Health Service Centre for Smoking Cessation and Training. Authors of this study report that although standards for training and delivery exist in the UK, they are not mandatory, and practice has drifted away from initial guidance. There are no minimum entry requirements to work as a stop smoking practitioner and practitioners have a wide range of professional backgrounds (e.g. nursing, pharmacy and administration). These variations may impact smokers' chances of successfully quitting.⁹⁶ The training program was used for an average of 145 minutes (SD 172 minutes), with the time spent on the program significantly predicting the change in overall assessment scores for knowledge ($p < 0.001$). A quadratic trend identified that after spending 441 minutes (7 hours and 21 minutes) on the training, any additional time would not further increase knowledge scores. Improvements in knowledge for those who spent at least five minutes on the training was significantly larger than for those who spent less time on training ($p < 0.001$).

A study by Michie, Churchill and West in 2011 developed and applied a system to identify competences required to deliver individual and group-based behavioural support for smoking cessation.⁹⁷ Ninety-four competencies were identified of which 59 were cited in at least two guidance documents. Seventeen of these were supported by RCT evidence and nine by evidence from the services. However, these competencies are not specific to quitline services. Fourteen competencies were cited in at least two source documents and at least two RCTs, being: ability to: (1) provide information on the consequences of smoking and smoking cessation; (2) provide information on withdrawal symptoms; (3) facilitate barrier identification and problem solving; (4) facilitate relapse prevention and coping; (5) facilitate action planning/develop treatment plan; (6) facilitate goal setting; (7) measure CO; (8) advise on stop smoking medication; (9) assess current and past smoking behaviour; (10) assess current readiness and ability to quit; (11) assess past history of quit attempts; (12) offer appropriate written materials; (13) prompt commitment from the client there and then; and (14) give options for additional and later support. The nine behaviour change techniques associated with higher success rates in the English Stop Smoking Services were: (1) strengthen ex-smoker identity; (2) elicit client views; (3) measure CO; (4) give options for additional and later support; (5) provide rewards contingent on stopping smoking; (6) advise on changing routine; (7) facilitate relapse prevention and coping; (8) ask about experience of stop smoking medication being used; and (9) advise on stop smoking medication.

Behaviour change counselling approaches and adherence to these

Cognitive and behavioural therapy is the standard behavioural change technique used to underpin quitline counselling. The addition of other theoretical models, including acceptance and commitment therapy (ACT)¹ and motivational interviewing (MI)^{2,3} have demonstrated the potential for increased quitting benefits. However, other techniques, such as the addition of gain-framed messaging, have not shown benefits in long-term quitting outcomes.^{4,5}

Within the Schwindt et al. systematic review of quitline services for patients with mental illnesses⁵⁴, one study by Rogers et al. (2015)³, used a multi-session manual-based counselling protocol based on motivational interviewing and CBT with accompanying homework assignments. This study identified a significantly higher 30-day abstinence rate compared to the control.

An RCT comparing ACT with CBT for smoking cessation delivered to quitline callers in South Carolina, US, identified that ACT was more effective than CBT for increasing the number of completed calls ($p = 0.001$), though no statistically significant benefit was observed for point prevalence abstinence by 6-month follow-up.¹ In this context ACT focuses on willingness to experience physical cravings, emotions and thoughts that trigger smoking (i.e. acceptance) while making value-guided behaviour changes (i.e. commitment). Although similar to CBT in terms of teaching skills to cope with smoking cues, the philosophy of ACT is based on Relational Frame Theory.⁹⁸ This theory posits that trying to control learned associations, such as between an urge and smoking, creates a paradox whereby new associations are formed that interfere with behaviour change. For example, distraction from urges leads to more urges.¹ Both the ACT and CBT interventions were delivered over a five-session counselling protocol in combination with NRT. In the case of this RCT, ACT acceptance components taught skills on: increasing willingness to experience urges that cue smoking; changing the function of smoking urges, and; responding differently to smoking urges (e.g. noticing and not acting on urges). Commitment components focused on helping individuals articulate values guiding quitting (e.g. love of one's children) and taking actions to quit that are guided by those values. CBT was the standard CBT-based counselling intervention delivered by Alere, the organisation that runs the South Carolina quitline, and offered through that quitline. Sessions focussed on assisting participants to develop a quit plan and teaching skills such as distraction, stimulus control, and changing the content of thoughts about smoking. The first session for both groups was 30-minutes with each subsequent call lasting 15-minutes. Adherence to ACT and CBT were evaluated by audio recording calls, which were then each independently rated by two trained raters. Inter-rater agreement was high and did not differ by study arm (proportion of positive agreement 0.99 for ACT and 0.91 for CBT based on the ACT adherence raters' manual and the Alere Call Quality Management Tool, which is used in multiple National Institute of Health (NIH)-funded trials.

A 2010 study by Toll et al.⁵ and subsequent secondary analysis of the same dataset by Fucito et al.⁴ assessed the effectiveness of using gain-framed messages within counselling ($n = 810$) compared to standard care counselling and printed materials ($n = 1,222$) within the New York State quitline service. Gain-framed messages emphasise the benefits of quitting smoking (i.e. gain-framed) compared to the losses of continued smoking (i.e. loss-framed). Delivery of counselling by specialists trained to use gain-framed statements resulted in a significantly higher rate of abstinence at two-week follow-up for the gain-framed group (23.3%) compared to standard care (12.6%). However, these significant results were not maintained by three-month follow-up (abstinence levels were 28.4% and 26.6% for intervention and control groups respectively).

A study evaluating the Swedish Quitline (SNTQ)⁹⁹ reported that standard counselling consisted of a mixture of motivational interviewing, cognitive behavioural therapy and pharmacological consultation. Regular call monitoring with supervisors is performed for quality assurance in addition to quality assessment (fidelity)

for provision of motivational interviewing assessed by an independent, university-based coding laboratory. No data was reported on adherence to counselling protocols within this study and both intervention and control comparison groups received the same counselling, but on a proactive schedule (where clients are offered a number of callbacks) or reactive schedule (where only incoming calls by clients are attended). No differences were observed in quit outcomes at six- or 12-month follow-up. Another study of the SNTQ² evaluated the addition of motivational interviewing to standard quitline counselling compared to standard counselling alone. Audio-recordings of the treatment sessions at six-week intervals were undertaken with the five randomly selected sessions from each counsellor, coded using the Swedish translation of the motivational interviewing treatment integrity code. Based on this coding, counsellors trained in motivational interviewing delivered a significantly higher level of motivational interviewing compared to the standard treatment counsellors for all skills variables assessed. This includes: empathy; motivational interviewing spirit; complex reflections; motivational interviewing adherent utterances ($p < 0.001$ for all); and open questions ($p = 0.009$). A significant benefit was observed for the motivational interviewing group by six-month follow-up, improving continuous abstinence quit rates by 5%.

Another study this time by Lindqvist et. al also evaluated the SNTQ², in a controlled clinical trial design ($n = 772$) comparing standard treatment or standard treatment with motivational interviewing added to the treatment protocol of the first session. Motivational interviewing was delivered by six to eight different counsellors who underwent training in motivational interviewing through a two-day workshop made up of didactics and practical exercises. No difference between groups was observed for seven-day point prevalence. However, a statistically significant benefit was observed for six-month continuous abstinence, with motivational interview increasing quit rates by 5% (19% versus 14%; $p = 0.047$).

Additional relevant data from studies not meeting criteria for inclusion in the rapid review:

A study by Lorencatto et al. 2014⁴⁸ which did not meet criteria for inclusion in this rapid review of evidence, did evaluate treatment manuals and transcripts of 75 audio-recorded behavioural support sessions from the UK national quitline service. The purpose of this study was to evaluate fidelity, as behavioural support is often not delivered as specified in the service treatment manual.⁴⁸ In this study, fidelity was evaluated by coding interview transcripts using taxonomy of 45 smoking cessation behavioural change techniques within treatment manuals. An average of 41.8% of manual-specified behavioural change techniques were delivered per session (Standard Deviation (SD) 16.2), with fidelity varying by counsellor (32%–49%). The highest fidelity was observed in pre-quit sessions (46%) and the behavioural change technique of 'give options for additional support' (95%). The lowest fidelity was reported among quit-day sessions (35%) and the technique of 'set graded tasks' (0%). The duration of the session produced a positive correlation with fidelity, showing a longer session included higher compliance to the treatment protocol ($p < 0.01$).

Relevant results from grey literature search not meeting inclusion criteria for this rapid review:

A study by West, Evans and Michie also published in 2011¹⁰⁰ evaluated a taxonomy of behavioural change techniques compared to service success rates across UK stop-smoking services. Of the 30 treatment manuals available for coding (from a possible 145 services that were contacted), 14 group-support behavioural change techniques were identified. On average seven behavioural change techniques were identified in each manual and two were positively associated with four-week quit rates, being 'communicate group member identified' and a 'betting game' (where a financial deposit is lost if a stop-smoking 'buddy' relapses). However, this is not specific to quitline counselling.

Another study by West et al. identified the behavioural change techniques from treatment manuals across 43 UK-based stop-smoking services.¹⁰¹ From 43 possible behavioural change techniques, stop-smoking service manuals included a mean of 22 (range 9–37). As described above, nine behavioural change

techniques were significantly associated with both self-reported and carbon monoxide validated four-week abstinence rates.

Quality assessment of service and/or counsellors

Participant satisfaction with quitline service and/or counsellors:

Among studies reporting on participant satisfaction with the service and/or counsellors, satisfaction is rated as high and the service reported to be helpful. Assessment is by self-report among follow-up participants, which typically only represents half of the initial enrolling population. Therefore, these responses need to be considered in the context of the larger study population of non-responders, where non-responders stereotypically are relapsed smokers. Of the two included studies reporting that fidelity of counselling was undertaken, neither reported satisfaction results related to these assessments.

Participant satisfaction with a one-off quitline counselling session with the addition of two weeks of NRT and self-help materials was reported among 373 callers to the Nevada quitline (25.4% of initial sample).⁸² Data analysis identified that 68.4% were very satisfied, 9.2% were mostly satisfied, 0.4% were somewhat satisfied, 9.4% were not at all satisfied and 12.6% responded 'don't know'. Fildes et al. concluded that satisfaction level is likely related to the participants smoking status post-intervention. The intervention consisted of a single nurse-designed counselling session that was holistic in nature and included physical, emotional, mental and spiritual effects of nicotine dependence, two weeks of NRT by mail and a packet of self-help and other education materials collaboratively developed by a nurse researcher and certified addictions registered nurse-advanced practice, health educator and clinical counselling director. By seven-month follow-up, 34.6% of contactable participants (n = 373) reported continuous abstinence, 35.1% reported seven-day point prevalence and 31.9% reported 30-day point prevalence. The reporting of a continuous abstinence rate that is higher than the 30-day and seven-day point prevalence abstinence rates is odd and suggests a reporting error. Authors of this study compare the smoking cessation outcomes to an older (1996) study comparing single-session counselling with 7.5% quit rates and 9.9% quit rates for the multiple session counselling by 12-month follow-up.¹⁰² However, this study did not include pharmacotherapy as part of the intervention.

Another study evaluating participant satisfaction was the Rabinus et al. study, which assessed the effectiveness of quitline services in African American callers from Texas, Louisiana, Washington and District of Columbia African Americans through an RCT.⁸⁷ Mean satisfaction on a four-point Likert scale showed no difference between callers from the three locations (3.5, 3.3 and 3.3 respectively) or between non-Hispanic White's from the same three locations (3.4, 3.3 and 3.2). By seven-month follow-up quit rates (30-day point prevalence) were 10% and 12% among African Americans and non-Hispanic Whites.

No difference was observed between groups for satisfaction among callers of the New York State Smokers' quitline⁵ for gain-framed messages (92.4% reporting 'very satisfied' with the initial quitline contact) compared to standard-care (91.4% reporting 'very satisfied' p = 0.32). Another assessment of the New York State Smoker's quitline, this time by Unrod et al.¹⁰³ also reported that participants were highly satisfied with the services they received with an overall mean score on the Client Satisfaction Questionnaire of 25.47 (SD 2.85; questionnaire range 8–32) at baseline with no differences observed between the three treatment groups evaluated. High levels of satisfaction were also reported among the groups that received *Forever Free* relapse prevention booklets, with a mean score of 25.76 (SD 4.61) at six months and 26.09 (SD 4.69) by 12 months.

Satisfaction was also measured in the Saul et al. study which asked the question: "How helpful was the Quitplan Helpline as a whole?"¹⁶ Nearly three-quarters (73.8%) of callers reported a response of 'very

helpful', with responses differing significantly between the different NRT protocol groups, which compared an eight-week shipment of NRT compared to a split-shipment of five weeks then three weeks. A response of 'very helpful' was reported among 77.2% of the single-shipment group (i.e. one shipment of eight weeks), compared to 81.1% in the two-shipment group (i.e. full eight-week supply over two shipments) and 57.8% of the five-week one-shipment group (i.e. those only receiving the first part of the intended eight-week shipment; $p = 0.004$). No difference in 30-day point prevalence abstinence was observed between groups by seven-month follow-up. Therefore, although participant satisfaction increased when more NRT was provided, this had no impact on quit rates.

In the Segan et al. RCT comparing extended callbacks to ex-smokers to prevent relapse over the longer term (beyond one-month cessation), 97% of participants in both trial groups rated the callback service as helpful (83% very and 14% somewhat). Belief that the callbacks made a difference to the success of their quit attempt was reported by 87% of participants and most believed that the number of calls received from quitline was 'about right' (84% in usual care group and 81% in intervention). Intervention participants were more likely to say that they received too many calls (11% compared to 2%), while usual care participants were more likely to say they received too few calls (14% versus 8%; $p < 0.001$).

Among the 347 participants in the Danaher et al. 2015⁵⁸ study who received at least one quitline counselling call about smokeless tobacco use, 85.6% described the call as helpful and 93.8% stated that they would recommend the program, with 63.3% recording the highest rating of 'definitely will recommend'. When comparing quitline-only with the web and quitline groups, participants in the web and quitline groups reported higher ratings of both program helpfulness ($p < 0.05$) and ratings of recommendation ($p < 0.05$). Among the 1147 participants who reported on the usefulness of the self-help material, 79% described it as useful, with level of reported usefulness varying by condition ($p < 0.001$), being: web-only (mean 2.70), web and quitline (mean 2.61), quitline only (mean 2.49) and control (mean 2.35). This suggests that the participant assessment of usefulness was dependent on what other service they received at the time.

A study by Kerkvliet, Wey and Fahrenwald⁸⁴ which evaluated prevalence and outcomes of quitline among people with and without a mental health condition, assessed satisfaction of the service to be high. The service consisted of five follow-up counselling sessions by trained health coaches from the South Dakota quitline, combined with a tobacco cessation product including NRT (in the form of gum, patch or lozenge) or medications bupropion hydrochloride or varenicline tartrate, provided free for an eight-week trial period. Medications were delivered in staggered increments following designated coaching sessions and mailed directly to the participant's home (physician referral required for varenicline or bupropion). Of the 12,173 quitline callers who enrolled in the service between September 2010 and August 2012, 951 did not receive an evidence-based service (i.e. no medication or at least one counselling session). Using a four-point Likert scale, with one being 'most satisfied' and four being 'least satisfied', the average service satisfaction rating was 1.36 (SD = 0.71) for the group with a mental health condition ($n = 894$) compared to 1.5 (SD = 0.73) for the group without a mental health condition ($n = 4041$), showing no evidence of any significant differences between groups. The extent to which quitline met the participants' needs was assessed as 87.7% for the mental health condition group and 89.8% for the 'no mental health condition' group ($p = 0.06$). When asked if they would use the quitline again, 96.3% of participants with a mental health condition responded 'yes definitely' or 'yes I think so' compared to 96.9% of the 'no mental health condition' group. Of note, participant satisfaction responses were taken between 6.5 months and 7.5 months post enrolment, with response rates from 44.0% of the original callers self-reporting a mental health condition compared to 48.0% of the group with no mental health condition ($p < 0.001$). The main reported difference for the response rates were a greater proportion of invalid phone information in the mental health condition group. A significantly higher abstinence rate was observed for varenicline tartrate plus coaching compared

to coaching only or coaching with NRT after a seven-month follow-up.¹³ The range of abstinence across these four treatment protocols was similar, being 49.8% for varenicline tartrate plus counselling; 47.3% for bupropion hydrochloride plus counselling; 42.9% for NRT plus counselling; and 40.3% for counselling alone.

Fidelity of counselling

A study evaluating the Swedish Quitline (SNTQ)⁹⁹ reported that standard counselling consisted of a mixture of motivational interviewing, cognitive behavioural therapy and pharmacological consultation. Regular call monitoring with supervisors was performed for quality assurance in addition to quality assessment (fidelity) for provision of motivational interviewing assessed by an independent university-based coding laboratory. No data was reported regarding adherence to counselling protocols within this study and both intervention and control comparison groups received the same counselling, but on a proactive schedule (i.e. quitline counsellor offers a number of callbacks) or reactive schedule (i.e. where only incoming calls are attended). Likewise, the McDaniel et al.⁶¹ study evaluating a three-arm RCT centred around the Quit for Life program assessed fidelity through compliance ratings from recorded counselling sessions. This was undertaken by two independent reviewers (a staff member and a quit coach supervisor). Any protocol deviations were addressed with individual feedback from the quit coach supervisors and ongoing training for all quit coaches. However, no outcomes about fidelity were reported. An evaluation of the New York State Smokers' quitline by Toll et al. in 2010⁵ assessed fidelity of counselling delivery through ratings of interview audiotapes with eight independent tape raters blinded to study hypothesis, rating a random sample of approximately 20% of all tapes (around 400 tapes divided into 50 per rater). A validated adherence system was used by raters that evaluated discriminability (i.e. the capacity to discriminate) between the two types of counselling in the use of two gain-framed statement items, being: achieving benefits and avoiding negative consequences; and four standard quitline interview items, being: assessing current smoking, assessing quit attempts, assessing medication use and assessing intentions to quit. Seven-point scales were used to evaluate adherence, where 1 was 'not at all' and 7 was 'extensively'. A reliability sample of 10 recordings revealed a high level of inter-rater reliability by use of the model for random effects (range of average intraclass correlation coefficient estimates for all six items = 0.87–0.99). Statistically significant differences were observed between groups on the two gain-framed statement items, with specialists trained in gain-framed messaging providing gain-framed counselling more frequently than those providing standard-care counselling (for achieving benefits, gain-framed mean frequency rating was 3.9 versus 1.4 in the standard-care group; $p < 0.001$; and for avoiding negative consequences, mean frequency rating was 1.5 compared to 1.0 in the standard care group; $p < 0.001$). No differences were observed between the two counselling groups on the four standard quitline interview items. Similar methodology was applied in the Toll et al. 2015 study, which evaluated the use of brief motivational counselling to limit or abstain from alcohol plus an alcohol reduction booklet added to standard quitline tobacco counselling, as compared to smoking cessation counselling plus a smoking cessation booklet added to standard care.¹⁰⁴ Reliability sample with 10 recordings coded by seven raters revealed a high level of inter-rater reliability (mean intraclass correlation coefficient = 0.88–0.99). Adherence outcomes differed significantly in the expected directions, with the alcohol plus tobacco group using alcohol-focused statements significantly more frequently compared to the tobacco-only group. Standard care quitline outcomes did not differ significantly between the two groups. Unlike the 2010 Toll study that showed no statistically significant difference at long-term follow-up, the 2015 Toll study did result in a statistically significant 7-day point prevalence abstinence from smoking at seven-month follow-up in the alcohol plus tobacco quitline intervention arm (13.5%) compared to the tobacco only comparison arm (10.3%; OR 1.37; 95% CI 1.04–1.80; $p = 0.03$).

Additional relevant data from studies not meeting criteria for inclusion in the rapid review:

A study by Lukowski et al.¹⁰⁵, which was not identified for inclusion in this rapid review as it only evaluated participant demographics among quitline callers, did mention a minimum dataset for evaluation as part of North American Quitline Consortium (NAQC) recommendations. In addition to the 18-question version of the NAQC checklist, a series of mental health screening questions were also asked during the intake interview among quitline callers. However, results regarding implementation of this checklist and degree of adherence were not reported.

Identified in the grey literature search, the full NAQC dataset includes nine broad categories and is available via the NAQC website.¹⁰⁶ A copy of the checklist is included in Appendix 2. This checklist is a supplement to the *"Quitline services: Current Practice and Evidence Base"* guide.¹⁰⁷ The checklist includes a summary of the evidence, current status of each service among quitlines and recommendations and questions for consideration. Additional older resources were also identified as being produced by the NAQC regarding quality assessment of service provision, including:

- Telephone Quitlines: A resource for development, implementation and evaluation published in 2004¹⁰⁸
- Quitline Operations: Back to basics: A compilation of lessons learned from the North American
- Quitline Consortium's third conference call training series published in 2005¹⁰⁹
- Quitline Operations: A practical guide to promising approaches also published in 2005.¹¹⁰

A study by Lorencatto et al. 2014⁴⁸, which did not meet criteria for inclusion in this rapid review of evidence, did evaluate treatment fidelity by comparing counselling manuals and to 75 audio-recorded transcripts from the UK national quitline service. Compliance varied substantially across the 45-different smoking cessation behavioural change techniques being evaluated, with less than half (41.8%) of the treatment manual successfully delivered on average. The researchers report that identifying gaps in current practice by coding recorded interviews to treatment manuals can be used as a means to identify training needs. Moreover, the low fidelity identified in this study highlights the need to establish routine procedures for monitoring delivery of behavioural support.

Relevant results from grey literature search not meeting inclusion criteria for this rapid review:

Evaluation of quitline operations is encouraged in the NAQC 2003 resource.¹¹¹ These guidelines recommend the implementation of a quality improvement plan to measure and track the program's performance, involving the collection of objective behavioural data, as well as subjective satisfaction data, from telephone follow-up surveys conducted with randomly selected callers.

Counsellor- or client-initiated follow-up calls

Across a wide array of study designs, counsellor-initiated calls do offer a benefit on smoking cessation outcomes compared to client-initiated calls based on level 1 evidence.

Twelve studies delivering counsellor-initiated calls pooled together in a meta-analysis by Stead et al. identified a benefit in quitting outcomes at final follow-up compared to different comparator groups. The sub-group of studies (n = 15) evaluating trials of interventions for people calling quitlines within the Stead et al. Cochrane review⁶ identified 12 studies with counsellor calls back to people who had initiated contact with the quitline. The number of calls varied with three studies reporting more than one schedule and small differences were observed in level of support across the control groups. Twelve studies with 30,182 participants were able to be pooled within a meta-analysis to assess the effect of additional counsellor-initiated support, identifying a statistically significant benefit on quitting outcomes at longest follow-up in favour of the counsellor-initiated support (RR 1.38; 95% CI 1.28–1.49; p<0.00001; n = 12 studies with 30,182 individual participants). Due to substantial heterogeneity (I² = 71%) re-analysis using the random effect

model was undertaken, providing a very similar estimate of effect (RR 1.41; 95% CI 1.20–1.66). The three studies carrying the most weight within the meta-analysis all had significant results, as did three additional studies, suggesting benefit from these types of interventions in many settings but not all. Telephone counselling initiated by quitline counsellors for the initial call identified increased quitting (51 studies, $n = 30,246$ participants; RR 1.27; 95% CI 1.20–1.36). Following a meta-regression controlling for differences in baseline support, maximum number of calls and motivation, the smoking cessation benefit was slightly better among those offered more calls and among smokers who were motivated to try a quit attempt. For studies that did not identify a benefit for counselling, author's report that the unstructured counselling provided in those interventions might have explained the lack of effect and that counselling and pharmacotherapy support received within the control group due to the well-developed Stop Smoking Service provided by the UK health system may contribute to the lack of effect. Other studies showing a lack of effect offered free NRT included one study with a factorial design and the another that was conducted in young adults, a population for whom Stead et al. report there is limited evidence for any effective interventions. One study of a Medicare Stop Smoking program compared an intervention giving participants access to a quitline that offered the choice of a client-initiated hotline with pre-recorded messages and ad hoc counselling; or a practice service in addition to coverage for the nicotine patch.¹¹² The control group consisted of pharmacotherapy coverage only. The quitline significantly increased quitting at 12 months from 15.8%–19.3% (RR 1.22; 95%CI 1.07–1.39).

Another systematic review by Tzelepis et al.⁷ found that quitline counsellor-initiated telephone counselling increased prolonged and continuous smoking abstinence for both actively recruited smokers (first call initiated by quitline counsellors) and passively recruited smokers (first call initiated by the client). Among the 24 RCTs published prior to 31 December 2008, seven studies had active recruitment, 16 passive recruitment and one mixed recruitment. When compared with control groups receiving self-help materials or no intervention, the counsellor-initiated telephone counselling resulted in a statistically greater effect for seven-day point-prevalence abstinence at 6–9 months (R 1.26; 95% CI 1.1–1.43; $p < 0.001$) but not at 12–15 - month follow-up.

Among the five lower level evidence studies evaluating differences between counsellor- and participant-initiated follow-up calls, four reported no difference between groups at final follow-up (usually from six to 12 months), but typically did report short-term cessation benefits. The one study showing a significant benefit on quitting outcomes by 12 months⁸ was undertaken in a military population with differing levels of NRT provision between the intervention and control groups (four to eight-week supply compared to two-week supply). The potential additive benefit of more NRT was not evaluated. Moreover, the quitline-initiated group received substantially more counselling sessions at all follow-up periods, with high retention rates across the six counselling sessions. However, another study^{9–11} did evaluate the additive benefit of a six-week supply of free NRT, identifying no evidence of any effect above that of standard counselling.

Three distinct studies by Klesges et al. evaluated the efficacy of either counsellor-initiated or client-initiated follow-up calls for tobacco quitline services among active duty military and TRICARE beneficiaries (the health plan of military personnel)⁸, adult cancer survivors⁵⁹ and adult survivors of childhood cancer.⁶⁰ Participants ($n = 1,298$) evaluated in the military and TRICARE study, received eight weeks of counselling and up to an eight-week supply of free NRT, with the reactive group receiving a two-week NRT supply. Proactive treatment was associated with greater odds of prolonged abstinence (44.22% vs 24.96%; OR = 2.7; $p < 0.0001$) and seven-day point prevalence abstinence (22.03% vs 13.41%; OR = 1.81' $p < 0.0001$) by 12-month follow-up. However, for both cancer survivor studies^{59, 60}, no difference in long-term smoking abstinence was observed for proactive (counsellor-initiated phone calls) compared to reactive counselling (participant-initiated calls). The adult survivors of childhood cancer study ($n = 519$) showed a significant

benefit of the proactive counselling plus four-weeks of NRT compared to reactive counselling with two-weeks of NRT by eight-week follow-up (33.2% vs 17.0%; $p < 0.001$), but this was not maintained at 12 months (23.0% vs 18.7% $p = 0.29$). Of note, in both cancer survivor studies, falsification of self-reported abstinence through biochemical validation was very high (80% in adult survivor of childhood cancer and 48% in the adult cancer survivor studies). Klesges et al. report that traditional smoking cessation interventions are ineffective among cancer survivors, which is consistent with other studies researching this area.

A study by Nohlert, Ohrvki and Helgason also reported no evidence of any effect on tobacco cessation outcomes by 12-month follow-up in a study comparing proactive services (i.e. quitline counsellors offering a number of callbacks) and reactive services (where only incoming calls are attended) at the Swedish Quitline, SNTQ.⁹⁹ The counselling program is delivered by trained health professionals including nurses, dentists, dental hygienists or psychologists with primary or secondary prevention experience. In addition, callers are provided with printed material partly tailored to the client's needs and motivation to quit is offered free of charge. Among the 586 participants responding at 12 months (59% of original sample), intention-to-treat point prevalence abstinence was 26% in the proactive group and 29% in the reactive group ($p = 0.331$). Six-month continuous abstinence (at the 12-month contact period) was 36% and 34% (responder only) for proactive and reactive counselling groups respectively (20% and 22% respectively for intention to treat).

One multifactorial 2 x 2 study called the PORTSSS trial (Proactive or Reactive Telephone Smoking ceSsation Support) from the UK evaluated the efficacy of more intensive proactive counselling (i.e. once or twice before quit date, then at 3, 7, 14 and 21 days post quit date), versus standard telephone counselling (i.e. one week before quit date, day of quit date, as well as two days and three weeks post quit date) and whether the offer of a voucher for six-weeks of free NRT has any additional impact over standard counselling.⁹⁻¹¹ No difference in smoking cessation outcomes for counsellor or participant-initiated follow-up calls were observed.

A study by Carlini et al.⁷³ used multiple means to re-initiate contact with past quitline participants as the focus of the study (quitline intervention incorporating strategies to re-engage past callers), resulting in 12.2% of intervention participants ($n = 859$ people) compared to 1.9% of the comparison group re-engaging with the quitline service ($p < 0.001$). Just over half of participants were available for follow-up with 79.9% reporting a quit attempt lasting 24 hours or more in the last 90 days with the intention-to-treat analysis identifying quit attempts of 42.6%. Seven-day point prevalence abstinence was observed in 24.5% of participants, with the intention to treat analysis identifying a quit rate of 13.1%.

Counselling protocols and adherence to these

Level 1 evidence identified that quitline initiated first calls increased quit attempts (51 studies), with effect estimates being slightly larger if more calls were offered and in trials specifically targeting smokers motivated to try to quit.⁶ Another systematic review identified that quitline-initiated first calls are less effective than client-initiated first calls, likely related to the initial level of motivation to quit and readiness to quit.⁷ However, this evidence only comes from one included study within the systematic review (also described above under 'counsellor- or client-initiated follow-up calls').⁷

Evidence from other lower quality studies around the impact of different counselling protocols was also mixed. Some studies showed no additive benefit for quitline-initiated follow-up versus client-initiated follow-up counselling¹¹ or the use of NRT^{11, 12} compared to standard counselling without NRT. Others, however, did show that quitline-initiated follow-up counselling⁸ and the addition of pharmacotherapy^{13, 14} do have greater efficacy on quitting outcomes. No dose-response correlation was observed for the duration

of NRT provision, indicating that giving quitline callers higher quantities of pharmacotherapy like NRT above that of a starter-pack does not result in better smoking cessation outcomes.¹⁵⁻¹⁷ However, a dose response was observed between the number of counselling sessions and likelihood of successful quitting outcomes regardless of NRT provision.¹⁴ Note: adherence to counselling protocols by quitline counsellors is assessed under the 'Fidelity of counselling' sub-heading above.

Medication such as NRT as an adjunct to standard quitline protocols

After six months follow-up in the PORTSSS RCT⁹⁻¹¹ involving 2,591 smokers, 17.7% of those offered NRT reported smoking cessation compared with 20.1% not offered the therapy.¹¹ Of those offered more intensive proactive counselling (i.e. once or twice before quit date, then at three, seven, 14 and 21 days post quit date), 18.2% reported abstinence compared to 19.6% receiving standard support (i.e. one week before quit date, day of quit date, as well as two days and three weeks post quit date). Of participants eligible to receive NRT, 71.9% redeemed the vouchers and were sent at least one supply with 21.0% requesting a second supply. The use of non-trial cessation support (i.e. obtaining NRT via a pharmacist or doctor) did not explain the smoking cessation outcomes showing no evidence of any effect for the addition of NRT over counselling alone.¹⁰

Another study by Klesges et al. evaluating proactive counselling (i.e. quitline-initiated follow-up calls) plus an eight-week supply of NRT versus reactive counselling (i.e. client-initiated follow-up calls) with a two-week supply of NRT among military personnel identified a significant benefit in favour of the proactive arm on prolonged abstinence and seven-day point prevalence by 12-month follow-up.⁸ The proactive arm had a higher retention rate within the smoking cessation service with 79% of participants receiving three or more intervention calls, compared to 14% of those in the reactive condition. In the proactive group, only 3.54% of participants did not receive a single call compared to 46.84% in the reactive group. Call completion rates for remaining counselling sessions were as follows: at least one call (53.16% vs 96.46%), two calls (30.20% vs 87.37%), three calls (13.87% vs 78.89%), four calls (6.93% vs 71.34%), five calls (2.93% vs 64.10%) and six calls (2.47% vs 55.47%) for the reactive and proactive conditions respectively ($p < 0.0001$ for all). The counselling protocol consisted of six phone sessions, with the first continuing from the screening call if the participant had time, each session lasted <40 minutes covering the following:

- Session 1: preparing the smoker to quit and facilitating a targeted quit date
- Session 2: setting a quit date, preparing to quit and using the nicotine patch
- Session 3: the targeted quit date, problem solving strategies for difficult situations
- Session 4: provision of support
- Session 5: developing an individualised short-term relapse prevention plan
- Session 6: developing a long-term relapse prevention plan.

Participants in the reactive group were encouraged to call the quitline at their convenience. If they called on at least six occasions, they would receive the same intervention as those in the proactive condition.

Participants in the proactive condition were recommended the nicotine patch with dosage based on smoking rate. If participants had successfully quit on their targeted quit date, they received another four weeks of patches with tapered dosing up until eight weeks. Those in the reactive condition received two weeks of NRT with instructions to buy more on their own. Authors did not report treatment efficacy based on participants who actually used NRT compared to those who did not. Therefore, it is not possible to determine from this study if using different doses of NRT had an impact on treatment efficacy. Evaluation of different NRT doses was, however, evaluated in the Cummings et al. study.

The Cummings et al. 2010 study, which evaluated four different durations of free nicotine patches (two-, four-, six- and eight-weeks supplies), found that quit rate for the four-week supply group did not

significantly differ from the six- and eight-week supply groups.^{15,76} However, quit rates at 12-month follow-up were higher for smokers in the groups who received either two-, six- or eight-weeks of NRT. These results identify no clear dose response relationship between smoking outcomes and the number of free nicotine patches sent to smokers. This suggests that providing callers with additional free NRT above that of a starter pack does not increase their chances of quitting and remaining smoke-free. The lowest quit rate was observed among Medicaid/uninsured smokers who could receive up to six weeks of patches based on quitting efforts made in the first two weeks of calling the quitline. A correlation was seen between the number of patches actually used and quitting outcomes in a multivariate logistic regression model where a positive relationship was observed between the number of patches used and quitting success. This is to be expected as those who quit are more likely to continue using the patches, while those who relapse will discontinue use.

Another study by Saul et al. which evaluated two different regimens of NRT supply—an eight-week single-shipment supply or a split supply of five weeks, followed by a further three-week supply of NRT if callers continued with counselling—determined no difference in 30-day point prevalence by seven-month follow-up.¹⁶ Callers in the eight-week two-shipment group completed significantly more calls (mean 3.0) compared to the five-week one-shipment group (2.4) or eight-week single-shipment group (1.7; $p < 0.001$). For individuals completing follow-up at seven months, participants in the two-shipment group used NRT significantly longer (48.8 days) compared to those in the single-shipment group (33.5 days) or five-week one-shipment group (28.9 days; $p = 0.007$).

One Australian pseudo-RCT evaluated the addition of subsidised NRT to a standard population quitline service as an incentive to motivate low-income smokers into a quit attempt.¹⁴ At study entry, participants were mailed vouchers in packs of 10 (one weeks' worth) for redemption of NRT at a subsidised rate of 75% off the usual recommended retail price. The standard quitline program incorporated multiple sessions of counselling, with the number and length of sessions determined by the caller over a 12-week period. The intervention group included 1000 participants (65.3% female) and the control group consisted of 377 participants (62.1% female). Of the 10,170 vouchers that were distributed, pharmacy records indicate that 3,741 were redeemed (36.8% uptake), with 80.9% of those who received vouchers reporting using at least one of them. The majority of study participants were contacted at least once for a proactive counselling session (quitline-initiated follow-up), with no significant differences evident between study groups (94.7% of intervention participants and 95.9% of comparison participants received one or more calls). The average number of calls in total from quitline was 6.6 (SD 3.7) for the intervention arm and 5.8 (SD 3.9) in the control arm ($p < 0.001$). Participants in the NRT group received more follow-up quitline calls than those in the comparison group (mean 6.3 vs 5.5 calls respectively; $p < 0.001$). Of note, individuals who successfully quit in the NRT group had a similar number of callbacks compared to those who successfully quit in the comparison group (mean 7.8 and 7.7 callbacks respectively). This suggests that the provision of more counselling sessions among individuals motivated to quit, regardless of the addition of NRT, is associated with better quitting outcomes. However, the proportion of quitters in the intervention group was higher than the control group for unadjusted quit rates at three-month (46.0% and 29.5%; $p < 0.001$) and six-month follow-up (37.1% and 26.2%; $p < 0.001$) but not at 12 months (33.2% and 28.0%). Quit attempts were also higher in the intervention arm compared to control arm (83.8% versus 74.8%; $p < 0.001$).

Another factorial RCT conducted on the Wisconsin quitline by Smith et al.¹⁷, tested the effect of different NRT durations (two-week supply versus six-week supply), NRT type (nicotine patch-only compared to nicotine patch plus nicotine gum) and standard four-call counselling compared to the same counselling in addition to medication adherence counselling. This $2 \times 2 \times 2$ design yielded eight possible treatment combinations. Counselling was consistent with the US Public Health Clinical Practice Guideline.⁹³ For the primary outcomes of seven-day and 30-day point prevalence abstinence at six-month follow-up, a

statistically significant result was only observed for the NRT type main effect, with a higher abstinence rate observed for combination NRT (49.9%) compared to nicotine patch only (42.3%; OR = 1.36; 95% CI 1.06–1.75). Of note, smoking cessation guidelines recommend combination NRT for nicotine-dependent smokers.¹¹³ No significant difference was observed comparing six-weeks of NRT (48.9%) to two-weeks of NRT (43.3%; OR = 1.26; 96% CI 0.98–1.61) or standard counselling (47.6%) to medication adherent counselling (44.6%; OR = 0.89; 95% CI 0.69–1.14). An analysis evaluating the joint effect of NRT duration and type on seven-day point prevalence abstinence at six months revealed that participant quit rate for those who received two weeks of patch-only NRT (38.4%) and six weeks of patch-only NRT (46.2%) did not significantly differ. However, participants receiving combination NRT for two weeks (48.2%) or six weeks (51.6%) had a significantly higher abstinence rate when compared with the two-week patch-only NRT.

The Bullen et al. 2010 study¹² evaluated standard quitline services in NZ compared to the addition of pre-cessation NRT. A reduction in daily cigarette consumption was observed in both the pre-cessation NRT intervention group and the usual practice control groups by their quit date, going from 19 cigarettes per day to seven in the intervention arm and 16 in the control arm. However, no difference was observed between groups on quitting outcomes. By six-month follow-up among those who relapsed, both groups reported smoking significantly fewer cigarettes than at entry into the trial, with an average of approximately 11 cigarettes per day in both groups. This suggests that standard quitline services in NZ can significantly reduce the number of cigarettes smoked among callers after relapse, but the addition of pre-cessation NRT does not provide any additional benefit to this outcome. No significant differences were observed by six-month follow-up between intervention participants who received NRT two weeks before their quit date plus usual quitline care or the control population who received usual quitline care, for either seven-day point prevalence (22.7% and 21% respectively), or continuous smoking abstinence (18% in both groups).

A study by Kerkvliet and Fahrenwald involving 11,603 callers to the South Dakota quitline evaluated the frequency of specific service requests where pharmacotherapy was provided at no cost to the caller.¹³ The most common request was coaching with varenicline tartrate (64.6%) followed by coaching with NRT (22.6%), coaching alone (5.4%) and coaching with bupropion hydrochloride (5%). Although a significantly higher abstinence rate was observed for varenicline tartrate plus coaching compared to coaching only or coaching with NRT after seven months follow-up, all service options resulted in cessation rates of over 40% (range 40.3%–49.8%).

Other quitline protocols:

The doctoral thesis by Goesling¹¹⁴ discusses the Free and Clear telephone quitline service based in Washington, US, where participants receive up to five outbound follow-up phone calls made proactively by a team of quit coaches. There were 5,291 eligible participants enrolling in the quitline in the study evaluation period of November 2009 and February 2010. Three items were added to the standard telephone protocol: confidence, stress and urges. To standardise delivery and timing of questions, quit coaches received multiple in-depth training sessions for the new protocol and were provided with instructions on how to incorporate these new items in follow-up calls. The questions asked were:

- On a scale from 1–10, where 1 is 'not at all confident' and 10 is 'highly confident', how confident are you that you can quit (or stay quit if already quit) for good?
- On a scale from 1–10, in the last week, how often have you felt difficulties were piling up so high that you could not overcome them? (1 = never; 10 = very often)
- On a scale from 1–10 where 1 is 'no urges' and 10 is 'strongest urges', how strong have your urges or cravings been to smoke during the past day?

During the initial quitline call, counsellors collected information on: smoking variables, nicotine dependence, confidence to quit and current stress level. Participants were then given the opportunity to set a quit date and the counsellor assisted the participant to develop a personalised plan to prepare for meeting the quit date. Barriers to success were identified with potential strategies to overcome these. Dysfunctional cognitions were identified, such as 'I probably won't succeed because I failed in my last attempt', with alternative cognitions such as 'quitting is like learning to ride a bike, falling off is part of the process' developed in their place. Participants were also given practical advice such as removing exposure to cigarettes in the house, and had scripted discussions around smoking cessation medication use, including contraindications and appropriateness. Following the initial counselling session, proactive follow-up counselling initiated by quitline counsellors was offered within a few days of the quit date and, assuming the participant reported abstinence at the first follow-up call, the next call was provided within 7–10 days, then again in two- to three-weekly intervals after that until a maximum of four follow-up calls were provided. If the participant reported a relapse at any time period, the next call would be scheduled based upon a new quit date. The follow-up calls were less structured than the baseline assessment with information collected about: date of call, how call was completed (intervention or letter if unable to reach), quit status, duration of quit attempt, self-efficacy, urge to smoke, stress and medication status. Call variables shifted based on availability at contact, quit status and willingness to set a new quit date if the participant had relapsed, allowing for comparison based on number of completed calls/counselling sessions rather than on number of attempts to contact the participant.

A Wisconsin-based RCT of 410 young adult smokers (18–24 years)⁶³ compared a quitline-based counselling intervention with up to four callbacks plus self-help materials with self-help material alone mailed to the participant. No difference was observed for intention-to-treat seven-day point prevalence abstinence at one-, three-, or six-month post-enrolment. Intervention group participants were more likely to set a quit date (59.8%) compared to the self-help group by one-month post-enrolment (43.3%; $p < 0.002$), however, this result was not carried over to subsequent follow-up periods. Participants who received two or more counselling sessions were somewhat more likely to report making a quit attempt (44.4%) compared to those who received zero to one session (31.1%; $p = 0.06$). Similarly, participants who received more counselling sessions had a higher abstinence rate (14.1%) compared to those with fewer counselling sessions (5.4%; $p = 0.06$).

Adherence to the protocol in the Unrod et al. study¹⁰³ was assessed by asking participants whether they received and read the intervention materials (repeated mailings of eight "Forever Free" relapse prevention booklets, or massed mailings with all eight booklets sent upon enrolment or usual care consisting of brief counselling and NRT). Among responders, 12.5% of the mass mailings group and 8.0% of the repeated mailings group did not report receipt of a single booklet and 90% of those who received them reported having read the booklet. Those who did not receive the booklets had a lower abstinence rate across all follow-up points compared to those who received the booklets. However, the difference was not statistically significant. At the six- and 12-month follow-up periods, abstinence rates were 42.8% and 43.7% respectively among those who reportedly read the booklets compared to 27% and 29% among those who reportedly did not read the booklets ($p < 0.03$). When comparing groups, repeated mailings produced higher abstinence rates, though the results did not produce a statistically significant differences at six-, 12-, 18- and 24-month follow-ups.

Differences in counsellors delivering the quitline protocols

Among individual studies within the Stead et al. Cochrane review⁶, those that did not recruit participants on the basis of their willingness to make a quit attempt typically included content that was individualised to enhance motivation or to support a quit attempt where appropriate. Counselling was most commonly

provided by professional counsellors or trained healthcare professionals, not necessarily by government funded quitline counsellors. One trial used trained postgraduate students and three used trained peer counsellors.

A study by DeLaughter et al.⁸⁰ also explored the role of training peers to increase referrals to quitline in Alabama and Mississippi, US. Of the initial 96 successful quitters who were contacted by quitline, 24 were recruited agreeing to participate (75% women) and of these 11 were trained with four actively referring 23 friends and family over two months. From these 23, three friends/family (all women) were enrolled in quitline.

Additional relevant data from studies not meeting criteria for inclusion in the rapid review

A study by Linde et al.¹¹⁵ that did not meet criteria for inclusion in this review surveyed quitlines across 50 states in US, Washington DC and Guam to identify the number of treatment protocols offered, types of tobacco products they were intended to treat (e.g. cigarettes or cigars) and how counsellors triaged callers reporting use of non-cigarette tobacco and nicotine containing products. Thirteen organisations provided USA quitline interventions and 11 of these made up the evaluation sample. Every quitline service participating in the evaluation had at least one established tobacco cessation intervention protocol, i.e. a plan for treatment with specific procedures/languages used when someone called the quitline. Seven out of the 11 providers (63.6%) reported treating every caller the same, adapting words such as 'cigarette' with 'hookah' or 'cigar' depending on the individual's reported smoking habits. Only one service provider used a specialised protocol for smokeless tobacco use in addition to a standard protocol for all other callers. Three service providers referred participants to third party resources for other information about non-cigarette tobacco and nicotine containing products. No tailored protocols were available for non-cigarette tobacco and nicotine containing products, therefore the efficacy of such a protocol is unknown.

Relevant results from grey literature search not meeting inclusion criteria for this rapid review

Declining success rates across stop smoking services were observed in England between 2004 and 2007, with substantial variability identified across the 151 local services.¹¹⁶ In response, the Department of Health in England commissioned the National Centre for Smoking Cessation and Training (NCSCT) in 2009. Objectives of this centre were to 1. identify competencies required to deliver, manage, and commission smoking cessation reports, 2. develop and implement methods of assessment to ensure that practitioners, managers and commissioners obtain these competencies, and 3. commission and provide training and continuing support to enable staff to achieve the required level of competence.¹¹⁶ NCSCT Directors Andy McEwen, Robert West and Susan Michie and Leonie Brose (post supported by the NCSCT) have undertaken several research evaluations in line with these objectives as reported below.

An audit by Brose et al. in 2011¹¹⁷ covering 126,890 treatment episodes across 24 stop-smoking services in the UK, identified substantial variation in success rates among smokers depending on the treatment protocols used. Smokers using single NRT had higher quit rates compared to those not using medication (OR 1.75; 95% CI 1.39–2.22, $p < 0.001$), combination NRT was more effective than single NRT (OR 1.42; 95% CI 1.06–1.91; $p = 0.019$) and varenicline tartrate was more effective than single NRT (OR 1.78; 95% CI 1.57–2.02, $p < 0.001$). Carbon monoxide validated four-week abstinence did not significantly differ among those using bupropion hydrochloride compared to single-dose NRT (OR 1.12; 95% CI 0.96–1.30, $p = 0.16$). Of note, those using pharmacotherapy such as varenicline tartrate and combination NRT to assist with quit attempts had a significantly higher nicotine dependence level than those without medication or single NRT ($p < 0.001$).

Another audit by Brose, McEwen and West⁹⁵ evaluating 46,237 one-to-one treatment episodes in the UK produced similar results. Clients who used single NRT, bupropion hydrochloride, combination NRT and

varenicline tartrate were significantly more likely to have successful four-week carbon monoxide validated quit attempts compared to those using no medication.

A 2014 Brose et al. study evaluated if variability in stop-smoking services across England were due to variable uptake in training provision of the NCSCT. It was identified that 22.7% of practitioners completed the online knowledge training with 4.3% completing the face-to-face skills training during the evaluation period. A 2.5% improvement in success rate was observed between 2008 and 2010 (pre) and 2011 and 2013 (post) across all services ($p = 0.01$). The degree of improvement in successful abstinence among clients for each service was predicted by the number of practitioners completing the face-to-face skills-based training, adjusted for the number completing online training. While associated with improvement, for those who just completed the online knowledge training, improvement was marginal.¹¹⁶ This suggests that face-to-face training to improve compliance with best-practice guidelines is more effective than online training. On average, for every additional practitioner who completed the face-to-face training there was an additive increase of 0.22 points in smoking cessation success rates among clients.¹¹⁶

Frequency and length of calls/counselling sessions

While there is Level 1 evidence for follow up calls to increase cessation, there is mixed evidence about the optimal number of quitline calls/counselling sessions, optimal timing and length of calls to be provided. Most studies suggest no evidence of significant increased benefit with an increased number of quitline calls^{6, 18, 19, 118}, while a few studies report that a higher number of calls is significantly associated with better quitting outcomes.^{6, 20} Certainly, this rapid review did not identify any strong evidence to deviate from the current Victorian Quitline™ protocol consisting of two pre-quitline-initiated follow-up calls plus four post-quitline calls (based on recommendations in the seminal paper by Zhu and Pierce²¹). A paucity of evidence was available to enable any recommendation about the length of calls.

Studies evaluating frequency/length of counselling as primary focus

Level 1 evidence identified in the Stead et al. systematic review, which included 77 studies, evaluated differences in the number of calls to/from a quitline ranging from one to 12. The duration and frequency of these calls were also variable, with between 10- and 20-minutes being common, although the initial call could be longer, and calls spaced over weeks or months.⁶ Within the sub-group of studies investigating the effect of additional quitline-initiated first calls, review authors separated studies by intensity of intervention. Using only the more intensive interventions (those with more follow-up counselling sessions) in two trials that reported outcomes for two different interventions (opposed to an intervention and control group), a marginal increase in the pooled effect size was observed (data was not shown). One study, Smith et al. 2004, did not detect a difference between groups receiving two or six follow-up calls after an initial 50-minute session.¹¹⁹ Another study, Rabinus et al. 2007, evaluated six different intervention formats that differed in number of calls, duration and use of brief booster calls at four and eight weeks after counselling. No clear dose response effect was observed.¹²⁰ Five brief counselling calls plus boosters were no less effective than the standard American Cancer Society protocol of five longer calls and boosters. Direct comparison between two studies reporting more and less intensive interventions showed marginally significant differences in favour of the more intensive intervention in one study (RR 1.32; 95% CI 1.01–1.74,¹⁰²), but not in the other (RR 1.05; 95% CI 0.89–1.23,¹²¹).

A study by Carlin-Menter et al. comparing the efficacy of offering two versus four counselling callbacks after the initial call to the New York State Smokers quitline found no significant difference between study groups for seven- or 30-day cessation rates.¹⁸ Overall, 48% of participants who continued smoking had reduced their cigarette consumption by 50% or more by three-month follow-up. The use of NRT did not differ between groups nor did the cost per quit attempt. However, it is worth noting that the average number of callbacks actually completed in the two-callback group was 0.89 compared to 1.04 in the four-

callback group, with only 14% of the four-callback participants completing more than two counselling callbacks. This suggests that adherence to the protocol may be an important contributor to the outcome suggesting no evidence of an effect, more so than the actual provision of two compared to four callbacks. When evaluating smoking cessation outcomes on a dose response basis, a positive association was observed between the number of completed callbacks and quit rates at three months for seven- and 30-day quit rates.

Another study by Segan et al. evaluated the impact of extended callback counselling to prevent relapse over the longer term (beyond one-month cessation). They provided the intervention group with 4–6 extra calls delivered 1–3 months after quitting compared to the usual four calls provided in the first month after quitting. They found no significant difference on continuous abstinence at 12-month follow-up.¹¹⁸ Of the 352 intervention participants (those scheduled to receive the extra post quitting calls), 74% accepted extra post-quitting calls with a mean of 4.3 calls received. The average total number of post-quitting calls between groups was 7.1 in the intervention arm (over 60.9 days) and 5.4 in the usual care arm (over 42.0 days), a difference of 1.7 calls ($p < 0.001$). Standard post-quitting calls were longer in the intervention group (mean 16.2 minutes) compared to usual care group (15.0 minutes; $p = 0.001$), and integration callbacks (extended intervention) was even longer (18.0 minutes). Intervention participants were more likely to say that they received too many calls (11% compared to 2%), while usual care participants were more likely to say they received too few calls (14% versus 8%; $p < 0.001$).

Studies where frequency/length of counselling was impacted by intervention

For some studies, delivery of certain interventions such as AC¹, a weight control program as an adjunct to quitline¹⁹ and acceptance of an eight-week supply of NR⁵⁶, resulted in an increased utilisation of counselling calls compared to the control group. In the Bricker et al. RCT¹, delivery of ACT instead of CBT (standard care) resulted in 1.1 more calls on average ($p < 0.001$), in a protocol originally outlining a total of five calls for each group. For every one-call attempt, ACT participants completed a call 36% of the time compared with only 13% of the time for CBT participants ($p < 0.0001$). Importantly, more calls predicted higher 30-day point prevalence abstinence at six-month follow-up for ACT (31%; OR 1.6; 95% CI 1.1–2.6; $p = 0.03$) but not for CBT (22%; OR 1.6; 95% CI 0.9–3.0; $p = 0.10$) when evaluating the dose-response association. The length of calls did not significantly differ by treatment arms with an average of 23.64 minutes for ACT compared to 22.01 minutes for the CBT group. However, a comparison of abstinence among the 47 participants who were identified as depressed at baseline identified an increased quit rate of 33% with delivery of ACT compared to 13% with CBT (OR 1.2; 95% CI 1.0–1.6).

A study by Bush et al. evaluating the impact of a weight control program as an adjunct to quitline practices experienced an average of 4.1 successful calls by quitline counsellors in the intervention arm compared to 3.0 in the control arm.¹⁹ However, the weight control intervention was designed to include more calls compared to the usual care control population (five compared to eight counselling calls). No significant difference in 30-day abstinence outcomes at six-month follow-up were observed, with the intervention arm reporting 36.8% compared to the control population with 33.3%. Likewise, intention-to-treat quit rates identified no differences between intervention and control groups (17.1% and 17.8% respectively).

Intervention participants in the Burns et al. 2016 study who requested the full eight-week supply of NRT were significantly more likely to complete all counselling calls (33.5%) compared to the intervention participants who only received the four-week supply of NRT (1.6%; $p < 0.0001$).⁵⁶ Smoking rates including seven-day and 30-day point prevalence as well as continuous abstinence did not differ between study groups by six-month follow-up among those actually receiving the intended interventions. However, intervention participants who requested the full eight-week supply of NRT were significantly more likely to obtain 30-day point prevalence abstinence (29.3%) compared to intervention participants receiving the

four-week supply of NRT (15.7%; $p < 0.001$). This suggests that sustained dedication (and motivation) to quit was more likely to predict abstinence rather than the provision of additional NRT.

Population-wide studies impacting frequency of calls to quitline

Similarly, some population-wide interventions did result in an overall increase in quitline calls during the study evaluation period, such as following targeted advertising^{70, 79} and the introduction of increased tobacco taxation.⁷⁸ An increase in quitline calls were observed among Latino quitline callers in the Burns et al. 2010 study, from 390 per month during the pre-campaign period (1,169 over three months) to an average of 614 per month during the campaign.⁷⁰ During the campaign, Latino participants were less likely to stop being coached after one call, more likely to complete the program and were more likely to receive one NRT package (four-week supply), compared to pre-campaign counterparts, however, these results were not statistically significant. The average number of counselling calls was marginally higher among Latinos than non-Latinos during the campaign (3.0 compared to 2.6 calls respectively; $p = 0.06$). Six-month abstinence was significantly higher among Latinos during the culturally-tailored media campaign (18.8%) compared to pre-campaign (9.6%; $p < 0.05$). However, there was a significantly lower six-month abstinence rate among non-Latinos during the campaign (8.8%) compared to before the campaign (16.5%; $p = 0.01$). Authors of this study speculate that the media campaign was most effective at recruiting Mexican men living and working in Colorado, comprising the largest demographic segment of US immigrants coming from a country where 39.1% of men are smokers. Therefore, this culturally-tailored campaign reached an audience in demand of this service who were not previously accessing it. Authors report that additional research is needed about changes in knowledge, attitudes and cessation, quitlines and NRT usage to determine the exact components of the media campaign that may have contributed to the improved quit rates. A similar pattern was identified for seven-day point prevalence identified with a benefit among Latino smokers during the media campaign compared to pre-campaign (41.0% and 29.6% respectively; $p = 0.06$) and a significant worsening among non-Latinos post-campaign compared to pre-campaign (24.9% compared to 34.8%; $p < 0.05$).

Another study^{79, 81} evaluating the addition of 100 television gross rating points per week for quitline-tagged ads was associated with an increase of 89 calls per week to the quitline in a typical area code in the US ($p < 0.001$). The 'Tips' campaign reportedly was responsible for an additional 170,000 calls to quitline during the campaign. The same campaign was evaluated by other authors across 23 US states in a 2014 study⁹⁰, identifying that the number of quitline callers increased by 88.6% (48,738 in 2011 to 91,911 during Tips) and the number of callers who received counselling and/or NRT increased by 70.8% (40,546 in 2011 to 69,254 in Tips) during similar weeks in 2011 (i.e. the previous year).⁹⁰

A 23.5% increase in total call volume was observed in the Bush et al. study⁷⁸, which compared call volume in periods before and after the federal tax on cigarettes increased, and the price of packs rose by \$1.01 on 1 April 2009. Call volume increased from pre-tax (85,541 calls) to post-tax periods (104,452 calls), with the largest percent increase of 94.1% occurring in March 2009. The number of tobacco users per month who received at least one counselling call increased during March and April 2009 compared to the same time in the previous year. Although fewer calls enrolled in the multi-call program (4–5 counselling calls) after tax, they completed slightly more counselling sessions compared with those who enrolled before tax (1.9 versus 2.2 sessions respectively; $p < 0.0001$). In the after-tax period, differences were identified in characteristics of callers including: age slightly younger (41.9 versus 41.2 years); fewer callers aged 18–24 years (11.5% after tax compared to 13.6% before tax); more white callers; higher number with less than a high school education; more likely to live with a smoker; shorter duration of cigarette smoking and more likely to report hearing about the quitline from family or friends or their healthcare provider rather than from the media.

No significant difference was observed in seven-day and 30-day quit rates by seven-month follow-up before versus after the tax increase (seven-day rates were 30.7% before and 28.7% after the tax increase).

Studies reporting data on utilisation of counselling protocols (frequency of calls)

Among other studies, process measures for counselling implementation have been reported, showing a significant drop-off in counselling numbers after the first call. Moreover, a greater uptake of counselling (higher treatment compliance) is associated with increased efficacy for smoking cessation outcomes. The interaction is likely bi-directional, meaning better quit smoking outcomes lead to better treatment compliance, as people who relapse and return to smoking are more likely to drop-out of the counselling service.

In the Zhu et al. study⁶⁷ of Asian-language tailored counselling compared to self-help material in the US, the initial counselling session was received by 86.9% of the 2,277 participants. This fell to 11.8%, 12.7%, 13.3% and 12.4% for the remaining four counselling sessions respectively. Thirty-nine percent of participants received five or more follow-up calls as specified in the quitline protocol. This resulted in a quit rate in the counselling group double that reported in the self-help group. Six-month prolonged abstinence was higher in the counselling group than in the self-help group (20.0% vs 9.5%; $p < 0.001$) as was seven-day point prevalence at four-months (38.2% vs 18.6%) and seven-months (40.0% vs 23.9%; $p < 0.001$). When expressed in terms of an odds ratio, the odds of achieving six months prolonged abstinence were 2.26 times higher in the counselling group than among those who received only self-help materials in the intention-to-treat analysis, and 2.38 times higher in the complete-case analysis.

A three-state evaluation of the same Asian-language counselling program had a higher rate of receiving the initial counselling call (91.6%).⁷⁴ Although participants in the multi-state program were more likely to be counselled, they received fewer counselling sessions (mean 4.1 compared to 4.9 in the one-state Zhu et al. study) and fewer minutes of counselling across the sessions (58.2 vs 72.0; $p < 0.05$). However, multi-state participants reported a much higher nicotine patch use (43.0% vs 9.1%) and use of any quitting aids (53.1% vs 12.8%). Of note, the one-state Zhu et al. study involved randomisation of participants into either the counselling or self-help arms, while the multi-state study allowed for self-selection. Therefore, those who chose to undertake counselling may have a higher motivation to quit than those randomised in the RCT. Among the 5,771 callers in the nation-wide Kuiper et al. evaluation¹²², 85% received counselling (92% among Chinese callers, 88% for Korean callers and 76% among Vietnamese callers). Callers participating in counselling and attended at least one session had an average number of four counselling sessions in total, with no difference between language groups. Nearly all (99%) of eligible callers received nicotine patches and had heard about the quitline from advertising in newspapers and magazines. Across all three studies, the majority of callers were male (80%–90%).

Reported counselling implementation in the New York quitline evaluation of a three-month recruitment period by Goesling 2012¹¹⁴ reflects a similar pattern of attrition over time. The initial data set consisted of 7,357 callers, of which 5,291 callers were included in the evaluation, with 75.2% speaking with a quit coach on the same day as their registration call ($n = 3,981$). Of the 5,291 callers, 88.3% ($n = 4,671$) received at least one follow-up counselling session, 67.8% ($n = 3,591$) had two follow-up calls, 44.2% ($n = 2,338$) received three follow-up calls and 21.1% ($n = 1,119$) received all five counselling sessions. Characteristics of participants less likely to receive follow-up calls were: being female, younger age, higher nicotine dependence, self-efficacy and stress. Based on a chi-squared analysis, females were less likely to be adherent to counselling (receive fewer calls) and were more likely to only receive a baseline call ($p < 0.001$), one follow-up call ($p < 0.001$) and two follow-up calls ($p < 0.05$). However, by the third counselling session, this difference shifted with no gender difference observed, though more men were likely to complete all four calls ($p < 0.001$). An association was observed between the number of calls received and quitting, with

people who received more calls being more likely to have quit at least once during the data collection period ($p < 0.001$). Of the 5,291 participants, 68% ($n = 3,128$) reported a quit attempt at some point during the study period.

The Miller et al. study evaluated the addition of subsidised NRT to a standard population quitline service as an incentive to motivate low-income smokers into a quit attempt.¹⁴ The average number of total calls from quitline was 6.6 (SD 3.7) for the intervention arm and 5.8 (SD 3.9) in the control arm ($p < 0.001$). However, participants in the NRT group received more follow-up quitline calls than those in the comparison group (mean 6.3 vs 5.5 calls respectively; $p < 0.001$). Of note, individuals who successfully quit in the NRT group had a similar number of callbacks compared to those who successfully quit in the comparison group (mean 7.8 and 7.7 callbacks respectively). This suggests that the provision of more counselling sessions among individuals motivated to quit, regardless of the addition of NRT, is associated with better quitting outcomes. However, the proportion of quitters in the intervention group was higher than the control group for unadjusted quit rates at three-month (46.0% and 29.5%; $p < 0.001$) and six-month follow-up (37.1% and 26.2%; $p < 0.001$) but not 12 months (33.2% and 28.0%). Quit attempts were also higher in the intervention arm compared to control arm (83.8% versus 74.8%; $p < 0.001$).

Another NRT based study by Saul et al. evaluated the impact of an eight-week shipment of NRT compared to a split-shipment at five-weeks then a further three-weeks' supply if they continued with counselling.¹⁶ Participants in the eight-week two-shipment group received significantly more calls (3.0) compared to those in the five-week one-shipment group (2.4) or eight-week single-shipment group (1.7; $p < 0.001$). The average minutes of counselling was highest in the eight-week two-shipment group (66.6 minutes) compared to the eight-week single-shipment group (45.8 minutes) and five-week single-shipment group (42.8 minutes; $p < 0.001$). Yet no difference in 30-day point prevalence abstinence was observed between groups by seven-month follow-up.

A study by Danaher et al. 2015⁵⁸ evaluated a 2 x 2 factorial study of a web-based smoking cessation platform, quitline only, web plus quitline or control of self-help materials. Of the 838 participants assigned to a group with the quitline intervention, 41.4% had a quitline call (45.6% among the quitline only group and 37.2% among the web and quitline group). The mean number of calls for the quitline-only group was 3.13 compared with 3.10 for the web and quitline group. Of those receiving a quitline call, 9.7% had one call, 10.1% received two-calls, 6.7% had three-calls, 8.0% had four-calls and 6.9% received all five calls. The rate of drop-off is similar to the Zhu et al.⁶⁷ study mentioned above. Receiving at least one call was significantly associated with six-month abstinence ($p < 0.005$; OR 1.61; 95% CI 1.15 –2.26), with six-month abstinence reported by 48% of participants receiving quitline calls and 37% not receiving a call. On the intention-to-treat analysis at both three- and six-month abstinence time periods, results for each group were 27.3% for web-only, 29.5% for quitline only, 28.1% for web and quitline and 21.2% for the control condition. Another factorial study by Smith et al.¹⁷ evaluated the impact of different NRT durations (two-week supply versus six-week supply), NRT type (nicotine patch only compared to nicotine patch plus nicotine gum) and standard four-call counselling compared to the same counselling in addition to medication adherence counselling. Nearly 60% of the 987 participants completed at least three proactive counselling sessions and 18.4% completed just one. No significant difference was observed for the main effects (i.e. NRT duration, NRT type and medication adherent counselling) on counselling utilisation. A significant interaction was observed for total number of counselling minutes for six-week NRT provision (65.3 minutes) compared to the two-week group mean (61.9 minutes; $p < 0.05$) and medication adherence counselling compared to standard counselling, with an additional seven minutes added to the call time ($p < 0.001$). No significant gender or ethnicity differences were observed for between group interactions on smoking abstinence rates. No statistically significant difference was observed for the primary outcomes of seven-day and 30-day point prevalence abstinence at six-month follow-up.

No difference was observed in counselling calls completed for an evaluation of the 'Tips' campaign⁸⁹ across three US states (Nebraska, North Carolina and Texas) with a mean of 2.1 (SD 1.4) for the total population of 715 participants. Callers who completed more counselling sessions were more likely to have successfully quit than those who completed fewer calls using seven-day point prevalence abstinence at seven-month follow-up (OR 1.15, 95% CI 1.01–1.30, $p = 0.03$).

Number and length of calls provided in an evaluation of reactive counselling (i.e. where only incoming calls are answered) versus proactive counselling (i.e. where a number of callbacks are offered) among 586 callers to the Swedish Quitline, SNTQ⁹⁹, identified significant differences between groups. The mean number of calls was 4.3 (SD 4.7) and 2.1 (SD 4.3) with a range of 1–40 and 1–70 for the proactive and reactive groups respectively ($p < 0.001$). The percentage of reactive and proactive participants receiving different numbers of calls were: one call: 19% vs 50%; two calls: 27% vs 36%; and three calls: 15% vs 7%, respectively ($p < 0.001$ for all). The total length of calls ranged from six to 591 minutes (mean 60.1) in the proactive group compared to five to 707 (mean 34.8) in the reactive group ($p < 0.001$). The first call was typically longer for both groups (mean 25.1 minutes; no difference between groups) with the average call time for the second call significantly longer in the proactive group (9.6 minutes) compared to the reactive group (6.8 minutes; $p = 0.004$).

Another study identifying differences in frequency of calls between treatment arms was the McDaniel et al. study⁶¹ investigating three treatment arms in the US-based Quit for Life program (five-call program): standard quitline care; standard care plus technology-enhanced quitline with 10 risk assessments; or standard care plus 20 risk assessments. In the technology-enhanced groups, participants were contacted using interactive voice response technology 10 times during the treatment period to screen on either 10 or 20 relapse risk variables. An algorithm was applied to flag participants 'at risk' if they answered screening questions over an established threshold. Those at risk were then transferred directly to a quit coach for brief intervention (approximately 15 minutes) to specifically address the risk factors that triggered the transfer. The average number of completed calls was 3.9 (SD 1.7; range 2–19) with the two intervention arms that included risk assessments receiving significantly higher calls than the standard care group, due to the additional transferred counselling calls participants received after a positive screen was identified ($p < 0.001$). Quitline calls across groups were: standard care mean calls: 3.66 (SD 1.48, range 2–13, $n = 592$); 10 risk factor group mean: 4.11 (SD 1.82, range 2–19, $n = 602$); 20 risk factor group mean: 4.06 (SD 1.77, range 2–17, $n = 591$). No significant differences in quit rates at six and 12-month follow-up were observed on intention-to-treat quit rates. A positive risk assessment did identify participants less likely to be abstinent at six-months (OR = 0.56; 95% CI 0.42–0.76).

The average frequency of counselling sessions for pregnant women in the Bombard et al. 2013 study was 2.3 occasions compared to 2.5 occasions among non-pregnant women.⁷⁷ By seven-month follow-up, 26.4% of pregnant women and 22.6% of non-pregnant women had reported quitting. After adjusting for non-responders and non-disclosers, the adjusted quit rate was approximately twice as high for pregnant and non-pregnant women who received counselling, compared to those who received self-help material only (2.9% and 3.5% respectively).⁷⁷

This Wisconsin-based RCT of 410 young adult smokers (18–24 years) by Sims et al.⁶³ compared a quitline-based counselling intervention with up to four callbacks plus self-help materials, with self-help material alone mailed to the participant. Participants who received two or more counselling sessions were somewhat more likely to report making a quit attempt (44.4%) compared to those who received 0–1 session (31.1%; $p = 0.06$). Similarly, participants who received more counselling sessions had a higher abstinence rate (14.1%) compared to those with fewer counselling sessions (5.4%; $p = 0.06$). Call completion was: 26% one call, 29% two calls, 22% three calls and 14% all four calls. The mean number of calls was 2.05 (SD 1.20) with total

minutes averaging 41 (SD 25). No difference was observed for intention-to-treat seven-day point prevalence abstinence at one, three, or six-month post-enrolment.

Additional relevant data from studies not meeting criteria for inclusion in the rapid review

A study that wasn't identified for inclusion in this review (as it was conducted in the emergency department setting of a North-eastern US hospital)²⁰, evaluated the impact of no quitline usage (n = 583), one call only (n = 99) or greater than one call (n = 98) on smoking outcomes. By three-month follow-up the biochemically-confirmed abstinence rates were 7.2%, 9.1% and 15.3% respectively (p = 0.03). Participants who used the quitline had a median counselling time of 28-minutes. Looking at this from a different perspective, the total call duration and associated smoking abstinence rates at three-months were 0 minutes (7.2%), 1–27 minutes (11.2%) and 28–143 minutes (13.1%); p = 0.09). Although the sample size is relatively small (total n = 780) and limited to one US population, the results suggest that receiving more than one call is associated with slightly better quitting outcomes than one call only, but that having a total duration of calls that is high did not show a significant difference between the two categories of counselling.

Relevant results from grey literature search not meeting inclusion criteria for this rapid review

A study by West et al. identified the behavioural change techniques from treatment manuals across 43 UK-based stop-smoking services.¹⁰¹ From 43 possible behavioural change techniques, stop-smoking service manuals included a mean of 22 (range 9–37). The number of sessions used for delivery of the smoking cessation intervention (not limited to quitline services) ranged from 1–13.

Hours of operation

No studies evaluated the impact of differing or extended operating hours for quitline services.

One US study by Klesges et al.⁸ comparing proactive counselling (quitline-initiated follow-up calls) to reactive counselling (client-initiated follow-up calls) reported the hours of quitline operation being 08:00 to 17:00 Central Standard Time. These operating hours were available to participants in the reactive condition, though hours of operation were not reported for the proactive condition. Another Swedish study⁹⁹ reported operating hours of 09:00–20:00 Monday to Thursday and 09:00–16:00 on Friday, operating two or three lines a total of 51 hours per week. No evaluation was undertaken to evaluate any data around operating hours for these services.

Pathways for recommendation to the service

Interactive voice response technology was used in two studies by the same author Carlini^{57, 73}, to re-engage relapsed quitline callers to commence a new cycle of counselling. The automated technology resulted in a significantly increased enrolment rate compared to the control populations in both studies. In the Carlini et al. RCT⁵⁷, 66.7% of re-enrolled participants in the intervention group accepted a direct transfer to the quitline and registered in services immediately after the interactive voice response call. Remaining participants provided contact information and registered in services with quitline staff returned their voicemail. Participants who accepted re-enrolment were typically older than those who declined a new treatment cycle (mean 45.2 years compared to 41.8 years; p = 0.013) and more likely to report a chronic condition (60.9% compared to 43.4%; p = 0.001).

The most common means by which a quitline service was recommended to pregnant women differed from non-pregnant women in the Bombard et al. 2013 study.⁷⁷ Pregnant women were more likely to have quitline recommended by a health professional, while non-pregnant women were made aware of the quitline through mass media channels.

Sub-group analysis of specific populations

Limited data was available across the different sub-groups examined within this rapid review. In the absence of any eligible study data, information was obtained from studies not meeting the inclusion criteria for this review (e.g. observational studies, surveys, qualitative evaluations) to provide some dialogue around quitline efficacy within these populations.

Tailoring quitline interventions for these specific populations have been identified as a priority in a 2003 report by NAQC, developed to provide guidance to state health departments, healthcare organisations and employers for the development and maintenance of state quitlines.¹¹¹ These guidelines recommend specialised protocols for pregnant smokers (with some promising efficacy evidence) and underage smokers (where evidence is lacking). Additionally, it recommends careful consideration of cultural appropriateness of services for culturally and racially diverse callers, the provision of and access to pharmacotherapy quit aids, comprehensive staff training and supervision, as well as opportunities for constructive feedback and development, and targeting of low-income tobacco users.

Culturally and linguistically diverse (CALD) populations

Cultural tailoring of tobacco cessation interventions has potential for improved engagement and cessation benefits above that of standard smoking cessation programs. Five studies evaluated the impact of quitline services culturally tailored to CALD populations.

Within the Stead et al. 2013 Cochrane review⁶, one study of quitline counselling included culturally-tailored resources for the African-American population. However it was unable to detect a significantly increased benefit from counselling with the addition of tailored print materials.¹²³

A media campaign that was culturally tailored for the Spanish Latino population in Colorado, US, identified a statistically significant increase in six-month abstinence and seven-day point prevalence abstinence among Latino callers during the media campaign compared to pre-campaign.⁷⁰ Of note, an adverse effect was observed among non-Latino callers with a significant reduction in abstinence during the campaign compared to pre-campaign.

Other studies, all co authored by Shu-Hong Zhu, have evaluated the implementation and/or efficacy of an Asian-language tailored tobacco quitline protocol into Chinese, Korean and Vietnamese languages. This has been evaluated in a single randomised study in California, US, with 2,277 Asian smokers⁶⁷ across three states (California, Colorado and Hawaii) following promotion of the service with 2004 smokers⁷⁴, and on a nationwide scale across 48 states and 5,771 callers over two-years.¹²² Across two of the three studies, a benefit was identified for the culturally-tailored intervention arm compared to standard callback service on smoking outcomes. The third nationwide study did not evaluate this outcome. The nationwide RCT⁶⁷ found an overall increase in six-month prolonged abstinence among all smokers compared with self-help materials (16.4% vs 8.0%; $p < 0.001$), and among interventions tailored for the three different language groups compared to self-help (Chinese 14.8% vs 6.0% $p < 0.001$; Korean 14.9% vs 5.2% $p < 0.001$; Vietnamese 19.8% vs 13.5% $p = 0.023$). Similar efficacy results were obtained in the three-state evaluation⁷⁴, with six-month abstinence of 18.8%.

Indigenous populations

No studies were included that identified a program culturally tailored for the Indigenous population. This is despite the fact that a Cochrane review of Indigenous smoking cessation programs has identified the potential for increased efficacy among studies tailored to these populations.¹²⁴ An observational study by Cosh et al. evaluated the utilisation and effectiveness of quitline services in South Australia, identifying that

demographic variables and smoking addiction at time of registration with the quitline were similar for both Indigenous and non-Indigenous Australians.¹²⁵ Indigenous callers received significantly fewer callbacks and were significantly less likely to set a quit date compared to non-Indigenous callers. Subsequently, fewer Indigenous callers reported a successful quit outcome by three-month follow-up. The authors reported that additional research is needed to explore whether the quitline service could be tailored to make it more engaging for Indigenous Australians who smoke.

An audit of quitline callers across 14 US states (approximately 60% female) found a higher rate of tobacco use onset (i.e. commencement of smoking in the population) among American Indian/Alaskan Native (AI/AN) callers, who made up 3.5% (n = 5,957) of the study population compared to callers identifying as other ethnic groups.¹⁰⁵ AI/AN callers had an earlier age of tobacco use onset compared to other groups (15.9 years compared to 16.7 years respectively; $p < 0.001$) and were more likely to live with another commercial tobacco user (45.4% and 42.1% respectively). Approximately 63% of participants in both groups (i.e. AI/AN callers compared to other racial/ethnic groups) reported using NRT, with a slightly higher proportion of AI/AN callers reportedly using prescription smoking cessation medications (17.6% compared to 16.2%). A history of mental or emotional problems was more likely to be reported by AI/AN callers ($p < 0.001$) as well as symptoms causing interference with life functioning ($p < 0.001$). However, no difference was observed between groups about the expectation that mental or emotional issues would interfere with their quit attempts. AI/AN callers were more likely to report comorbidities related to lung health (asthma, chronic obstructive pulmonary disease and cancer), cardiovascular illnesses (heart disease, heart attack, high blood pressure; $p < 0.001$ for all) and diabetes, but not stroke.

Mental health

Mental health conditions are commonly reported among smokers at levels higher than those experienced in the general population.¹²⁶ Therefore, strategies that address or consider the presence of mental health conditions among smokers who are trying to quit may improve rates of quit attempts and cessation success.¹²⁷ Five studies were identified for inclusion, one of which was a systematic review containing four additional studies.

One study by Kerkvliet, Wey and Fahrenwald⁸⁴ evaluated the prevalence and outcomes of quitline use among people with and without a mental health condition, identifying a self-reported prevalence of mental health conditions of 19.8% in the 10,720 callers to South Dakota quitline between September 2010 and August 2012 (n = 2,086 callers). The self-reported quit rate following delivery of the standard quitline service (five counselling sessions plus up to eight-weeks' supply of free NRT or other smoking cessation pharmacotherapy) among the group reporting a mental health condition was 16.4% at seven-months follow-up, compared to 21.5% among those without a mental health condition ($p < 0.001$; intention-to-treat). The responder quit rate for those with and without a mental health condition was 36.9% and 44.4% respectively. The adjusted odds ratio describing the association between mental health status and tobacco cessation indicated that participants with a mental health condition are 23% less likely to quit ($p < 0.05$) than those without.

CBT is reportedly the theoretical approach typically used to underpin quitline counselling protocols.^{1, 6, 113} However, one alternative theoretical framework was identified as having the potential to increase quitting efficacy among quitline callers with mental health issues, above that of CBT. In the Bricker et al. study¹, a comparison of abstinence among the 47 participants who were identified as depressed at baseline identified an increased quit rate of 33% with delivery of Acceptance and Commitment Therapy (ACT) via the quitline, compared to 13% with CBT (OR 1.2; 95% CI 1.0–1.6).

The Schwindt et al.⁵⁴ systematic review of quitline services for smoking cessation among people with a mental illness identified four studies for inclusion. All four studies identified positive outcomes associated with quitline services plus an adjunctive component for smoking cessation. Only one study was associated with significant improvements in depressive and psychotic symptoms as well as mental health functioning for all groups.¹²⁸ However, between group differences were not observed for these factors, meaning both the intervention and comparison groups benefited. Likewise, in the van der Meer et al. study⁶⁶, quitting was associated with reduced depressive symptoms regardless of treatment group assignment. Exacerbations of depression were not associated with cessation outcomes in a third study⁶² and the fourth included study did not report on mental health outcomes. Results from these trials suggest that mental health benefits can be observed among smokers quitting via quitline services regardless of treatment intensity, as quitting benefits can be observed even in the lower intensity interventions. Significantly higher cessation rates were observed in two of the four studies at different follow-up periods. The van der Meer et al. study⁶⁶ observed significantly higher cessation rates at both six- and 12-month follow-up assessments among participants receiving assistance from a quitline service that included a mood management component. Participants in the Rogers et al. 2016³ study using a multi-session manual-based counselling protocol based on motivational interviewing and CBT with accompanying homework assignments identified a significantly higher 30-day abstinence rate for the intervention arm compared to control arm.

Analysis of an RCT within the Swedish quitline setting comparing proactive counselling (i.e. quitline offers a number of follow-up callbacks) and reactive counselling (i.e. where only incoming calls are attended) showed no evidence of effect between groups on quitting outcomes.⁹⁹ Secondary analysis of this data identified that perceived ability to handle stress and depressive mood was a significant predictor of both point-prevalence and continuous abstinence by 12-month follow-up.⁸⁶

A study by Simonavicius et al. that was identified through the grey literature but did not meet the criteria as an included study, evaluated resources and training needs to support smokers with mental health problems via a survey of 717 smoking cessation practitioners across the UK.¹²⁹ More practitioners believed that smoking cessation helped smokers with mental health problems to feel better (37%) compared to those who believed smoking cessation would exacerbate mental health problems (17.2%). Just over half of practitioners reported that their service had a system to record mental health status (57.3%), 11.6% of services indicated that they had dedicated funding for people with mental health problems and over one-quarter of practitioners were (9.1%) or had (17.4%) staff members who were dedicated lead practitioners for mental health work. Less than one-fifth of practitioners reported that their service had a manual guiding support for smokers with mental health problems. More than two-thirds of practitioners (69.1%) reported asking clients about mental health very often or always, with practitioners significantly more likely to always ask clients about mental health problems if they had or were a lead support organisation for smoking cessation among clients with mental health issues ($p < 0.001$). Practitioners were the most confident in supporting smokers with depression or anxiety to quit and least confident in support those who reported schizophrenia. In terms of medication support, practitioners were most confident recommending NRT, moderately confident with varenicline tartrate and e-cigarettes and least confident with bupropion hydrochloride, which notably is also an antidepressant drug. Knowledge about interactions between smoking cessation and blood levels and metabolism of psychiatric medications indicated a need for improved education and training among smoking cessation practitioners. When asked about blood levels of psychiatric medications, 48.3% of practitioners correctly indicated that smoking may decrease blood levels of some medications, 52.7% correctly responded that quitting smoking may increase blood levels and 33.4% knew that nicotine does not affect psychiatric medication metabolism.

Pregnant women

One study evaluating quitline interventions among pregnant women was identified for inclusion in this rapid review. The Bombard et al. 2013 study evaluated quit attempts by both pregnant and non-pregnant women.⁷⁷ By seven-month follow-up, 26.4% of pregnant women and 22.6% of non-pregnant women had reported quitting. After adjusting for non-responders and non-disclosers, the adjusted quit rate was approximately twice as high for pregnant (2.9%) and non-pregnant women (3.5%) who received counselling, compared to rates among those who received self-help material only.⁷⁷ The average frequency of counselling sessions for pregnant women was 2.3 occasions compared to 2.5 occasions among non-pregnant women.⁷⁷ Pregnant women were more likely to be alerted to a quitline by health professionals, while non-pregnant women were made aware of quitline services through mass media channels.

A study by Cummins et al.¹³⁰ that was not included in this review as it did not examine any of the key components required to underpin quitline services, did examine pregnant smokers' use of a Californian quitline plus self-help materials compared to self-help materials alone. This RCT identified an increased 30-day abstinence at the end of pregnancy (29.6% vs 20.1%; $p < 0.001$), 90-day abstinence two months post-partum (22.1% vs 14.8%; $p < 0.001$) and 180-day abstinence six months post-partum (14.4% vs 8.2%; $p < 0.001$) among the intervention than the control group. Of pregnant women assigned to the counselling intervention arm, 71.2% received at least one session, with an average of 4.0 follow-up sessions. Only one-fifth of participants received counselling post-partum, with the average number of post-partum calls being 1.5.

Substance use disorders

Only one study examining the addition of an alcohol cessation component to regular quitline smoking cessation services was identified for inclusion in this rapid review. The Toll et al. 2015 study evaluated the addition of alcohol-focused counselling plus an alcohol reduction booklet to standard New York Smokers' quitline counselling, compared to smoking cessation counselling plus a smoking cessation booklet added to standard care.¹⁰⁴ The addition of alcohol-tailored advice resulted in a significantly higher rate of smoking abstinence at seven-month follow-up (13.5%) compared to the control group (10.3%; $p = 0.03$). When analyses were undertaken to control for treatment conditions, participants who did not report any heavy drinking were significantly more likely to quit smoking compared to those who reported any heavy drinking (OR = 1.87; 95% CI 1.29–2.71; $p < 0.001$).

A study by Griffin et al. 2015 in the Bronx, New York, which was not eligible for inclusion in this review because participants were recruited from methadone treatment programs, evaluated the impact and uptake of quitline on opioid-dependent smokers also taking varenicline tartrate.¹³¹ Of the 112 participants recruited into the study, all were offered a written referral to quitline, yet only 22% utilised the service. Those who chose not to undergo quitline counselling were more likely to report mobile phone service lapse and difficulty charging mobile phones. The main reasons for quitline refusal included scepticism of quitline efficacy, aversion to telephone communication, competing life demands (e.g. drug treatment, shelter) and problems with mobile phone service and calls.

Young people

Utilisation and adherence to quitline services are reported to be lower among young people.^{132, 133} Yet, this rapid review of evidence only identified one study that evaluated quitline services specifically designed for younger smokers. This Wisconsin-based RCT of 410 smokers⁶³ compared a quitline-based counselling intervention with up to four callbacks with self-help material mailed to the participant. No difference was observed for intention-to-treat seven-day point prevalence abstinence at one, three, or six months post-enrolment. Study retention was low with 48.3% responding by six-month follow-up. Other smoking

cessation strategies such as use of pharmacotherapy are also underutilised by young smokers¹³³ and younger participants are less adherent to follow-up counselling sessions as part of standard quitline protocols.¹¹⁴ These results suggest that this demographic is difficult to engage and retain, and that targeted interventions relatable to young people are required. One RCT conducted among 50 high schools in Washington State, US¹³⁴ proactively recruited 2,151 smokers providing them with CBT and personalised motivational interviewing by phone compared to no intervention. This study was not identified for inclusion in this review because counselling was not conducted with quitline counsellors or within a quitline setting. By six-month follow-up, 21.8% of intervention participants reported prolonged smoking abstinence compared to 17.7% of control participants ($p = 0.06$), with a significant benefit among intervention participants compared to control among daily smokers (10.5 vs 5.9% respectively; $p = 0.02$).

Relatable interventions that utilise smartphone technology may provide an avenue to increase uptake and successful outcomes for quitline services among youth.¹³⁵ The benefits of using this type of technology among youth is that it is synchronistic with their lifestyle choices, being affordable, personalised, not location dependent and age appropriate.¹³⁶ For example, text messaging services¹³⁷, smoking cessation applications (apps)¹³⁸ or use of social media networks such as Facebook¹³⁹, may provide unique opportunities to engage with this cohort, although more research is needed.

Review Question 2

Enablers of, or barriers to, delivery of effective service components identified in Question 1

Several enablers and barriers were identified within studies reporting information on key components. This data has been supplemented with grey literature that specifically focus on identifying enablers and barriers to optimal service provision, such as surveys among smoking cessation practitioners.

There are mixed reports about the use of NRT as an adjunct to quitline services. A 2010 study by Burns et al.⁷¹ conducted with 1,710 smokers calling the Colorado quitline in the US investigated the impact of a protocol change to provision of NRT. Under the change, light to moderate smokers (≤ 20 cigarettes per day) were only eligible for a four-week supply of NRT compared to the previous eight-week supply available to this group. Abstinence declined by nearly a quarter under the reduced NRT protocol (29.9% compared to 39.3%; $p < 0.01$). Heavy smokers (> 20 cigarettes per day) who were still eligible for the eight-week supply of NRT experienced no change in abstinence rates over the same period of time. However, the same author conducted an RCT of eight-week compared to four-week provision of NRT which identified no difference in continuous abstinence or seven-day point prevalence between groups.⁵⁶ A statistically significant difference was observed for individuals within the intervention arm who received the full eight-week provision of NRT compared to those who only requested the four-week supply, suggesting that it was more likely the continued engagement and perhaps a higher motivation among participants to quit smoking that resulted in the benefit, rather than the availability of an eight-week supply of NRT. Another study by Bullen et al.¹² identified that the use of NRT two-weeks before the target quit date had no additive effect on cessation outcomes.

An RCT investigating the use of interactive voice response technology to re-engage relapsed quitline smokers across two US states reported low self-efficacy and lack of interest in quitting as barriers to re-engaging in continued counselling as part of a new treatment cycle.⁵⁷ After delivering interactive voice response messages designed to target these barriers, 32% of smokers who reported low self-efficacy and 4.8% of those who initially identified a lack of interest re-engaged with the quitline service.

Several factors have been associated with non-adherence to quitline services among smokers. Yet an exploratory study among more than 20,000 quitline callers across 50 US states, Canada and several other countries by Burns et al. (2012) identified that all significant predictors pooled together explained less than 4% of the variance observed¹³² This suggests that the characteristics of smokers who were non-adherent to quitline services explained very little about their retention in the service. Characteristics where a significant difference was observed included:

- Male callers were more likely to receive more than three, four and five quitline calls compared to female callers
- Black callers were less likely to remain in quitline counselling compared to Latino, white or other demographics;
- Younger callers had lower adherence to quitline compared to older callers
- Individuals who did not complete high school and those who completed additional study beyond high school had better outcomes than those who completed high school but had no further education beyond that
- People with insurance were more adherent to counselling than those without insurance
- Smokers without children at home had greater compliance with counselling compared to those with children at home
- Individuals smoking more than 20 cigarettes per day were more likely to remain in quitline programs compared to those smoking 20 or less cigarettes per day
- Individuals who lived with a tobacco user were less adherent to counselling compared to those who were not regularly exposed to a tobacco smoker in the home
- Smokers who had a failed quit attempt in the past were more likely to be adherent to counselling compared to those who had not attempted to quit smoking before
- The most significant characteristic that determined compliance with the full quitline program of five calls was the provision of NRT. Smokers who received NRT were more likely to be adherent to the counselling program compared to those who did not receive NRT.

The study authors suggested that a framework be proposed for directing research toward reducing quitline service non-adherence.

A study of training 'peer referrers' to quitline by DeLaughter et al.⁸⁰ identified several barriers to engaging successful quitters to provide their peers with written referrals to the service. One barrier was the time-point at which successful quitters were contacted to become 'peer referrers.' They felt that recruiting smokers at the beginning of quitting, with counsellor help (actively-quitting smokers), would be better than waiting until six-month cessation. Another issue was with the written referral forms, which were considered overwhelming to the peer referrers, with a text message-based referral processes suggested.

A study by Carlin-Menter et al. involving 1,923 participants examined reasons for quitline callers refusing a counselling callback, with 43% of responders at three-month follow-up acknowledging that they had not accepted the callback.¹⁸ The primary reasons cited were: too busy (39%); thought the calls would not be helpful (30%); and not ready to quit (14%). Of the 57% of responders who did accept the call, 89% said that the callback was helpful in assisting their efforts to quit smoking.

Additional relevant data from studies not meeting criteria for inclusion in the rapid review

Additional enablers and barriers were identified from alternative sources of evidence that weren't included in studies identified for this rapid review.

An evaluation of barriers and enablers to the adoption of 21 recommended quitline best practices was conducted by the US NAQC through annual surveys in 2016 and 2017, as well as telephone calls.¹⁴⁰ The report provides an overview of 21 recommended best practices, adoption rate for each and the enablers and barriers to reported uptake by state quitlines across the US (see Appendix 2). The following eight best practices were adopted by 90% or more of state quitlines:

1. Provide at least one FDA-approved cessation medication at no cost
2. Provide a minimum of a 2-week supply of cessation medications to eligible quitline participants
3. Put protocols in place so all quitline participants receive information on cessation medications
4. Offer proactive (quitline initiated follow-up) telephone counselling
5. Offer tailored intake protocol for pregnant and postpartum women
6. Promote cessation services and medications
7. Implement NAQC guidance on reaching priority populations and reengaging smokers
8. Adopt questions on electronic nicotine delivery systems (ENDS).

Follow-up phone conversations were conducted to evaluate common facilitators and barriers to adopting the 21 recommended best practices. Facilitators and barriers aligned with each other—for example, the cost of implementing the recommendation due to budget cuts in recent years was identified as a barrier, but there was an aligning facilitator reported in that there was minimal cost to implementing state quitline services and therefore sufficient budget was available. Key barriers and facilitators include:

- Cost of implementing/state quitline budget
- Priorities of the state quitline
- Technical capacity or capability of the state quitline's service provider.

Among 10 best practice recommendations with low levels of adoption (less than 30% of state quitlines), the state quitline budget appeared to be the primary barrier to adoption, with insufficient resources available. Examples of such recommendations included provision of cessation medications, eReferrals and other technology-based practices. Additional reasons for non-adoption of best practice recommendations included the lack of technical capacity by the service provider and that the recommended best practice did not align with priorities of the individual state quitline. Nuances were observed between different state quitlines, meaning that some services would only adopt part of the recommendation or would implement a modified version of the recommendation.

A 2016 report also by the US NAQC aimed to investigate current gaps in smoking cessation coverage for state employees, develop state-specific plans to address these gaps, and then promote comprehensive evidence-based cessation services.¹⁴¹ Enablers to service provision included: education of insurers and employers on the cost-benefit of tobacco cessation programs; support at the highest levels of government and state health departments; the publicisation of employee health program successes; awards programs to incentivise employers to increase coverage and receive recognition; and the building of relationships between insurance agencies and cessation service providers. For example, education of key political figures in North Carolina resulted in a state partnership with the tobacco program, increasing the quitline offering to include multiple telephone counselling calls, text services, a quit kit, 12 weeks of free NRT, as well as combination therapy and outcome evaluation. Smaller strategies such as the faxing of recommendations from the quitline to the participant's physician, and insurers liaising directly with quitlines as opposed to negotiating contracts through the state health department were also discussed. The main barrier identified

was the lack of clarity surrounding fiscal responsibility for these services—for example, insurers were less likely to purchase quitline services when the state provides free services to all callers. Some states have reduced quitline eligibility to serve only high-risk populations, which has prompted employers to purchase quitline services for their members, although this solution raises budget concerns.

A survey of 175 smokers who had previously used quitline services conducted by Tzelepis et al.⁴³ identified that more than 60% of smokers believed that their chances of quitting would have increased had they used the same quitline advisor for each call.

An audit by Brose, McEwen and West in 2012⁹⁵ evaluating 46,237 one-to-one treatment episodes in the UK identified similar results to the Burns et al. 2012 study from the US and Canada.¹³² The UK study also identified that age, gender, employment status, occupational grade, currently being in prison and exemption from prescription charges (as a surrogate measure for lower socio-economic status) were independently associated with the success of quit attempts.

In 2014 Brose et al. evaluated whether services that had greater utilisation of NCSCT training, using 16 competencies known to be associated with successful short-term smoking abstinence^{100, 101}, would show greater improvement in quitting success rates.¹¹⁶ Data from 146 services between 2008 and 2013 determined that practitioners who completed the face-to-face skills training had better smoking cessation treatment outcomes among clients compared to those who underwent online training. However, provision of any training compared to no training also increased quitting success rates ($p = 0.01$).

A survey of stop-smoking practitioners also reported by Brose et al. in 2015 suggested that ensuring practitioners had access to treatment manuals within their service, promoting manual use and training practitioners to completely apply manuals (i.e. implement the treatment manual in its entirety) was likely to contribute to higher success rates in clinical practice.¹⁴² Successful smoking abstinence rates among clients of smoking cessation practitioners (840 practitioners reporting on manual use and 713 on training) were higher among those who had a manual (54.0% compared to 48.0%; $p = 0.013$), used a manual ($p = 0.009$), perceived manuals as being more useful ($p = 0.034$) and had completed training ($p = 0.002$). Success rates were higher among specialist practitioners compared to non-specialist practitioners ($p < 0.001$).

The type of practitioner who delivered the treatment was also identified as a barrier/enabler, with another study among the same group of authors led by Hiscock determining that smoking cessation specialists were more likely to have clients successfully quit smoking compared to other practitioners such as nursing staff or general practitioners.¹⁴³ Authors reported that affluent smokers were more likely to quit than disadvantaged smokers, however, the classification of disadvantaged smokers was those eligible for free prescriptions compared to those who paid for prescriptions. Importantly, the fact that smokers had to pay for prescriptions could mean they were more motivated to quit rather than affluence being the primary factor leading to the successful quitting outcome. There is an economic principle of 'loss aversion' where an individual experiences more dissatisfaction from the loss of a certain dollar amount than satisfaction from gaining a certain dollar amount¹⁴⁴, meaning those who are financially committed to a quit attempt are more likely to succeed in that activity. This is supported in this study, as authors report that respondents who paid for prescriptions were more likely to quit. One-to-one smoking cessation therapy was received among 80% of service clients, however, open group forms of behavioural therapy were more successful (OR 1.26; 95% CI 1.12–1.41). The exception was among the most disadvantaged clients such as the long-term unemployed or prisoners.

Similarly, the same team conducted an online survey among 573 specialist practitioners and 466 community practitioners¹⁴⁵, identifying that smokers of specialist practitioners (63.6%) had better four-week carbon monoxide certified abstinence rates compared to community practitioners (50.4%; $p < 0.001$). This is

not surprising as for nurses and general practitioners, smoking cessation is a small part of their job as seen in the Hiscock et al.¹⁴³ study. However, specialist practitioners focus on smoking cessation as their primary role. Six modifiable variables were identified that showed a positive association in quitting outcomes among specialist practitioners above that of the non-modifiable variables such as age and gender, that accounted for 14.3% and 35.7% of variance in the total effect. These enablers resulting in higher efficacy in quitting outcomes included: a greater proportion of clients using the 'abrupt' quit model; a longer duration for the first counselling session; always providing advice on stop smoking medication options; greater number of days spent training; greater number of sessions observed by a specialist practitioner to improve compliance with guidelines before starting work, and; a larger number of sessions having been observed in practice with feedback received as part of a continual improvement process. Combination NRT was the most common medication recommended (26.4% among all practitioners), however, community practitioners were significantly more likely to recommend varenicline tartrate compared with specialist practitioners (19.3% compared with 11.9% respectively; $p = 0.001$), while specialist practitioners (44.9%) were significantly more likely not to recommend any specific medication compared to community practitioners (21.1%; $p < 0.001$). Specialist practitioners also reported that they were more likely to use behavioural change techniques with all clients and they had a greater total number of behavioural change techniques used with all clients compared to community practitioners.

Another 2012 study by the same team, led by McDermott¹⁴⁶, investigated self-reported practices, attitudes and level of training among smoking cessation practitioners through surveys conducted among 484 smoking cessation services. However, this investigation only provided a snapshot of current practice, rather than identification of specific barriers and enablers to optimal service delivery. Of note, just under half (43%) of services reported always using the abrupt quit model (i.e. they encouraged smokers to continue smoking as much as they want until the quit date and then stop abruptly at that point), the majority (53%) encouraged abrupt cessation but allowed smokers to cut down gradually until the quit date, while a minority (4%) encouraged smokers to cut down gradually before stopping.

Limitations

This rapid review of evidence includes several limitations. In particular, this is a rapid review of evidence rather than a comprehensive and systematic review of all available evidence. Therefore, there is potential for relevant studies to have been missed in the narrative synthesis of evidence. Furthermore, as both individual studies and systematic reviews have been included, there is potential for double counting of individual studies which may have also been included within a systematic review. Therefore, results should not be considered as a cumulative effect without first checking individual study details.

The quality of data varies substantially within the different levels of evidence as per the NHMRC evidence grading tool used to guide potentially included studies. Generalisability of findings is also limited with inclusion of evidence from across a broad cross section of populations from different countries, socio-economic backgrounds, ages, gender, smoking history etc. These issues have been described in more detail in section VI under the 'Quality assessment of evidence' for each review question.

Of particular note, a paucity of evidence was identified for many outcomes. Although some outcomes, such as 'Behavioural change techniques and adherence to these' may include many studies identified as included and relevant, the data provided within these individual studies that make up the body of evidence related to each specific outcome is often limited.

On a general note, there is an important methodological issue that some studies do not consider, being that analyses should be separated out for people smoking at the first call versus those who have already

quit as smoking status is a major predictor of later abstinence. This factor should be considered when interpreting and comparing study findings.

8 Recommendations

Inconsistent data was identified in this rapid review for most key components to underpin Quitline™ services. Certainly, this rapid review did not identify any strong evidence to deviate from the current Victorian Quitline™ protocol consisting of two pre-quitline initiated follow-up calls plus four post quitting calls (based on recommendations in the seminal paper by Zhu and Pierce²¹), underpinned by CBT using trained counsellors. Based on the available evidence, authors of this review recommend that state/territory and federal policy makers as well as senior managers of Quitlines™ consider implementing the following as a national set of minimum standards:

- A generic approach to counselling with a standardised core protocol can be considered for the majority of tobacco users, as extensive tailoring of services based on characteristics of individual participants contacting the Quitline™ do not appear to be associated with successful quitting; However, there may be some merit in considering a tailored approach for certain populations of Quitline™ callers, to provide services based on user characteristics. For example, young callers, pregnant women, CALD populations, Indigenous populations and those with mental health conditions
- Providing a two-week starter pack of free NRT to eligible Quitline™ callers is likely to increase smoking cessation outcomes
- All counsellors should be trained health professionals
- Counselling sessions should be monitored intermittently to measure compliance with best practice protocols, enabling identification of additional training requirements
- Face-to-face booster training should be provided to counsellors to supplement online training and easy access to treatment manuals provided within each service where possible, to reinforce compliance with best-practice guidelines
- The most commonly used behavioural approach is CBT, however, ACT and MI have also shown benefits in smoking cessation outcomes; therefore, consultation with an organisation such as the Australian Psychological Society could be made for advice on the best approach or combination of approaches, including the optimal number of sessions for the specific technique/s taken
- In the situation where a service needs to be scaled down due to limited resources, the focus should be on providing counselling to clients who initiate the first quitline contact, or to those known to be highly motivated to make a quit attempt, rather than quitline counsellors making the initial call to smokers who are less motivated to quit.

The above recommendations should not be considered in isolation, but rather considered as a package approach to increase the likelihood of successful increases in smoking abstinence among Quitline™ callers. The review authors strongly suggest that key stakeholders help to build the evidence base lacking for several key components including: the ideal number and duration of contacts; the addition of ACT and/or MI as an adjunct to CBT; ideal hours of quitline operation; and minimum counselling competencies required. This can be achieved by considering the following:

- It is likely that data are available within various Quitline™ services, however, publication of the results is required to enable consolidation of evidence and translation into standard practice
- To evaluate effectiveness and impact of different counselling protocols, for example frequency and duration of Quitline™ contacts, randomised controlled trials should be embedded into Quitline™

services; resource support should be provided to undertake a methodologically rigorous evaluation, with a plan of how to translate results into treatment protocols at conclusion of the evaluation period, with ongoing monitoring to confirm greater efficacy from the change has occurred.

When considering any change to standard practice, there needs to be an evaluation using methodologically rigorous techniques to quantify the impact alongside implementation. Considering the paucity of data available to address many of the key components to Quitline™ services, resources should be invested into supporting research activities directly within Quitline™.

9 Appendices

Appendix 1: Search strategies

Search strategy and results for database

Cochrane database search (29/10/2018)

Search: smoking cessation counselling

41 records imported

PubMed search (29/10/2018)

((Telephone OR phone OR quitline OR helpline OR hotline)) AND (smoking cessation OR quit)

1,373 records, 7 duplicates removed, 1,366 records imported

PsychInfo search (29/10/2018)

((Telephone OR phone OR quitline OR helpline OR hotline)) AND (smoking cessation OR quit)

775 records, 453 duplicates removed, 322 records imported

Embase search (29/10/2018)

#1 AND 'human'/de AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

#1: ('telephone'/exp OR telephone OR phone OR quitline OR helpline OR 'hotline'/exp OR hotline) AND ('smoking cessation'/exp OR 'smoking cessation' OR (('smoking'/exp OR smoking) AND ('cessation'/exp OR cessation)) OR quit)

814 records, 35 duplicates removed, 779 records imported

Total number of records identified: 3003

Duplicates removed: 495

Literature search total records after duplicates removed n = 2,508

Search strategy and results for grey literature

Identified directly from the Cancer Council Victoria: Nine references

Reference lists of included studies: One reference

World Health Organisation website search: Two references

US Department of Health and Human Services website search: One reference

North American Quitline Consortium (NAQC): 10 references

Cancer Council Victoria website: Two references

Australian Institute of Health and Welfare website: One reference

Department of Health website: One reference

Royal Australian College of General Physicians: One reference

Appendix 2

North American Quitline Consortium (NAQC) checklist

The NAQC produced a checklist for reviewing quitline services and activities, published in July 2017.¹⁰⁶ This checklist comprised of nine categories is a supplement to the “Quitline services: Current Practice and Evidence Base” guide.¹⁰⁷ The checklist includes a summary of the evidence, current status of each service among quitlines and recommendations and questions for consideration.

Intake – Field Tested Best Practice			
<i>Findings from the evidence:</i> - There is no evidence that intake helps tobacco users quit. Intake is a practical necessity and field-tested best practice. <i>Current status among quitlines (FY16):</i> 100% of quitlines have implemented this practice. Details on the recommendations and questions for consideration are available on pages 12-14.			
RECOMMENDATIONS	YES	NO	NOTES
Employ cost-efficient means to register new participants, while ensuring data accuracy and user satisfaction with the process.			
To the extent possible, make efforts to reduce the length and burden of intake by eliminating unnecessary questions and streamlining eligibility criteria.			
QUESTIONS FOR CONSIDERATION	YES	NO	NOTES
Have you evaluated the intake process to ensure that it does not hinder delivery of quitline services?			
Does your quitline collect the standard Minimal Data Set (MDS) questions during intake?			
Does your quitline have protocols for making intake less resource intensive, especially during high call volume periods?			
Does your quitline comply with best practices for “call centers”, such as: - Answering a high percentage of incoming calls received during business hours. - Returning voice mail message calls promptly. - Ensuring a high proportion of caller’s complete intake. - Ensuring a high proportion of participants complete intake and opt for and receive evidence-based service. - Having high rates of satisfaction from participants across all types of intake. - Delivering services soon after intake.			

Self-Help Materials – Field Tested Best Practice

Findings from the evidence:

- As a stand-alone intervention (i.e., when self-help materials are offered without counseling or medications), printed self-help materials can improve quit outcomes, though the effect just barely reaches statistical significance.
- Self-help materials confer no measurable benefit as an adjunct to personal contact (e.g., counseling) or NRT.
- Tailored self-help materials can improve quit outcomes, but the effect may be due to personal contact in which data used to tailor the materials are gathered, as opposed to the materials themselves.
- There is little evidence that providing self-help materials to quitline participants improves quit outcomes.

Current status among quitlines (FY16):

- 98% of quitlines offer mailed self-help materials
- 83% of quitlines offer recorded self-help messages
- 92% of quitline offer web-based self-help tools

Details on the recommendations and questions for consideration are available on pages 14-18.

RECOMMENDATIONS	YES	NO	NOTES
If sending printed, self-help materials to participants produces meaningful program benefits, provide concise, professionally produced materials that are culturally and linguistically appropriate and that meet health literacy standards.			
Consider replacing printed materials with web-based or other technological interventions designed specifically for those media, with input from e-health and health literacy experts and from members of the target audience.			
To the extent possible, reserve program funds for other quitline services that have stronger evidence.			
QUESTIONS FOR CONSIDERATION	YES	NO	NOTES
Have you evaluated your quitline's self-help materials using developmental or process questions?			
Have you assessed factors related to the cost of producing and disseminating self-help materials?			
Have you assessed various means for producing, warehousing and disseminating self-help materials (including electronic means) to ensure timely and efficient fulfillment?			

Telephone Counseling – Research Validated Best Practice

Findings from the evidence:

- Proactive, multisession telephone counseling is effective for smokers who call quitlines, the population which represents the largest category of quitline users.
- Telephone counseling is also effective for smokers who do not call quitlines themselves, such as patients who are referred by a health care provider (e.g. eReferral) rather than calling on their own.
- Telephone counseling is efficacious either by itself or as an adjunct to other treatments such as face-to-face counseling or NRT.
- Low-intensity telephone counseling does not have a measurable impact on quit outcomes; unless proven otherwise, a single call protocol—in the absence of other evidence-based treatments such as NRT—should be assumed to produce no significant effect on outcomes.

Current status among quitlines (FY16):

- 100% of quitlines offer it.

Details on the recommendations and questions for consideration are available on pages 18-25.

RECOMMENDATIONS	YES	NO	NOTES
Offer multisession, proactive telephone counseling as a standard quitline service, as it has the strongest evidence of any common quitline practice.			
If reverting to a single-call protocol becomes necessary during times of heavy demand, supplement the counseling with another evidence-based service such as free NRT.			
Exercise caution when comparing the quit rates of two or more quitlines, as results may only be comparable if the populations treated, types of services provided, quality assurance procedures, and evaluation methods are similar.			
QUESTIONS FOR CONSIDERATION	YES	NO	NOTES
Is the counseling protocol used by your quitline research validated or evidenced-based?			
Does the telephone counseling protocol used reflect the best available evidence?			
Are services evaluated using process questions to ensure fidelity to the protocol?			
Is a case management system used? If yes, what type and why?			

Interactive Voice Response (IVR) – Promising Practice

Findings from the evidence:

- IVR may not be effective as an adjunct to other high-intensity treatments.
- IVR can increase re-engagement by quitline participants.
- IVR can be an effective tool for recruiting smokers identified in the electronic health record (EHR).
- The efficacy of IVR may depend on how well it encourages participants to access other evidence-based treatments.

Current status among quitlines (FY16):

- 76% of quitlines use it to triage calls.
- 2% of quitlines use it to provide services
- 68% of quitlines use it in other ways (i.e., reengagement, referrals and confirmation of receipt of NRT)

Details on the recommendations and questions for consideration are available on pages 25-28.

RECOMMENDATIONS	YES	NO	NOTES
Consider uses of IVR beyond the basic triaging of incoming calls, such as asking intake and evaluation questions, recruiting new participants, re-engaging previous participants, promoting or supplementing the use of other quitline services, or helping tobacco users quit.			
Carefully evaluate any innovative use of IVR for its effects on program costs, use of other services, and participant satisfaction, and disseminate the findings.			
QUESTIONS FOR CONSIDERATION	YES	NO	NOTES
Do services available include IVR?			
Does your evaluation focus on narrowly defined process questions based on your actual uses of IVR?			
If IVR is not available, are plans in the works to incorporate these services to gather data, recruit or re-engage participants, promote or supplement the use of other quitline services, or help tobacco users quit?			

Text Messaging – Promising Practice

Findings from the evidence:

- Text messaging programs can be effective with smokers recruited online, through traditional advertising, or in health care settings.
- Text messaging can be effective either by itself or as an adjunct to in-person counseling.
- It is unknown whether text messaging is effective with quitline users, or in combination with other quitline services.

Current status of quitlines (FY16):

- 68% of quitlines offer text messaging, including:
 - 16% that offer one-way messages
 - 32% an interactive program
 - 20% both

Details on the recommendations and questions for consideration are available on pages 28-33.

RECOMMENDATIONS	YES	NO	NOTES
If a text messaging program is offered, ensure that it is closely based on interventions proven effective. Such interventions generally feature content scheduled around a quit date, frequent messages, extended duration, and basic interactivity and tailoring.			
Design and promote the text messaging program as a stand-alone service to attract tobacco users who may be less inclined to use traditional quitline services such as telephone counseling.			
For participants who are willing to use other quitline services, provide links from the text messaging program to telephone counseling and NRT.			
QUESTIONS FOR CONSIDERATION	YES	NO	NOTES
Is the content distributed via text messaging on par with other research-validated programs?			
Does the service utilize the four features common among programs proven effective? (see page 31)			
Are the services being offered currently serving a similar population as our quitline (e.g. recruited online)?			
Do the evaluation questions solicit direct feedback from users as well as process questions and reach questions?			

Mobile Apps – Insufficient Research Evidence

Findings from the evidence:

- There is no evidence to date that mobile apps help tobacco users quit.

Current status of quitlines (FY16):

- Extent of adoption unclear; the two largest service providers offer them.

Details on the recommendations and questions for consideration are available on pages 34-36.

RECOMMENDATIONS	YES	NO	NOTES
Monitor the scientific literature for emerging evidence of the efficacy of mobile apps for tobacco cessation.			
If offering a mobile app, take steps to ensure that it adheres to the USPHS clinical practice guideline for tobacco dependence treatment, makes sophisticated use of smartphone technology, has features important to providers and smokers, and is highly rated by users.			
QUESTIONS FOR CONSIDERATION	YES	NO	NOTES
How does the app rate against established scales/coding schema and against best practices documents for behavior change apps?			
Does evaluation include actual usage data and user feedback?			
If the services include a mobile app platform other than QuitGuide or quitSTART, is it highly rated by users?			

Web-based Services – Promising Practice

Findings from the evidence:

- Web interventions may be effective for adult smokers and young adult smokers, but it is unknown if they are effective with adolescents.
- Web interventions are probably not more effective than counseling.
- Web interventions may not be effective as an adjunct to counseling.

Current status for quitlines (FY16):

- 98% offer websites with basic info
- 92% self-help
- 66% chat rooms
- 76% email
- 58% online counseling

Details on the recommendations and questions for consideration are available on pages 36-43.

RECOMMENDATIONS	YES	NO	NOTES
If web-based services are offered, ensure that they are closely based on interventions proven effective in randomized, controlled trials. In general, such interventions are multimodal, intensive with respect to the frequency of messages, interactive, and tailored. Continue to monitor the scientific literature for emerging evidence of the efficacy of web-based interventions for tobacco cessation.			
QUESTIONS FOR CONSIDERATION	YES	NO	NOTES
Do evaluation questions reflect the aim of the web-based service (i.e., to promote the quitline or to help tobacco users quit)?			
Have quit rates been obtained using a controlled study with random assignment?			
Is an explanation offered regarding how the proposed web-based services are evidence-based?			
Do the web-based services attract users less likely to use phone counseling services?			
Do web-based services extend program resources?			
Do web-based services enable users to move seamlessly between services?			
Do web-based services demonstrate “added value” for the program?			

Medications – Research Validated Best Practice (for FDA-approved Medications)

Findings from the evidence:

- NRT, combination NRT, bupropion, nortriptyline, varenicline, and cytisine are all effective.
- No form of NRT is more effective than another, except that sprays and inhalers are slightly more effective than gum.
- Combination NRT is more effective than single formulation NRT, and nearly as effective as varenicline.
- Neither bupropion nor nortriptyline is effective as an adjunct to NRT.
- Varenicline is more effective than either single formulation NRT or bupropion.
- Despite earlier concerns about varenicline and bupropion possibly triggering adverse neuropsychiatric events, they have been proven to be safe, including for individuals with psychiatric disorders.
- Medication in combination with counseling significantly improves outcomes, relative to a control of usual care or minimal intervention.
- Behavioral support significantly improves long-term rates of abstinence over medication alone.
- The effect of telephone counseling is not subsumed by the effect of medication.
- NRT is effective as an adjunct to telephone counseling, and combination NRT is more effective in this context than single formulation NRT, but the optimal duration of NRT provision for quitline participants is unknown.

Current status for quitlines (FY16):

- 96% provide nicotine patches
- 82% nicotine gum
- 62% nicotine lozenges
- 8% varenicline
- 8% bupropion
- 2% nicotine inhalers
- 2% nicotine nasal spray
- 48% had adopted the recommendation to offer combination therapy

Details on the recommendations and questions for consideration are available on pages 43-48.

RECOMMENDATIONS	YES	NO	NOTES
Offer at least a 2-week starter kit of single-form OTC NRT to all quitline participants for whom NRT is indicated.			
If the budget allows, offer combination NRT or varenicline instead of single-form NRT, as they have the strongest documented effect on quit outcomes.			
If the budget allows, offer at least 6-8 weeks of medication, as longer courses may be more effective than shorter ones.			
Offer telephone counseling to all participants provided medications, but do not require it.			

QUESTIONS FOR CONSIDERATION	YES	NO	NOTES
Are proven and effective medications provided for a period of at least 2 weeks by a variety of means (<i>voucher, pharmacy benefits manager, mail</i>)?			
Does the evaluation of services include NAQC's recommended quit rate calculation as well as a process evaluation? (see http://tinyurl.com/yakd4ggq for how to calculate quit rate)			
Is NRT offered to all quitline participants for whom NRT is indicated?			

Referral – Research Validated Best Practice

Findings from the evidence:

- Interventions that incorporate referral to a quitline can significantly improve long-term quit outcomes.

Current status for quitlines (FY16):

- 100% accept fax referrals
- 85% email or online referrals
- 38% eReferrals

Details on the recommendations and questions for consideration are available on pages 43-48.

RECOMMENDATIONS	YES	NO	NOTES
Offer a range of direct and indirect referral options to allow providers in various settings to refer tobacco users to the quitline, and make patient materials freely available to encourage provider participation.			
Develop the capacity to accept eReferrals from a range of certified EHR's and to return automated, patient-specific reports.			
QUESTIONS FOR CONSIDERATION	YES	NO	NOTES
Are a variety of direct and indirect referral options offered to allow providers in various settings to refer tobacco users to the quitline, and make patient materials freely available to encourage provider participation?			
Do the services include capacity for bi-directional eReferrals from a broad range of EHR vendors?			
Is a process evaluation conducted that includes gaining feedback from referring organizations?			

Source: North American Quitline Consortium. Checklist for Reviewing Quitline Services and Activities. July 2017.
Available from:
https://cdn.ymaws.com/www.naquitline.org/resource/resmgr/reports_2010/CessationWorks_Checklist.pdf

Appendix 3

Excluded but relevant studies describing referral pathways to the service

Source and NHMRC evidence level	Referral pathway evaluated
Adsit 2014 Level IV	A closed-loop electronic health records (EHRs) referral system linking patients visiting healthcare clinics with a state tobacco quitline
Baskerville 2015 Level IV	Canadian tobacco package warning labels with a quitline toll-free phone number focusing on treatment reach and reach equity in selected vulnerable groups
Bernstein 2009 Level IV	Brief educational/administrative intervention (1-hour lecture) for emergency physicians on the health effects of smoking and strategies to counsel patients with cards promotion a national smokers quitline
Bernstein 2009 Level IV	Training and technical assistance provided to healthcare clinical sites to promote use of a faxed referral to state quitlines
Bernstein 2016 Level II	A motivational interview, along with 6 weeks of nicotine patches and gum, a referral faxed to the quitline, a booster call, and a Quitline brochure
Boykan 2016 Level IV	Smoking caregivers of paediatric patients referred to the New York State Smokers quitline through a standardised template built into the electronic health record
Brown 2013 Level IV	Various policies including excise taxes, workplace and public smoking bans and a Peter Jennings television-based program warning of the health risks of smoking
Brown 2017 Level IV	Individuals undergoing substance use disorder treatment services recruited during a hospital admission into the Tablet Intervention to Motivate Engagement with Tobacco quitline study
Cantrell 2009 Level IV	Implementation of a fax referral system paired with a chart stamp prompting providers to identify smoking patients, provide advice to quit and refer interested smokers to a state-based fax quitline
Carson 2014 Level II	Adult patients of South Australian hospitals were randomised to the state quitline in both intervention and control groups
Cheung 2018 Level II	Referral to a community counselling service that offers a quitline, a text-based program, and a Web-based program
Clayforth 2014 Level III	Non-television advertising media to encourage young male smokers to respond to a cessation-related call to action
Conde 2013 Level IV	E-tobacco protocol to increase referrals by health professionals to the state quitline; offering counselling and NRT to clinician-referred patients
Cummins 2016 Level III	A hospital-quitline partnership utilising nicotine patches and proactive telephone counselling or a combination of the two to help patients maintain smoking cessation after discharge
Drehmer 2016 Level II	Proactive enrolment of parents to quitlines by paediatric clinics, when compared with a suggestion by paediatric clinicians
Fenech 2012 Level II	Outpatients with chronic hepatitis C received a referral to the quitline by the nurse practitioner
Fu 2011 Level II	Utilisation of the Veterans Health Administration patient recording system to identify current smokers and proactively reach out with invitations to seek treatment with a

Source and NHMRC evidence level	Referral pathway evaluated
	choice of services
Gordon 2010 Level III	The Ask, Advise, Refer model—promoting a brief office-based intervention plus referral to a tobacco quitline
Greenwood 2012 Level IV	Incorporation of a workflow in the electronic health record (EHR) to empower medical assistants to become tobacco-cessation promoters and increase referral to quitline
Griffin 2015 Level IV	Patients in methadone treatment programs who were enrolled in a clinical trial were offered referral to a free, proactive quitline
Grossman 2014 Level IV	Patients received minimal counselling in the hospital emergency department, but were encouraged post-visit quitline contact for high quality telephone counselling
Haghpahanah 2017 Level IV	Scottish mass media TV campaigns to increase calls to the national Smokeline
Hammal 2015 Level IV	A kiosk in the foyer of two hospitals, staffed by volunteers trained in smoking cessation techniques to enhance quitline reach
Hudmon 2018 Level II	Academic detailing—on-site training—or mailed quitline materials to engage pharmacy personnel in referring patients to the tobacco quitline
Kaufman 2010 Level IV	Analysis of NHS data to understand current awareness of quitlines among the smoking population, and increase quitline use
Kennedy 2013 Level IV	A social media campaign—“ <i>One Tiny Reason to Quit</i> ”—to improve utilisation of quitline services by pregnant African American women
Kmietowicz 2014 Level IV	Plain tobacco packaging legislation
Kobinsky 2010 Level IV	Clinic-based Fax to Quit (FTQ) provider referral
Leuthard 2015 Level IV	Health system changes within hospitals and clinics including the identification of tobacco-using patients, and faxing a referral to the Oklahoma Tobacco Helpline
Macaller 2011 Level IV	Educational interventions—including presentations, smoking cessation materials, and a print media campaign—for diabetes educators to promote referrals to the state’s tobacco quitline
Martin 2017 Level IV	Examination of the barriers and facilitators among health professionals to providing referrals to quitline for Aboriginal and Torres Strait Islander clients
Mathew 2015 Level III	A brief telephone referral to the smoker’s state Quitline by research staff, including a discussion of past quit attempts, review of motivation to quit, benefits of quitlines, and state-specific quitline details
Mathew 2010 Level IV	A small-scale educational and promotional campaign to increase health care providers’ awareness and utilisation of a state tobacco cessation quitline fax referral service
Mowls 2017 Level IV	Fax referral to the state quitline by health practitioners in hospitals and clinics
Mussulman 2018 Level II	Warm handoff (on-the-spot enrolment and counselling by hospital staff) versus fax referral to the state quitline for smoking cessation among hospitalised smokers living with HIV/AIDS
Nash 2015 Level IV	Self-selection into an integrated phone/web tobacco cessation program, or a stand-alone web program offered by state quitlines
Neri 2016 Level IV	No referral – smokers contacted web-based or telephone quitline on their own initiative

Source and NHMRC evidence level	Referral pathway evaluated
Nonnemaker 2013 Level IV	Television antismoking advertisements for state quitline
Parks 2016 Level IV	Television advertisement with financial incentives for calling the state quitline
Patten 2011 Level II	An intervention including telephone counselling and education for non-smokers interested in helping a smoker to promote smoker utilisation of the state quitline
Peterson 2009 Level III	A proactive, personalised telephone-based motivational counselling intervention for adolescents
Ratner 2013 Level IV	Simplification of the existing quitline referral process in a University medical clinic
Richter 2016 Level II	Warm handoff—staff immediately called the quitline from patient bedside for enrolment and counselling—or referred to the quitline via fax on the day of hospital discharge
Russo 2018 Level III	Provider-referral strategy based in paediatric and dental clinics vs a targeted media campaign to promote self-referral to quitline
Sewali 2016 Level II	Motivational interviewing counselling or mailed promotional materials to promote the state quitline
Shah 2010 Level IV	Usual hospital care combined with pre- and post-visit expired carbon dioxide measurement
Sharifi 2014 Level IV	Brief clinician training, as well as electronic health record modification to include screening prompts, decision support, educational materials and a simplified referral process to the state quitline
Sheffer 2012 Level II	Increased academic detailing in clinics—on-site training, technical assistance, and performance feedback—to boost utilisation of a fax referral quit program
Sheffer 2010 Level IV	Policy, programmatic and communication initiatives, including free NRT and a media campaign to increase use of the state quitline
Song 2014 Level IV	Provider-referral vs self-referral to quitline
Stoltzfus 2011 Level IV	Script-based proactive approach to quitline fax referral (offering referral to all smokers) versus script-based reactive approach (assessing smokers' level of readiness to quit)
Sumner 2016 Level II	Workplace smoking-cessation campaigns offering a discounted health insurance rate in a hospital system and affiliated medical school
Szklo 2010 Level IV	Large positive-content or negative-content antismoking posters in subway stations to increase calls to quitline
Tzelepis 2009 Level II	Proactive telephone counselling or self-help materials to explore acceptability of active telephone recruitment to quitlines
Vidrine 2011 Level IV	Proactive telephone counselling delivered via state quitlines
Vidrine 2010 Level IV	Partnerships between quitlines and health care systems to increase dissemination and implementation of existing 'best practices' for tobacco cessation
Vidrine 2013 Level III	The names and telephone numbers of smokers attending family practice clinics who agreed to be contacted were sent electronically to the quitline daily, and patients were proactively called by the quitline
Wahl 2015 Level IV	Academic detailing and training of pharmacy personnel to improve counselling practices and increase referrals to the tobacco quitline

Source and NHMRC evidence level	Referral pathway evaluated
Warner 2012 Level IV	QuitWorks system which links healthcare organisations, providers, and patients to the state's tobacco cessation quitline and provides feedback reporting
Warner 2011 Level II	A brief clinician-delivered intervention to facilitate quitline use
Warner 2016 Level II	Intervention group received a brief quitline facilitation intervention with either a warm handoff or faxed referral to a quitline
Weaver 2015 Level II	Smoking cancer survivors recruited directly from the Community Clinical Oncology Program to quitline telephone counselling
Wilson 2010 Level IV	Quitline number advertised on cigarette packaging
Young 2014 Level IV	Quitline number advertised on cigarette packaging - tobacco plain packaging compared with cigarette package graphic health warnings
Zhang 2015 Level IV	Federally funded national tobacco education campaign, Tips From Former Smokers (Tips)

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Appendix 2 COPD EPAS Order Set

Order Entry Worksheet - TSOUVALAS, MILO

TSOUVALAS, MILO 340021030 / 100521391 36y (12-12-1980) Female
RGH-W2-R08-19 Penta, Mario 'ACD'
Allergies: amoxicillin, candesartan, Clomid, morphine, <other>...Intolerances: Peanuts and products

Requested By: ☒ Me ☐ Other: Source: Allergy Details

Date: --/--/-- Time: --:-- Session: Type: Standard

Manual Entry Searching for

Warning Message

Please note the following orders need to be ordered separately within EPAS by Medical Officer:

- Deteriorating Patient (RDR) Modification order
- Resuscitation Order (Note: This should be accompanied with completed Resuscitation Alert 7 Step Pathway document)

OK

Add... View... Item Info Add to Favorites Message Drug Info Edit... Delete Copy... Add Specimen... Indication... Mark as Done

Submit Order(s) for TSOUVALAS, MILO Hide Worksheet Cancel Help

COPD Management - Adult - TSOUVALAS, MILO

TSOUVALAS, MILO 340021030 / 100521391 36y (12-12-1980) Female
RGH-W2-R08-19 Penta, Mario 'ACD'
Allergies: amoxicillin, candesartan, Clomid, morphine, <other>...Intolerances: Peanuts and products

PULM. COPD Management - Adult [0 orders of 158 are selected] [Last clinically significant modification on Jun 08 2017]

Collection Date Collection Priority/Time Patient Fasting Sample Process Priority Pregnancy Status

Phone Results Contact Details for Results

Clinical Notes including Medications

Height/Weight/BSA
Height (cm) 155 Weight (kg) 67 BSA 1.66 BMI 27.9
26-07-2017 00:23 26-07-2017 00:21

Relevant Results

Renal Function (Actual)
Creatinine (micromol/L) Creat Clearance (mL/min) Actual Estimated

PATHOLOGY

Pathology - STAT

☐ Blood Gas Arterial (.) ☐ C-Reactive Protein (.) ☐ Complete Blood Examination (.) ☐ ECU LFT CAL PHO URA CHO GL (.)
☐ Electrolytes Level (.)

Pathology - Routine

☐ Blood Gas Arterial (.) ☐ Blood Group and Antibody Screen (.) ☐ C-Reactive Protein (.) ☐ Complete Blood Examination (.)
☐ ECU LFT CAL PHO URA CHO GL (.) ☐ Electrolytes Level (.)

MICROBIOLOGY

Order	Collection Date	Collection Priority	Specimen	Body Site	Clinical Notes including Medications
☒ Atypical Pneumonia (Legion, Myco IgG/M) (.)	T	Unit Collect			
☐ Culture Sputum (.)	T	Unit Collect			
☐ Legionella pneumophila 1 Ag Urine (.)	T	Unit Collect			
☐ Respiratory Pathogens NAT Sputum	T	Unit Collect			
☐ Respiratory Pathogens NAT Swab (.)	T	Unit Collect			

Requested For Date

ECG

Order	Requested Date	Requested Time	Clinical Question	Clinical Information
☒ Electrocardiogram 12 Lead	T			

MEDICAL IMAGING

Order	Requested Date	Requested Time	Portable	Clinical Question	Clinical Information	Required beyond Discharge	Urgent Contact Details
☒ XR Chest	T		☐				

RESPIRATORY

☒ Oxygen Therapy Administration ☐ Non Invasive Ventilator Management ☐ Spirometry

MEDICATIONS													
	Order	Ordered Dose	Max Amount / Dose	UOM	Route	Route Modifier	Frequency	Start Time	PRN	PRN Reason	Max Daily Dose	Duration	
Antibiotics - 2 item(s)													
☐	amoxicillin (capsule)	500		mg	oral		3 times a day		☐				
☐	doxycycline (capsule)			mg	oral				☐				
Corticosteroids - 2 item(s)													
☐	hydrocortisone sodium succinate injection (.)			mg	intraVENO..				☐				
☐	prednisONE (tablet)			mg	oral				☐				
Short-Acting Relievers - 4 item(s)													
☐	ipratropium 21microgram/dose (ATROVENT) inhaler (.)			Puff(s)	inhaled	via spacer			☐				
☐	salbutamol 100microgram/dose inhaler (.)			Puff(s)	inhaled	via spacer			☐				
☐	salbutamol 100microgram/dose inhaler (.)			Puff(s)	inhaled	via spacer			☒				
☐	terbutaline 500microgram/dose (BRICANYL TURBUHALER) (.)			Inhalation(s)	inhaled				☐				
Nebulised Medications - 3 item(s)													
☐	ipratropium nebuliser solution (.)			microgram	inhaled				☐				
☐	salbutamol nebuliser solution (.)			mg	inhaled				☐				
☐	salbutamol nebuliser solution (.)			mg	inhaled				☒				
Long-Acting Anti-Muscarinics - 5 item(s)													
☐	acclidinium 322microgram/dose (BRETARIS GENUAIR) (.)	1		Inhalation(s)	inhaled		TwICE a day		☐				
☐	glycopyrronium (SEEBRI) inhalation capsule (.)	50		microgram	inhaled	via inhalation device	every morning		☐				
☐	tiotropium (SPIRIVA) inhalation capsule (.)	18		microgram	inhaled	via inhalation device	every morning		☐				
☐	tiotropium 2.5microgram/dose (SPIRIVA RESPIMAT) (.)	2		Puff(s)	inhaled		every morning		☐				
☐	umeclidinium 62.5microgram/dose (INCRUSE ELLIPTA) (.)	1		Inhalation(s)	inhaled		every morning		☐				
Long-Acting Beta Agonists - 3 item(s)													
☐	eformoterol (FORADILE) inhalation capsule (.)	12		microgram	inhaled	via inhalation device	TwICE a day		☐				
☐	indacaterol (ONBREVZ) inhalation capsule (.)			microgram	inhaled	via inhalation device	every morning		☐				
☐	salmeterol 50microgram/dose (SEREVENT ACCUHALER) (.)	1		Inhalation(s)	inhaled		TwICE a day		☐				
LAMA/LABA Combinations - 4 item(s)													
☐	acclidinium - eformoterol 340microgram-12microgram/dose (BRIMICA GENUAIR) (.)	1		Inhalation(s)	inhaled		TwICE a day		☐				
☐	indacaterol - glycopyrronium 110microgram-50microgram (ULTIBRO BREEZHALER) inhalation..	1		Capsule(s)	inhaled	via inhalation device	every morning		☐				
☐	tiotropium - olodaterol 2.5microgram/2.5microgram/dose (SPIOLTO RESPIMAT) (.)	2		Puff(s)	inhaled		every morning		☐				
☐	umeclidinium - vilanterol 62.5microgram-25microgram/dose (ANORO ELLIPTA) (.)	1		Inhalation(s)	inhaled		every morning		☐				
ICS/LABA Combinations - 8 item(s)													
☐	buDESONide - eformoterol 200microgram-5microgram/dose (SYMBICORT RAPIHALER) (.)	2		Puff(s)	inhaled		TwICE a day		☐				
☐	buDESONide - eformoterol 200microgram-5microgram/dose (SYMBICORT TURBUHALER) (.)	2		Inhalation(s)	inhaled		TwICE a day		☐				
☐	buDESONide - eformoterol 400microgram-12microgram/dose (SYMBICORT TURBUHALER) (.)	1		Inhalation(s)	inhaled		TwICE a day		☐				
☐	fluticasone furoate - vilanterol 100microgram-25microgram/dose (BREO ELLIPTA) (.)	1		Inhalation(s)	inhaled		every morning		☐				
☐	fluticasone propionate - salmeterol 125microgram-25microgram/dose (SERETIDE) inhaler (.)	2		Puff(s)	inhaled		TwICE a day		☐				
☐	fluticasone propionate - salmeterol 250microgram-25microgram/dose (SERETIDE) inhaler (.)	2		Puff(s)	inhaled		TwICE a day		☐				
☐	fluticasone propionate - salmeterol 250microgram-50microgram/dose (SERETIDE ACCUHALER)...	1		Inhalation(s)	inhaled		TwICE a day		☐				
☐	fluticasone propionate - salmeterol 500microgram-50microgram/dose (SERETIDE ACCUHALER)...	1		Inhalation(s)	inhaled		TwICE a day		☐				
Nicotine Replacement - 3 item(s)													
☐	nicotine 15mg/cartridge (NICORETTE) inhaler (.)	1		cartridge	inhaled				☒				
☐	nicotine 24hour patch (.)			mg/24 hours	transdermal				☐				
☐	nicotine lozenge (.)			mg	oromucosal				☒				
VTE Prophylaxis - 3 item(s)													
☐	enoxaparin injection (.)			mg	subCUTA..				☐				
☐	heparin sodium injection (.)	5000		Unit(s)	subCUTA..				☐				
☒	CORE: Venous Thromboprophylaxis with Risk Assessment												
Reference Sets													
☒ COMMON: Antibiotics ☒ COMMON: Lab Orders													
	Order	Requested Volume	UOM	Route	Route Modifier	IV Rate	Infusion Time	Instructions					
Intravenous Therapy - 3 item(s)													
☐	glucose 5% infusion (.)		mL	intraVENOUS infusion									
☐	sodium chloride 0.9% infusion (.)	1000	mL	intraVENOUS infusion									
☒	COMMON: Infusion Therapy												
	Order	Requested Date	Reason For Consult										
Consults - 9 item(s)													
☐	Consult - Dietitian (.)	T											
☐	Consult - Occupational Therapist (.)	T											
☐	Consult - Physiotherapist (.)	T											
☐	Consult - Respiratory (.)	T											
☐	Consult - Respiratory Nurse	T											
☐	Consult - COPD Nurse	T											
☐	Consult - Home Oxygen Nurse	T											
☐	Consult - Social Worker (.)	T											
☐	Consult - Speech Pathologist (.)	T											



COPD Inpatient Management

Bedside Quick Reference Guide



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INPATIENT ASSESSMENT

- Complications/comorbidities related to worsening of disease status
- Level of mobility/activities of daily living
- Advanced care directives
- Commence discharge planning



TREATMENT / MANAGEMENT

- Vital signs: Temp, Pulse, Resp Rate, BP, SpO₂, 4 hourly for first 48hrs, then twice daily
- Controlled O₂ therapy
Guidelines: next page
- Pharmacotherapy
- Encourage mobility +/- exertional oxygen
→ refer physiotherapy
- Consider & address risk factors/other comorbidities
- Consider palliative approach
- Address inadequate treatment response



ASSESS SUITABILITY FOR HOSPITAL SUBSTITUTION

REFERRAL / ACTION

COMORBIDITY / RISK FACTOR	REFERRAL / ACTION
Aspiration	• If high risk, nil orally pending assessment • Speech Pathologist
Depression & Anxiety	• Social Worker • If severe, consider paroxetine
Heart Failure	• Pharmacotherapy • Cardiology
GORD / Swallow	• Pharmacotherapy • Gastroenterology
DVT	• LMW heparin until mobile
OSA	• Sleep study
Smoking	• Offer cessation advice/ pharmacotherapy • Clinical Pharmacy • Respiratory Nurse
Nutrition	• Dietitian
Osteoporosis	• BMD/pharmacotherapy • Radiology • Clinical Pharmacy

PALLIATIVE APPROACH

REFER TO PALLIATIVE CARE AND/OR CONSIDER PHARMACOTHERAPY:

Opioid-naïve-intermittent dyspnoea:

Morphine immediate release 1 – 2.5mg p/o every 30min if needed. Review after 3 doses

Opioid-naïve-continuous dyspnoea:

Morphine immediate release 1 – 2.5mg p/o 4 hourly. If ineffective but tolerated titrate up, once stable convert to modified-release

Currently on opioids-acute dyspnoea:

Morphine 1/10 – 1/6 of total daily dose as necessary max every 30min. Review after 3 doses

Currently on opioids-continuous dyspnoea:

Increase maintenance dose by 30-50%

STANDARD COPD INPATIENT ALGORITHM

OPTIMISE TREATMENT

DIRECT TREATMENT TO EACH OF THE BELOW:

- Increased airflow limitation
- Airway inflammation
- Hypoxia
- Acidosis
- Excess sputum production
- Infection
- Hypercarbia

BRONCHODILATORS

BRONCHODILATORS	INHALED WITH SPACER PREFERRED	NEBULISED
Salbutamol	400-600mcg (4-6 puffs)	2.5-5mg
Terbutaline	500-1000mcg	5mg
** If currently taking this consider switch to Salbutamol **		
Ipratropium	80mcg	500mcg
Titrate dose interval to patient response i.e. hourly – six hourly		

CORTICOSTEROID

CORTICOSTEROID	ORAL DOSE	IV DOSE
Prednisolone	37.5-50mg / day for 5 days*	
Hydrocortisone		100-200mg Qid
*Taper dose if use extends beyond 14 days		

ANTIBIOTICS

**** Check for allergies & consider response to antibiotic used prior to admission/presentation ****

ANTIBIOTICS	ORAL DOSE PREFERRED	IV DOSE
Amoxicillin	500mg, 8 hourly for 5 days	1g / 6-8 hourly
Doxycycline	200mg, then 100mg for 5 days	
If patient does not respond/ resistant organisms are expected:		
Amoxycillin-clavulanate	125/500mg TDS	
For atypical cover:		
Azithromycin	500mg daily for 3 days	500mg daily for 3 days

CONTROLLED OXYGEN THERAPY

CONTROLLED OXYGEN THERAPY	DOSE
Goal: Oxygen saturation 88-92%	Nasal prongs: 0.5-2.0L/min
** Consider ABG if hypoxic, CO2 retainer or potential need for NIV (PTO for NIV) **	Venturi mask: 24-28%

PHARMACOTHERAPY GUIDELINES



NIV ALGORITHM

CODE BLUE CRITERIA

Actual OR Impending

**CARDIAC / RESPIRATORY ARREST
THREATENED AIRWAY
SIGNIFICANT BLEEDING**

CALL #33

State: **CODE BLUE**, exact ward location

1



MEDICAL EMERGENCY RESPONSE CALL CRITERIA

PATIENT CLINICAL DETERIORATION AS LISTED BELOW

BREATHING

Respiratory rate: > 30 or ≤ 7
O2 saturation: ≤ 89

CIRCULATION

Systolic BP: ≤ 200 or < 90
Pulse: ≤ 140 or < 40

CONSCIOUSNESS SEDATION

Sedation score 3 – difficult to rouse (severe respiratory depression)
Unexpected or uncontrolled seizure

OTHER

Any patient about whom you are worried
Any observations in a PURPLE zone
3 or more observations in the RED zone
Unattended Multi Disciplinary Team Review (> 30 min)

CALL #33

State: **MER CALL**, exact ward location

2



CONSIDER ALTERNATE TREATMENT APPROACH

Is the patient for palliation, if **yes** refer accordingly. If **no**:

REPEAT ABG

Reassess gas exchange

Alternate diagnosis/comorbidities

Assess and refer accordingly

Consider NIV

Notify respiratory registrar/on-call consultant and ICU
See [NIV algorithm](#) (tab 3 of this flip chart)

Inadequate sputum clearance

Refer to Physiotherapy

Check [ADVANCED CARE DIRECTIVES](#) status and contact respiratory registrar (0800-1700) or on-call consultant after hours **before** proceeding with decision

3

ADDRESS INADEQUATE TREATMENT RESPONSE

DISCHARGE CRITERIA & PLANNING

- Completed COPD discharge checklist
- Clinically stable and have had no parenteral therapy for 24hrs
- Inhaled bronchodilators required less than 4 hourly
- Able to self care +/- home support and devices organised → Health Care at Home
- ABG prior to discharge on all patients admitted with respiratory failure
- Hypoxia stable – O₂ delivery ceased for 24hrs
- Referral to Respiratory Nurse if likely to require home O₂
- Hypercapnia resolved/stable
- Smoking cessation assistance/advice given
- Consider Pulmonary Rehabilitation
- COPD action plan and emergency pack

**COMPLETE: “.COPD DISCHARGE CHECKLIST” ACRONYM IN
EPAS → EXPORT TO DISCHARGE SUMMARY DOCUMENT**

SMOKING CESSATION

If not already completed: arrange pharmacotherapy/education

Refer – Respiratory Nurse
Refer – Clinical Pharmacy

PULMONARY REHABILITATION

Refer – Physiotherapy

COPD ACTION PLAN & EMERGENCY PACK

If patient doesn't already have one, provide.
Patient must be aware of and understand Action/Emergency Pack prior to discharge

Refer – Respiratory Nurse

**ARE ALL FOLLOW UP OUTPATIENT APPOINTMENTS ARRANGED
AND PATIENT NOTIFIED?**



**THE UNIVERSITY
of ADELAIDE**



**Government
of South Australia**
SA Health

DISCHARGE PLANNING

Table 1: Guide to addition of therapies

Green tick indicates therapies can be used together

	SABA	SAMA	LAMA	LABA	LABA/LAMA	ICS/LABA
SABA	✓	✓	✓	✓	✓	✓
SAMA	✓	✓	✓	✓	✓	✓
LAMA	✓	✓	✓	✓	✓	✓
LABA	✓	✓	✓	✓	✓	✓
LABA/LAMA	✓	✓	✓	✓	✓	✓
ICS/LABA	✓	✓	✓	✓	✓	✓

Relievers

SABA



Ventolin® MDI



Asmo® MDI



Airomir® MDI



Airomir® Autohaler®



Bricanyl® Turbuhaler®

SAMA



Atrovent® MDI

Maintenance

LAMA



Spiriva® HandiHaler®



Spiriva® Respimat®



Seebri® Breezhaler®



Bretaris® Genuair®

LABA/LAMA



Ultibro® Breezhaler®



Spiolto® Respimat®



Anoro® Ellipta®



Brimca® Genuair®

ICS/LABA



Symbicort® Turbuhaler®



Symbicort® Rapihaler®



Seretide® Accuhaler®



Seretide® MDI



Incruse® Ellipta®



Onbreo® Breezhaler®



*Foradil® Aerolizer®



*Oxis® Turbuhaler®



*Serevent® Accuhaler®



Breo® Ellipta®

ICS For patients with COPD and Asthma



*Flixotide® MDI



*Flixotide® Accuhaler®



*QVAR® MDI



*Pulmicort® Turbuhaler®



*Alvesco® MDI



*Flutiform® MDI

Flare Up Medicines

1. Antibiotics
2. Oral Steroids (Prednisone, Prednisolone)

Notes

- Handihaler, Breezhaler and Aerolizer devices require a capsule to be loaded into the device. All other devices are preloaded.
- Spacers are recommended to be used with metered dose inhalers (MDI)
- ICS monotherapy is not indicated for COPD without asthma
- *Not PBS listed • Shaded • *PBS listed for asthma only

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CORRECT INHALER TECHNIQUE

Appendix 4 Ethics approval letter: Qualitative study



Government of South Australia
SA Health

Central Adelaide Local Health Network
Human Research Ethics Committee
Level 3, Roma Mitchell House
North Terrace, Adelaide SA
Australia 5000

Approval Date: 26 March 2018
HREC Reference number: HREC/18/CALHN/150
CALHN Reference number: Q20180303

Ground Floor, Basil Hetzel Institute for Translational Research
28 Woodville Road, Woodville SA
Australia 5000

Ms Zoe Kopsaftis
Respiratory Medicine Unit
The Queen Elizabeth Hospital

T : 08 7117 2229
T : 08 8222 6841

E : Health.CALHNResearchEthics@sa.gov.au

Dear Ms Kopsaftis,

Project Title: Exploring health professional and patient perspectives of best practice care for people with chronic obstructive pulmonary disease, in the hospital and outpatient setting

Thank you for submitting the above project for ethical review. This project was considered by the Chairman of the Central Adelaide Local Health Network Human Research Ethics Committee. I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research* (2007) incorporating all updates. The documents reviewed and approved include:

Document	Version	Date
Covering Letter	-	13 March 2018
LNR Ethics and Governance Application Form	-	9 March 2018
Research Protocol	2.0	13 March 2018
Participant Information Sheet and Consent Form: COPD	1.0	6 March 2018
Participant Information Sheet and Consent Form: COPD	1.0	6 March 2018
Head of Unit email for Health Professionals	1.0	6 March 2018
Recruitment email – Health Professionals	1.0	4 March 2018
Questionnaire: COPD Patients	1.0	25 February 2018
Chronic Respiratory Questionnaire (Self Reported)	-	2001
Recruitment Flyer	1.0	6 March 2018
Recruitment Telephone Script	1.0	4 March 2018
Semi-structured interview moderator guide: patients with COPD	1.0	6 March 2018
Questionnaire Health Professions	1.0	25 February 2018
One-on-one interview moderator guide: Health Professionals	1.0	22 February 2018

Sites covered by this approval:

- Royal Adelaide Hospital, SA : Ms Zoe Kopsaftis
- The Queen Elizabeth Hospital, SA : Ms Zoe Kopsaftis

HREC approval is valid from 26 March 2018 to 26 March 2023

GENERAL TERMS AND CONDITIONS OF ETHICAL APPROVAL:

1. This HREC is the South Australian 'lead HREC' for the purpose of this ethics approval. Any study sites that are not listed on this letter are not covered by this ethics approval. For any SA study-sites within the public health system that are proposed to be added, the CPI must write formally to this HREC requesting the additional study site and a separate formal letter will be issued.

2. Adequate record-keeping must be maintained in accordance with GCP, NHMRC and state and national guidelines. The duration of record retention for all clinical research data is 5 years from the date of publication.
3. Researchers are required to immediately report to this HREC anything which might warrant review of ethical approval of the study, including:
 - (a) adverse events which warrant protocol change or notification to research participants;
 - (b) changes to the protocol;
 - (c) changes to the safety or efficacy of the investigational product, device or method;
 - (d) premature termination of the study.
4. The Committee must be notified within 72 hours of any Urgent Safety Measures (USMs) occurring at this or any approved sites.
5. Confidentiality of the research participants shall be maintained at all times as required by law.
6. Approval is valid for 5 years from the date of this letter, after which an extension must be applied for.
7. Investigators are responsible for providing an annual review to the CALHN HREC Executive Officer each anniversary of the above approval date, within 10 working days, using the Annual Review Form available at: <https://www.rahresearchfund.com.au/rah-research-institute/for-researchers/human-research-ethics/>
8. The REC must be advised with a report or in writing within 30 days of completion.

Should you have any queries about the HREC's consideration of your project, please contact Ms Heather O'Dea on 08 8222 4139, or Health.CALHNResearchEthics@sa.gov.au.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a SA Health site until governance authorisation at that site has been obtained. Please contact the CALHN Research Office Health.CALHNResearchLNR@sa.gov.au

This Committee is constituted in accordance with the NHMRC's *National Statement on the Ethical Conduct of Human Research* (2007).

The HREC wishes you every success in your research.

Yours sincerely

Ian Tindall
CHAIRMAN
CALHN HUMAN RESEARCH ETHICS COMMITTEE
26 March 2018

Appendix 5 Ethics approval letter: Intervention development process



Government of South Australia
SA Health

Approval Date: 2 January 2018
HREC Reference number: HREC/17/TQEH/259
CALHN Reference number: Q20171101

Ms Zoe Kopsaftis
Clinical Practice & Respiratory Medicine Unit
The University of Adelaide

Central Adelaide Local health Network
Human Research Ethics Committee (TQEH/LMH/MH)
The Queen Elizabeth Hospital
Basil Hetzel Institute – DX465101
28 Woodville Road
Woodville South SA 5011
Telephone: 08 8222 6841
Email: Health.CALHNResearchEthics@sa.gov.au

Dear Ms Kopsaftis,

Project Title: Technological applications for improving adherence to best practice guidelines for the management of chronic obstructive pulmonary disease in the hospital setting (Part 1: Resource Development).

Thank you for submitting the above project for ethical review. This project was considered by the Chairman of the Human Research Ethics Committee (TQEH/LMH/MH). I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research* (2007) incorporating all updates. The documents reviewed and approved include:

Document	Version	Date
LNR Ethics and Governance Application Form	-	4 December 2017
Protocol	1	1 November 2017
Participant Information Sheet and Consent Form	2	11 December 2017
Cover Letter	1	1 November 2017
Flipchart	1	1 November 2017
Order Set Screenshot	-	1 November 2017

Sites covered by this approval:

- The Queen Elizabeth Hospital, SA: Ms Zoe Kopsaftis

GENERAL TERMS AND CONDITIONS OF ETHICAL APPROVAL:

1. This HREC is the South Australian 'lead HREC' for the purpose of this ethics approval. Any study sites that are not listed on this letter are not covered by this ethics approval. For any SA study-sites within the public health system that are proposed to be added, the CPI must write formally to this HREC requesting the additional study site and a separate formal letter will be issued.
2. Adequate record-keeping must be maintained in accordance with GCP, NHMRC and state and national guidelines. The duration of record retention for all clinical research data is 15 years from the date of publication.
3. Researchers are required to immediately report to this HREC anything which might warrant review of ethical approval of the study, including:
 - (a) adverse events which warrant protocol change or notification to research participants;
 - (b) changes to the protocol;
 - (c) changes to the safety or efficacy of the investigational product, device or method;
 - (d) premature termination of the study.
4. The Committee must be notified within 72 hours of any Urgent Safety Measures (USMs) occurring at this or any approved sites.
5. Confidentiality of the research participants shall be maintained at all times as required by law.
6. Approval is valid for 5 years from the date of this letter, after which an extension must be applied for.
7. Investigators are responsible for providing an annual review to the RAH REC Executive Officer each anniversary of the above approval date, within 10 working days, using the Annual Review Form available at: <https://www.rahresearchfund.com.au/rah-research-institute/for-researchers/human-research-ethics/>
8. The REC must be advised with a report or in writing within 30 days of completion.

Should you have any queries about the HREC's consideration of your project, please contact Ms Heather O'Dea on 08 8222 4139, or Health.CALHNResearchEthics@sa.gov.au.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a SA Health site until governance authorisation at that site has been obtained. Please contact the CALHN Research Office Health.CALHNResearchLNR@sa.gov.au

This Committee is constituted in accordance with the NHMRC's *National Statement on the Ethical Conduct of Human Research* (2007).

The HREC wishes you every success in your research.

Yours sincerely,

Professor Richard E Ruffin
Chairman, Human Research Ethics Committee (TQEH/LMH/MH)