Draft: Systematic review of cost-effectiveness –

Management of Chronic Obstructive Pulmonary Disease in adults

DRAFT REPORT

June 2020

This research was funded by the Health Research Board HRB-CICER-2016-1871.

About HRB-CICER

In 2016, the Department of Health requested that the Health Research Board (HRB) fund an evidence synthesis service called HRB-CICER (Collaboration in Ireland for Clinical Effectiveness Reviews) to support the activities of the Ministerial appointed National Clinical Effectiveness Committee (NCEC). Following a competitive process, the Health Information and Quality Authority (HIQA) was awarded the contract for the five-year period from 2017 to 2022. The HRB-CICER team comprises a dedicated multidisciplinary research team supported by staff from the Health Technology Assessment (HTA) team in HIQA and the HRB Centre for Primary Care Research at the Royal College of Surgeons in Ireland (RCSI), as well as national and international clinical and methodological experts.

With regard to clinical guidelines, the role of the HRB-CICER team is to independently review evidence and provide scientific support for the development, by guideline development groups, of National Clinical Guidelines for the NCEC. The HRB-CICER team undertakes systematic reviews of the clinical effectiveness and cost-effectiveness of interventions included in the guidelines as well as estimating the budget impact of implementing the guidelines. The HRB-CICER team also works closely with the guideline development groups; provides tailored training sessions; assists in the development of clinical questions and search strategies; performs systematic reviews of international clinical guidelines and supports the assessment of their suitability for adaption to Ireland; and supports the development of evidence-based recommendations informed by the evidence produced by HRB-CICER within the National Clinical Guidelines.

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List of abbreviations that appear in this report

BIA	Budget impact analysis
CAT	COPD Assessment Tool
CCQ	Clinical COPD Questionnaire
CEA	Cost-effectiveness analysis
CHEC-list	Consensus Health Economic Criteria list
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Questionnaire
CUA	Cost–utility analysis
DALY	Disability-adjusted life year
DARE	Database of Abstracts of Reviews of Effects
EAD	Early assisted discharge
EBV	Endobronchial valve
ECT	Endobronchial coil treatment
ED	Emergency department
EQ-5D	EuroQol five dimensions
FEV_1	Forced expiratory volume in one second
GDG	Guideline development group
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
HCP	Healthcare professional
HRB-CICER	Health Research Board – Collaboration in Ireland for Clinical Effectiveness Reviews
HRQoL	Health-related quality of life
HSE	Health Service Executive
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
ICU	Intensive care unit
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
kPa	Kilopascal

LABA	Long-acting beta$_2$-agonists
LABD	Long-acting bronchodilator
LAMA	Long-acting muscarinic agents
LOS	Length of hospital stay
LTOT	Long-term oxygen therapy
LVRS	Lung volume reduction surgery
MMP	Medicines Management Programme
mMRC	Modified British Medical Research Council questionnaire
NCEC	National Clinical Effectiveness Committee
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NPPV	Non-invasive positive pressure ventilation
OWSA	One-way sensitivity analysis
PaO_2	Partial pressure of oxygen
PCRS	Primary Care Reimbursement Service
PICOS	Population, intervention, comparator, outcome, study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	Pulmonary rehabilitation programme
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SABA	Short-acting beta$_2$-agonists
SD	Standard deviation
SGRQ	Saint George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
WTP	Willingness-to-pay

1. Background

The development of evidence-based clinical guidelines requires a holistic approach to evidence identification and appraisal. Accordingly, the National Clinical Effectiveness Committee (NCEC) recommends inclusion of evidence on both the clinical and cost-effectiveness of health technologies in the development of all national clinical guidelines.[1] Additionally, the evidence should be identified by a systematic search that is thorough, reproducible and transparent.

This systematic review was conducted to support the Guideline Development Group (GDG), who are preparing the clinical guideline, Management of Chronic Obstructive Pulmonary Disease (COPD) in adults, for the Irish healthcare system.

1.1 Description of the condition

COPD is a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[2] The chronic airflow limitation is caused by a combination of small airway disease (for example, obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person.

Although effective management can improve health status, COPD is a life-long condition for which there is no cure currently available. Without treatment, people with COPD will experience gradual impairment as episodes of acute exacerbations contribute to the deterioration of the person's health. Consequently, the utilisation of healthcare services will often increase due to frequent hospitalisations in the later stages of the disease.

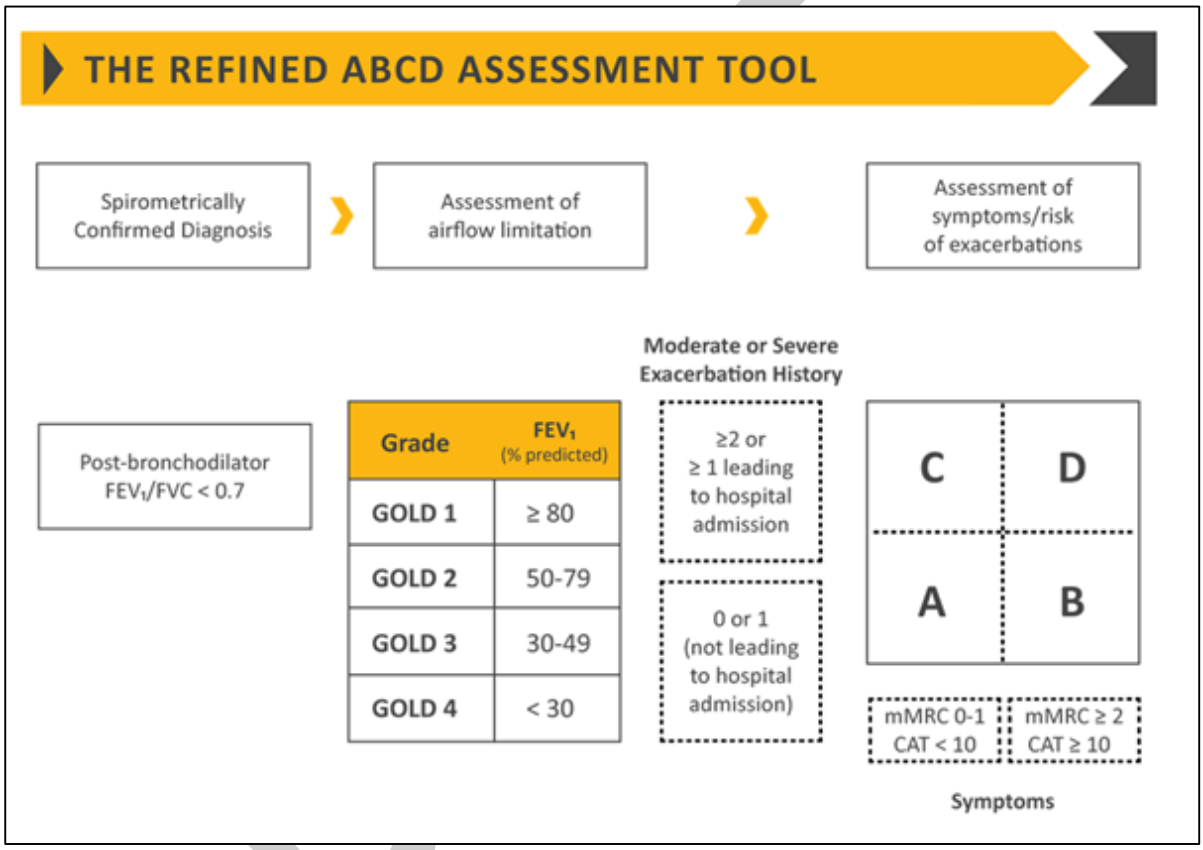
The severity of COPD is assessed using spirometry and classified according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria presented in Table 1.1. Additionally, since 2011, an ABCD classification is combined with the spirometric classification to guide treatment. The ABCD classification incorporates assessment of symptoms (using a tool such as the Modified British Medical Research Council (mMRC) Questionnaire or the COPD Assessment Tool (CAT)) and assessment of exacerbation risk (usually based on history of earlier treated events and GOLD stage) to categorise patients according to the criteria presented in Figure 1.1.

Table 1.1: GOLD criteria for classification of severity of airflow limitation in COPD[2]

GOLD stage	Level of severity	Airflow limitation
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

Key: COPD – chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; GOLD – Global Initiative for Chronic Obstructive Lung Disease.

Figure 1.1: The GOLD refined ABCD assessment tool for classification in COPD[2]



Key: CAT – COPD assessment tool; COPD – chronic obstructive pulmonary disease; FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; GOLD – Global Initiative for Chronic Obstructive Lung Disease; mMRC – modified British Medical Research Council questionnaire.

1.2 Description of the intervention

Effective management of COPD aims to relieve symptoms, prevent complications and exacerbations, improve health status and exercise tolerance, and reduce mortality. The guideline makes recommendations on a range of interventions regarding the pharmacological and non-pharmacological management of COPD; the management of exacerbations in COPD; oxygen therapy prescribing and monitoring in COPD; and pathways, bundles and checklists for managing acute exacerbations of COPD. This systematic review searched for health

economic evidence in relation to each of these approaches to the management of COPD in adults.

1.3 Purpose of this systematic review

Given a rising prevalence of chronic conditions in higher income countries, the economic and social burden associated with COPD, in terms of morbidity and healthcare utilisation, is becoming an increasingly important public health issue.[3, 4] The recommendations in this guideline aim to standardise treatment of COPD in Ireland in order to improve patient outcomes.

The purpose of this systematic review was to identify and appraise the international evidence of cost-effectiveness for interventions for the management of COPD in adults identified in the draft clinical recommendations, to determine their applicability to the Irish healthcare setting and inform the recommendations of this national clinical guideline.

2. Methodology

A systematic review was undertaken to assess the available cost-effectiveness evidence for the following 10 interventions relating to the management of COPD:

- pulmonary rehabilitation
- COPD outreach service
- oxygen therapy
- long-acting bronchodilator combination therapy
- inhaled corticosteroids
- prophylactic use of macrolide antibiotics
- lung volume reduction surgery, endobronchial valve and coil treatment
- lung transplantation
- monitoring of spirometry
- non-invasive ventilation.

In general, it is considered best practice to develop economic review questions in conjunction with clinical research questions and to conduct the literature searches in tandem. Reviewing the evidence in this manner allows for explicit consideration of the economic evidence during formulation of the clinical recommendations. For this review, preliminary clinical recommendations had already been developed (Appendix 1). These recommendations were based on two international guidelines (GOLD 2017 report on the global strategy for the diagnosis, management and prevention of COPD and the clinical guideline published by the United States Department of Veteran Affairs on the management of COPD)[2, 5] as well as the expert opinion of the multidisciplinary GDG. Given that draft clinical recommendations had already been developed, a sequential approach was adopted whereby the economic questions were formulated on the basis of the draft clinical recommendations. In this regard, the purpose of the systematic review was to identify economic evidence that would inform the finalised guideline recommendations.

The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[6] The review also follows the national guidelines for the retrieval and interpretation of economic literature.[7] The proposed methodology for the systematic review was outlined in a protocol and registered on PROSPERO.[8]

2.1 Review questions

The systematic review was developed to answer 10 review questions. Each review question was formulated in line with the PICOS (population, intervention, comparator, outcome, study design) framework presented in Tables 2.1 to 2.10.

The relevant clinical recommendation is listed above each review question to clearly demonstrate the progression from clinical recommendation to health economic review question. Three interventions (pulmonary rehabilitation programmes, long-term oxygen therapy and COPD outreach programmes) were used to inform a concurrent budget impact analysis and were prioritised. The remaining interventions were categorised under the following headings:

- pharmacological management of COPD (recommendations 1 to 10)
- non-pharmacological management of COPD (recommendations 11 to 20)
- management of acute exacerbations of COPD (recommendations 21 to 28)

Recommendations which are excluded from this review are outlined in Section 2.2, including the rationale for their exclusion.

Interventions informing the budget impact analysis

Pulmonary rehabilitation (recommendation 14)

Clinical recommendation(s):

- We recommend the provision of pulmonary rehabilitation to stable patients with exercise limitation despite pharmacological treatment.
- We recommend the provision of pulmonary rehabilitation to patients who have recently been hospitalised for an acute exacerbation of COPD.

Economic review question 1:

- In adults with stable COPD who have exercise limitation despite pharmacological treatment or who have been hospitalised with an acute exacerbation of COPD, what is the cost-effectiveness of adding pulmonary rehabilitation to usual care?

Table 2.1: PICOS for review question 1 — pulmonary rehabilitation

Population	Adults with stable COPD who have exercise limitation despite pharmacological treatment or adults with COPD that have recently been hospitalised with an acute exacerbation of COPD
Intervention	Pulmonary rehabilitation* plus usual care
Comparator	Usual care (without pulmonary rehabilitation)
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Key: COPD – chronic obstructive pulmonary disease.

*Minimum inclusion criteria for pulmonary rehabilitation programmes are defined in section 2.7.1.

COPD outreach service (recommendation 25)

Clinical recommendation(s):

- We recommend the involvement of the COPD outreach team at the earliest possible time during a COPD exacerbation when it is being treated in hospital.

Economic review question 2:

- In adults who have been hospitalised with an exacerbation of COPD, what is the cost-effectiveness of involving a COPD outreach service at the earliest possible time versus usual care?

Table 2.2: PICOS for review question 2 — COPD outreach service*

Population	Adults who have been hospitalised with an exacerbation of COPD
Intervention	COPD outreach service within 72 hours of admission**
Comparator	No outreach service
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis) and comparative resource use studies.

Key: COPD – chronic obstructive pulmonary disease.

*Minimum inclusion criteria for outreach services are defined in section 2.7.2.

**This broad inclusion criterion was applied to the intervention to enable review of all relevant literature.

Long-term oxygen therapy (recommendation 15)

Clinical recommendation(s):

- We recommend the provision of long-term oxygen therapy to patients with chronic stable hypoxemia with a PaO_2 less than 7.3 Kpa or a $Pa0_2$ between 7.3 and 8Kpa with signs of tissue hypoxia (haematocrit greater than 55%, pulmonary hypertension or cor pulmonale)
- We do not recommend the provision of oxygen for patients with moderate hypoxemia, nocturnal de-saturation, nocturnal or exercise-induced de-saturation in patients with COPD.

Economic review question 3:

- In adults diagnosed with chronic stable hypoxemia, what is the cost-effectiveness of adding long-term oxygen therapy (LTOT) to usual care?*

Table 2.3: PICOS for review question 3 — long-term oxygen therapy

Population	Adults diagnosed with chronic stable hypoxemia with a PaO_2 less than 7.3 Kpa or a $Pa0_2$ between 7.3 and 8Kpa with signs of tissue hypoxia (haematocrit greater than 55%, pulmonary hypertension or cor pulmonale)
Intervention	LTOT plus usual care
Comparator	Usual care
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Key: Kpa – kilopascal; LTOT – long-term oxygen therapy; PaO_2 – partial pressure of oxygen.

*Recommending against the provision of oxygen does not require economic consideration. The recommendation is based on evidence from the clinical literature and a reduction in inappropriate oxygen provision is likely to lead to cost savings. Therefore, the economic question does not address the second component of recommendation 15.

Pharmacological management of COPD

Long acting bronchodilator combination therapy (recommendation 2)

Clinical recommendation(s):

- We recommend offering long acting bronchodilators to patients with confirmed stable COPD who continue to have respiratory symptoms (for example, dyspnoea or cough).
- We recommend offering inhaled long-acting muscarinic agents (LAMAs) as first line maintenance therapy in patients with confirmed stable COPD who have continued respiratory symptoms (for example, dyspnoea or cough) or who have a history of exacerbations with COPD.
- In patients with confirmed stable COPD who are on inhaled LAMAs or inhaled LABAs (long-acting beta$_2$-agonists) alone and have persistent dyspnoea on monotherapy, we recommend combination therapy with both LAMAs and LABAs.

Economic review question 4:

- What is the cost-effectiveness of inhaled long acting beta$_2$-agonist (LABA) and long acting muscarinic antagonist (LAMA) combination therapy versus LABA or LAMA monotherapy in adults with stable COPD who have persistent dyspnoea?*

Table 2.4: PICOS for review question 4 — long acting bronchodilator combination therapy

Population	Adults diagnosed with stable COPD on either LABA or LAMA monotherapy that present with continued respiratory symptoms (for example persistent dyspnoea) or with a history of exacerbations**
Intervention	Inhaled LABA and LAMA combination therapy
Comparator	Inhaled LABA or LAMA monotherapy
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Key: COPD – chronic obstructive pulmonary disease; LABA – long acting beta$_2$-agonist; LAMA – long acting muscarinic antagonist.

*Offering long acting bronchodilators (LABAs or LAMAs) to COPD patients who continue to have respiratory symptoms is considered standard practice. Therefore, the economic question does not address the first two components of recommendation 2.

**Exacerbations are defined by GOLD as an acute and sustained worsening of respiratory symptoms that result in additional therapy. These events may be: mild (where the patient is treated with short acting bronchodilators only); moderate (where the patient is treated with steroids); or severe (where the patient is hospitalised).

Inhaled corticosteroids (recommendation 3)

Clinical recommendation(s):

- We recommend against offering an inhaled corticosteroid (ICS) in symptomatic patients with confirmed stable COPD as first line therapy.
- In patients with confirmed COPD who are on combination therapy with LAMAs and LABAs and have persistent dyspnoea or frequent COPD exacerbations, we suggest that the addition of an ICS may be reasonable.

Economic review question 5:

- In adults with confirmed COPD who have persistent dyspnoea or frequent exacerbations despite inhaled LABA and LAMA combination therapy, what is the cost-effectiveness of adding ICS?*

Table 2.5: PICOS for review question 5 – inhaled corticosteroids

Population	Adults diagnosed with COPD who have persistent dyspnoea or frequent exacerbations despite LABA and LAMA combination therapy
Intervention	ICS in addition to inhaled LABA and LAMA combination therapy
Comparator	Inhaled LABA and LAMA combination therapy only
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Key: COPD – chronic obstructive pulmonary disease; ICS – inhaled corticosteroid; LABA – long acting beta$_2$-agonist; LAMA – long acting muscarinic antagonist.

*Recommending against offering ICS does not require economic consideration. The recommendation is based on evidence from clinical literature and a reduction in inappropriate provision of ICS is likely to lead to cost savings. Therefore, the economic question does not address the first component of recommendation 3.

Prophylactic use of Macrolide Antibiotics (recommendation 7)

Clinical recommendation(s):

- In patients who have severe COPD with two treated exacerbations and who are non-smokers, the addition of azithromycin may be considered for one year. This needs to be done in conjunction with respiratory specialist advice with surveillance for bacterial resistance and side effects such as impaired hearing and cardiac arrhythmias.

Economic review question 6:

- In adults with severe COPD that have had one or more treated exacerbations* and who are non-smokers, what is the cost-effectiveness of prophylactic oral azithromycin in addition to usual care?

Table 2.6: PICOS for review question 6 — prophylactic use of azithromycin

Population	Adults with severe COPD that have had one or more treated exacerbations and are non-smokers (former or never smokers)**
Intervention	Addition of oral azithromycin prophylaxis to usual care for one year only
Comparator	Usual care (inhaled LABA, LAMA, combination or triple therapy)
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Key: COPD – chronic obstructive pulmonary disease; ICS – inhaled corticosteroid; LABA – long-acting beta$_2$-agonist; LAMA – long-acting muscarinic antagonist.

*A broader inclusion criterion of one or more exacerbations was considered for the economic review question to capture all available relevant literature.

**Exacerbations are defined by GOLD as an acute and sustained worsening of respiratory symptoms that result in additional therapy. These events may be: mild (where the patient is treated with SABAs only); moderate (where the patient is treated with corticosteroids); or severe (where the patient is hospitalised). In this case, severe refers to patients that fall into the severe category or Group D according to the GOLD refined ABCD assessment tool. The refined ABCD assessment tool combines information regarding severity of airflow limitation (see Table 1.2) with information regarding symptom burden and risk of exacerbation.

Non-pharmacological management of COPD

Lung volume reduction procedures (recommendation 17)

Clinical recommendation(s):

- We recommend lung volume reduction surgery for carefully selected patients with upper lobe emphysema and low post rehabilitation exercise capacity.
- In selected patients, bullectomy can also be recommended.

Economic review question 7.1:

- In adults with upper lobe emphysema and low post-rehabilitation exercise capacity, what is the cost-effectiveness of lung volume reduction procedures relative to no surgery or delayed surgery?

Table 2.7.1: PICOS for review question 7.1 — lung volume reduction procedures

Population	Adults with upper lobe emphysema and low-post rehabilitation exercise capacity
Intervention	Lung volume reduction procedures (including surgery, endobronchial coils and endobronchial valves)
Comparator	No surgery or delayed surgery
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Economic review question 7.2:

- In adults with upper lobe emphysema and low post-rehabilitation exercise capacity, what is the cost-effectiveness of lung volume reduction surgery with bullectomy relative to no surgery?

Table 2.7.2: PICOS for review question 7.2 — lung volume reduction surgery

Population	Adults with upper lobe emphysema and low-post rehabilitation exercise capacity
Intervention	Lung volume reduction surgery with bullectomy
Comparator	No surgery
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Lung transplantation (recommendation 18)

Clinical recommendation(s):

- We recommend that appropriately selected patients with very severe COPD be considered for lung transplantation surgery.

Economic review question 8:

- In adults with very severe COPD, what is the cost-effectiveness of lung transplantation surgery relative to no transplant surgery?

Table 2.8: PICOS for review question 8 — lung transplantation

Population	Adults with very severe COPD*
Intervention	Lung transplantation surgery plus usual care
Comparator	Usual care without transplant surgery
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Key: COPD – chronic obstructive pulmonary disease.

*Very severe COPD or Group D as defined according to the GOLD refined ABCD assessment tool. The refined ABCD assessment tool combines information regarding severity of airflow limitation (see Table 1.2) with information regarding symptom burden and risk of exacerbation.

Monitoring of spirometry (recommendation 19)

Clinical recommendation(s):

- In stable COPD patients, decline in FEV_1 can be tracked by spirometry performed every two years.

Economic review question 9:

- In adults with stable COPD, what is the cost-effectiveness of spirometry performed every two years relative to more frequent spirometry testing?

Table 2.9: PICOS for review question 9 – monitoring of spirometry

Population	Adults diagnosed with COPD that is stable
Intervention	Spirometry performed every two years
Comparator	Spirometry performed more frequently than every two years
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Key: COPD – chronic obstructive pulmonary disease.

Management of exacerbations in COPD

Non-invasive ventilation (recommendation 24)

Clinical recommendation(s):

- We recommend the early use of non-invasive ventilation in patients with acute exacerbations of COPD who develop acute respiratory failure associated with respiratory acidosis, that is, a $PaCO_2$ greater than 6kPa and an arterial pH less than 7.35.

Economic review question 10:

- In adults with an acute exacerbation of COPD that develop respiratory acidosis, what is the cost-effectiveness of non-invasive ventilation versus usual care?

Table 2.10: PICOS for review question 10 — non-invasive ventilation

Population	Adults with acute exacerbations of COPD that develop respiratory acidosis*
Intervention	Non-invasive ventilation plus usual care
Comparator	Usual care
Outcomes	Any relevant measures of costs and benefits
Study design	Systematic reviews of economic evaluations, full economic evaluation studies (cost-effectiveness analysis, cost–utility analysis and cost–benefit analysis), costing studies and comparative resource use studies.

Key: COPD – chronic obstructive pulmonary disease.

*Respiratory acidosis was defined as an arterial pH less than 7.35.

2.2 Excluded recommendations

This section provides the rationale for each of the clinical recommendations that are excluded from this review (See Appendix 1 for list of all clinical recommendations).

Recommendations 1 and 21, which relate to the use of short-acting bronchodilator therapy when needed as a rescue therapy for COPD and for managing COPD exacerbations, are interventions that are considered standard practice with no reasonable alternative available. As such, these recommendations have been excluded from this review.

Recommendation 4 advises that patients are provided with instructions on and demonstration of inhaler technique. As instruction and demonstration of inhaler technique would be considered best practice, it is not relevant to this review. However, it could be applicable to a budget impact analysis if the demonstration were to lead to an additional resourcing burden on the part of the physician or another clinician. This demonstration is generally provided by pharmacists when dispensing the inhaler.

Recommendations 5 and 10, relating to prescription of roflumilast and alpha one anti-trypsin augmentation therapy, are conditional upon reimbursement approval and, thus, have been excluded from this review. Reimbursement decisions are informed by an evidence review, which includes consideration of cost-effectiveness. Appraisal of dossiers submitted by manufacturers to support reimbursement decisions is undertaken by the National Centre for Pharmacoeconomics (NCPE) and, thus, is outside the scope of this review. It should be noted that the NCPE recommended against reimbursement of roflumilast following review in 2010.[9] It is also acknowledged that the UK's National Institute for Health and Care Excellence (NICE) released updated guidance on roflumilast in 2017.[10] However, as of June 2020, no updated submission has been made for reimbursement in Ireland.

Recommendation 6 advises that the addition of theophylline may be reasonable in certain selected patients. However, with consideration of the relatively low cost of theophyllines and the infrequent prescribing of theophylline due to associated side effects, the addition of theophylline is likely to be determined by clinical, as opposed to economic, circumstances. Therefore, this recommendation is excluded from the review.

Recommendations 8, 9, 27 and 28 advise against the prescription of particular therapies (such as oxygen therapy) in patient populations and, thus, are excluded from the review.

Recommendations 12 and 13 are already implemented under national immunisation guidelines. Thus, provision of the influenza and pneumococcal vaccinations to people with COPD represents established practice within the Irish healthcare system and was not considered in this review.[11, 12]

Recommendations 11 and 16 were not considered in this review because they are linked to evidence underpinning other national clinical guidelines (which were in development during

the undertaking of this review). These recommendations represent existing practice, and it is unlikely that restricted provision of nutritional support to malnourished COPD patients or restricted provision of smoking cessation advice and measures would be acceptable comparisons.

Recommendation 20 is excluded from this review because it advises referral to specialist care only and is not intervention-focused. Similarly, recommendation 29 advocates the application of an admission and discharge bundle, the constituents of which are unclear and, thus, is excluded from this review.

Recommendation 22 relates to limiting the course of systemic corticosteroids to five days. This has been shown to be non-inferior compared with 14-day treatment with respect to re-exacerbation but with significantly reduced corticosteroid exposure; this is associated with adverse effects and is a risk factor for increased mortality in COPD.[13, 14] Given that the recommendation is for a shorter rather than a longer treatment course, this recommendation is excluded from this cost-effectiveness review.

Recommendation 23 advises first line antibiotic use for patients with exacerbations of COPD associated with increased dyspnoea and increased sputum purulence or volume. Reserving broader spectrum antibiotics is a good practice point in accordance with national antimicrobial stewardship guidance.[15, 16] Therefore, this recommendation is excluded from this cost-effectiveness review.

Recommendation 26 entails the inclusion of a respiratory physiotherapist as part of the assessment or management teams for a range of interventions (pulmonary rehabilitation, COPD outreach, non-invasive ventilation and oxygen assessment). The involvement of a physiotherapist is specified as an inclusion criteria for the relevant review questions rather than as a standalone review question.

2.3 Types of studies

The review aimed to identify health economic studies including economic evaluations (cost-effectiveness analysis, cost–utility analysis, cost-minimisation analysis and cost–benefit analysis), costing studies, comparative resource-use studies and related systematic reviews.

Where sufficient full economic evaluations (cost-effectiveness analysis or cost–utility analysis) were identified, costing studies were not considered during critical appraisal, data extraction and synthesis of the literature. This reflects a pragmatic approach to support guideline development, consistent with the hierarchy of evidence, where duplication of effort is minimised.

2.4 Types of participants

The population of interest was adults (aged 18 and above) with diagnosed COPD.

2.5 Types of outcome measures

The following is a non-exhaustive list of economic outcome measures applicable to this review:

Economic evaluations

Cost–utility and or cost-effectiveness analysis:

- incremental cost-effectiveness ratio (ICER)
- cost per unit of effect (such as cost per life year gained) or effects per unit cost (for example, life years gained per euro spent)
- quality-adjusted life years (QALYs), disability-adjusted life years (DALYs), or health/life years equivalent
- incremental net monetary benefit.

Cost–benefit and or cost-minimisation analysis:

- net monetary benefit
- incremental costs.

Other economic outcome measures

Costs and resource use:

- direct (for example, cost of staffing and equipment) and indirect (for example, transport for home-based pulmonary rehabilitation programmes) costs, offsets and savings
- length of hospital stay
- inpatient and emergency department admissions
- implementation costs (for example, training and education)
- service utilisation costs.

2.6 Search methods for identification of studies

On 19 June 2018, electronic searches were conducted in Medline (via Ovid), Embase and the Cochrane Library (which includes the Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and the National Health Service Economic Evaluation Database (NHS EED)). A search string (see Appendix 2) adapted from the clinical search undertaken in the systematic review of pulmonary rehabilitation by Wuytack et al.[17] was used, coupled with a modified version of the Scottish Intercollegiate Guidelines Network (SIGN) economic studies search filters.[18]

A grey literature search was also conducted in national and international electronic sources and Google Scholar (see Appendix 3).

2.7 Minimum inclusion criteria for complex interventions

Interventions for managing COPD can vary in their content and scale across healthcare systems and may include different components of care delivered by a range of providers. Therefore, minimum inclusion criteria based on national models of care[19, 20] were applied to two of the complex interventions to reflect the draft recommendations of the GDG. The inclusion criteria outlined below applied to review questions 1 and 2.

2.7.1 Pulmonary rehabilitation (review question 1)

The inclusion criteria for pulmonary rehabilitation were as follows:

- programme duration of at least six weeks (excluding pre- and post-programme assessment)
- a structured and supervised exercise programme (entailing at least two supervised exercise sessions of one hour duration)
- patient education and behavioural programme intended to foster health enhancing behaviours
- patient assessment and outcome measures (such as exercise capacity, dyspnoea and health status)
- provision of recommendations for home-based activity
- multidisciplinary team (including a respiratory nurse and a respiratory physiotherapist).[19]

2.7.2 COPD outreach service (review question 2)

The minimum inclusion criteria for an outreach service were as follows:

- multidisciplinary team (including a respiratory nurse and respiratory physiotherapist)
- patients are discharged from hospital within 72 hours of admission with a home care package
- the patient is visited at least once by a member of the outreach team within the first three days following hospital discharge
- the patient is contacted at least twice during the next six weeks
- at each visit, a member of the outreach team performs a medical assessment, records vital signs, chest auscultation and records various questionnaires on symptom perception of breathlessness, impact of the disease and quality of life
- the patient receives education on medication and disease management as guided by the British Thoracic Society and GOLD guidelines for home management.[20]

2.8 Exclusion criteria

The following studies were excluded:

- cost analyses and comparative resource use studies where full economic evaluations were identified
- economic evaluations where a systematic review of economic evaluations was identified
- studies which were not available in English
- conference papers, letters, commentaries and abstracts where the full paper was unobtainable
- protocols where the full study was not published
- papers published before 2008 (This date filter was applied on the basis that the cost-effectiveness results beyond 10 years would be of limited usefulness due to changes in technology, patents, and the organisation and funding of healthcare systems).

2.9 Data collection and analysis

Selection of studies

Citations were screened by two reviewers to eliminate clearly irrelevant studies based on the title and abstract. The full text of the remaining citations were then independently reviewed by two reviewers as per the inclusion criteria, with any disagreements resolved through discussion.

Data extraction and management

Data extraction was performed independently by two people with any disagreements resolved through discussion.

Assessment of risk of bias in included studies

Risk of bias was assessed using the Consensus Health Economic Criteria (CHEC-list) quality appraisal tool.[21] Studies were assessed as high, moderate or low quality. Additionally, studies were evaluated for transferability and applicability to the Irish setting using the International Society for Pharmacoeconomics (ISPOR) questionnaire,[22] which examines the relevance and credibility of studies. The evaluation was performed independently by two reviewers with any disagreements resolved through discussion.

At the time of writing, no validated tool existed for appraising the quality of systematic reviews of economic evaluations. Therefore, systematic reviews of economic evaluations were evaluated using a modified checklist that was adapted from existing appraisal tools for economic evaluations and systematic reviews (including AMSTAR-2, BMJ, CHEC-list, ISPOR and SIGN). The modified checklist accounts for the transferability of results and the level of attention paid by the authors to economic concepts such as analysis perspective and

modelling approaches as well as to factors purely assessing systematic review quality. The modified checklist is presented in Appendix 4. Studies were deemed as either high, moderate or low quality.

Data synthesis

A narrative synthesis of the results was provided due to the heterogeneity of the economic studies.

In accordance with national health technology assessment (HTA) guidelines, the costs from previous economic evaluations were adjusted and are presented in 2019 euro in parentheses.[23, 24] Cost calculations were undertaken by one reviewer and checked by a second reviewer. Where the cost year was not clearly reported by the study's authors, the unit cost year was based on the average time difference between publication year and cost year reported in the other relevant studies included within each review question.

2.10 Protocol deviations

Protocol deviations are outlined in Appendix 5.

3. Overview of results

The search of electronic databases and grey literature sources identified a total of 8,661 citations. Following removal of duplicates, the title and abstract of 7,377 citations were screened independently by two reviewers. Following screening, a total of 194 full text articles were assessed for eligibility. Of these, 159 papers were excluded according to the inclusion criteria (see Appendix 6) and 35 studies were identified for inclusion in the synthesis. Of these, eight were systematic reviews.[25-32] However, these were excluded from the synthesis following further investigation (see Appendix 7 for explanation). In line with the predefined hierarchy of economic evidence,[33] four costing studies were also excluded where full economic evaluations had been identified for inclusion.[34-37] Overall, 23 studies were included in the synthesis, one of which addressed three of the review questions.[25]

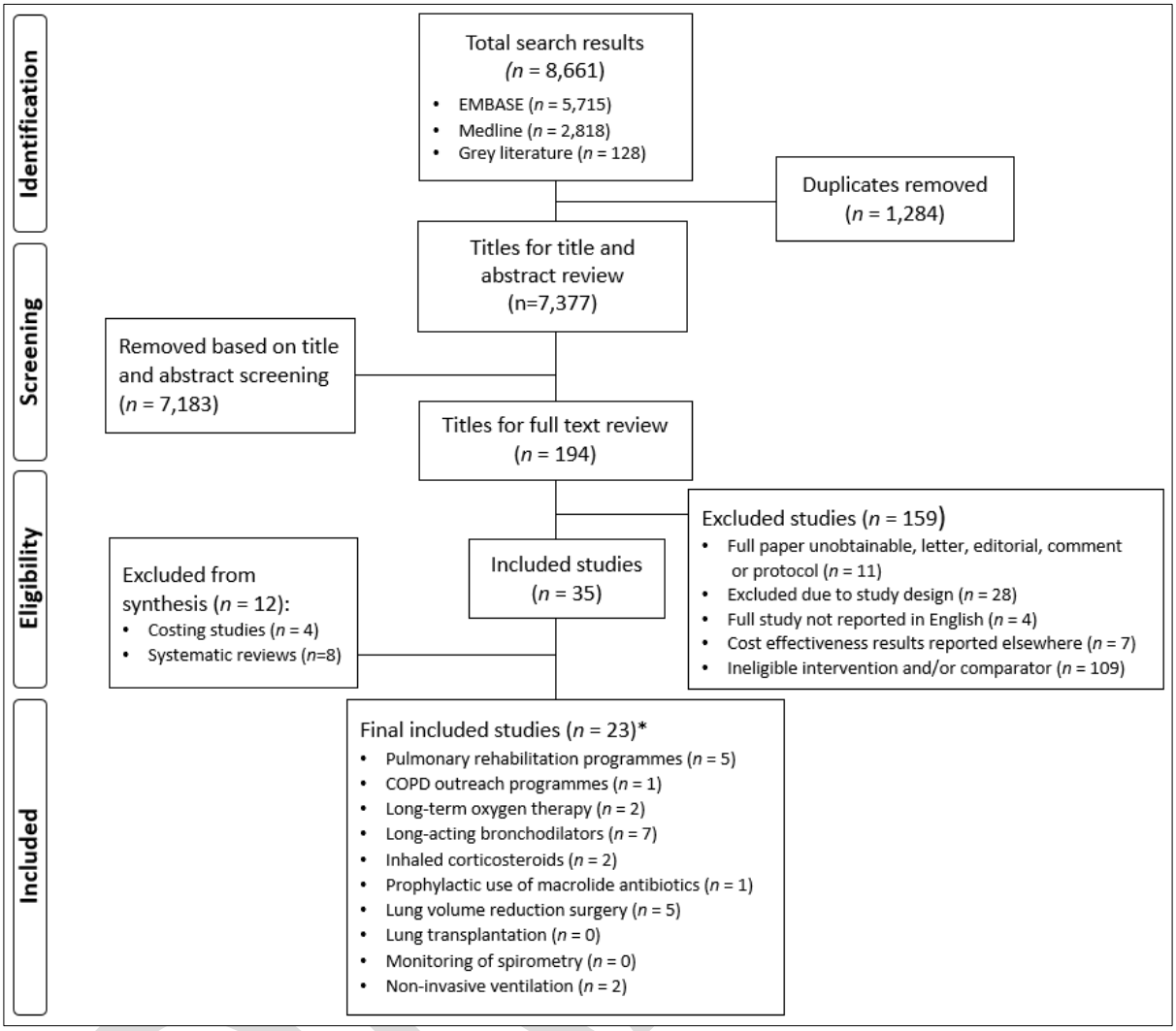
No studies were identified for research questions 8 (lung transplantation) and 9 (monitoring spirometry). A summary of the number of studies by chapter and review question are as follows:

- Five studies addressed pulmonary rehabilitation (Chapter 4)
- One study addressed COPD outreach programmes (Chapter 5)
- Two studies addressed long-term oxygen therapy (Chapter 6)
- Seven studies addressed long-acting bronchodilators (Chapter 7)
- Two studies addressed inhaled corticosteroids (Chapter 7)
- One study addressed prophylactic use of macrolide antibiotics (Chapter 8)
- Five studies addressed lung volume reduction surgery (Chapter 9)
- Two studies addressed non-invasive ventilation (Chapter 10).

The PRISMA flow chart (outlining the search, screening and selection of economic studies) is presented in Figure 3.1.

The three chapters on pulmonary rehabilitation, long-term oxygen therapy, and COPD outreach programmes were used to inform a concurrent budget impact analysis and are, therefore, discussed in greater detail than the remaining four chapters (long-acting bronchodilators and inhaled corticosteroids, prophylactic use of macrolide antibiotics, lung volume reduction surgery, endobronchial valve and endobronchial coil treatment, and non-invasive ventilation).

Figure 3.1: PRISMA flow chart of article selection for the systematic reviews



Key: PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

* The study by Chandra et al.[25] contained analyses relevant to three of the review questions.

4. Pulmonary rehabilitation

4.1 Description of the intervention

Pulmonary rehabilitation is a comprehensive intervention based on patient-tailored therapies (including exercise training, education and behaviour change) which are designed to improve the physical and psychological condition of people with COPD and to encourage long-term adherence to health-enhancing behaviours.[17] The aim of a pulmonary rehabilitation programme (PRP) is to reduce symptoms, promote autonomy, increase participation in activities of daily living and improve health-related quality of life (HRQoL) by focusing on aspects of COPD that are common among patients.[38]

This chapter focuses on the economic evidence to support the guideline's recommendations to provide pulmonary rehabilitation to stable patients with exercise limitation despite pharmacological treatment and to provide pulmonary rehabilitation to patients who have recently been hospitalised for an acute exacerbation of COPD.

4.2 Overview of included studies

Five economic evaluations were included in the economic review of PRPs: two from Canada[25, 39] and one each from France,[40] Ireland[41] and the Netherlands.[42] The included studies were published between 2010 and 2016. A summary of the characteristics of the included studies is presented in Table 4.1.

Three systematic reviews were identified during the search,[25-27] but were excluded in line with the protocol.[33] See Appendices 7 and 8 for a brief summary and quality assessment, of these systematic reviews.

Table 4.1: Characteristics of interventions and comparators of the included studies

Author, country (year)	Intervention	Comparator
Atsou, France (2016)[40]	Hypothetical PRP based on the average cost of outpatient, inpatient and home-based PRPs in France – no duration reported. Effects (HRQoL) were based on a structured literature review of PRPs. The PRP was led by a physiotherapist but required MDT involvement (including physician and nurse input). Patients received one course every two years.	Usual care
Chandra, Canada (2012)[25]	Hypothetical four week* outpatient-based PRP, consisting of 5.5 sessions per week each lasting 1.8 hours. The PRP was delivered by an MDT comprising a dietician, GP, nurse, OT, pharmacist, physiotherapist, respiratory therapist, respirologist and social worker input.	Usual care (no PRP)
Gillespie, Ireland (2013)[41]	Eight week community-based PRP delivered by a nurse and physiotherapist. The PRP consisted of a two hour group education and exercise session each week.	Usual care in general practice

Author, country (year)	Intervention	Comparator
Hoogendoorn, Netherlands (2010)[42]	Community-based PRP comprising four months of intensive standardised and supervised rehabilitation followed by 20 months of active maintenance. The PRP was delivered by a physiotherapist, and respiratory nurse, with counselling delivered to nutritionally depleted patients by a dietician. During the intensive exercise phase: ▪ Patients trained twice per week (lasting 30 minutes) in supervised setting and twice per week at home. ▪ Patients received an individualised education programme. ▪ During the active maintenance phase: ▪ Patients visited the physiotherapist once per month to monitor exercise capacity and adherence. ▪ Nutritionally depleted patients also visited the dietician four times during the maintenance phase.	Usual care comprising pharmacotherapy, smoking cessation advice from respiratory physician and nutritional advice from respiratory physician (if nutritionally depleted).
Xie, Canada (2015)[39]	Standardised eight week PRP delivered across outpatient, community and home settings. The PRP comprised three supervised sessions (lasting 1.5–2 hours) per week totalling 40 hours over eight weeks. PRP sessions included education (self-management, smoking cessation, nutritional and medication information), exercise and psychosocial support. The PRP was delivered by an MDT consisting of a physiotherapist, respiratory therapist, OT, dietician, GP and respirologist. Group sizes were four and eight for exercise and education sessions, respectively, in the outpatient and community settings. A single HCP delivered all components in the home setting.	Usual care

Key: CEA – cost-effectiveness analysis; CUA – cost-utility analysis; GP – general practitioner; HCP – healthcare professional; HRQoL – health-related quality of life; MDT – multidisciplinary team; OT – occupational therapist; PRP – pulmonary rehabilitation programme; QALY – quality-adjusted life year; SGRQ – Saint George's Respiratory Questionnaire.

*mean length of 3.9 weeks, with a range of 1.7 to 6.1 weeks, based on the average duration of PRPs in Canada. As the mean length was based on a range which exceeded six weeks, this study was deemed to fulfil the minimum criterion of a six week programme.

4.3 Summary of included studies

In accordance with the methods outlined in Chapter 2, all costs are presented as they were reported in the original studies with the adjusted 2019 Euro (€) equivalent presented in parentheses. Where the cost year was not reported by the study's authors, it was assumed that the unit costs were from two years prior to study publication (based on the average difference between publication year and cost year reported in studies included within this review). A summary of the characteristics, methods and results of the included studies is presented in Table 4.2.

Atsou et al. developed a Markov model to conduct a cost–utility analysis (CUA) of a hypothetical PRP compared with usual care (that is, no PRP) from the societal perspective in France.[40] The model adopted a lifetime time horizon with discounting applied to costs only at a rate of 3.5%. Costs were presented in 2015 euro. The authors did not define the average length or composition of the hypothetical PRP, but reported the cost as €1,583 (€1,680) per patient based on a French study[43] that estimated the average cost of PRPs across various settings (home, inpatient or outpatient). It was assumed that patients attended one course every two years over their lifetime. The study assumed a willingness-to-pay (WTP) threshold of €50,000 and reported that pulmonary rehabilitation was cost-effective at this level, with an incremental cost-effectiveness ratio (ICER) of €17,583 (€18,664) per quality-adjusted life year (QALY) gained compared with usual care. The authors adopted a conservative approach, assuming the programme would not affect the rate of exacerbations, mortality or smoking cessation. This may have been overly conservative, as studies have reported statistically significant clinical benefits in reduced hospitalisations from exacerbations.[44, 45]

The study by Atsou et al. was deemed to be of low quality and only partially applicable to the Irish context due to a number of limitations. For example, insufficient details on the outcomes and descriptions of the intervention and comparator were reported. Notably, the authors did not report the duration of the PRP evaluated (making its applicability uncertain). Additionally, a 3.5% discounting rate was applied to costs only. Irish national guidelines for economic evaluation recommend a 4% discounting rate,[23] which should be applied to both costs and benefits. The cost of the PRP was reported as an average across all settings (home, inpatient and outpatient) and, thus, the applicability of the reported ICER to any one individual setting is limited. Finally, the authors stated that the study adopted a societal perspective, but did not include any indirect costs, such as productivity losses or out-of-pocket expenses.

Chandra et al. developed a Markov model to compare a four week PRP with usual care in an outpatient setting.[25] The study comprised a CUA from the publicly funded Canadian healthcare system's perspective. The authors adopted a lifetime time horizon and applied discounting to costs and benefits at a rate of 5%. The cost of PRP was estimated, in Canadian dollars, as CAN$1,527 (€1,098) per patient, adjusted from the findings of a 2005 Canadian

national survey of 98 PRPs. The effects of the programme were derived from a systematic review of the clinical effectiveness of PRPs which identified five randomised controlled trials (RCTs) and found statistically significant reductions in hospital readmissions.[44] Chandra et al. reported small increments in terms of both life years and QALYs gained, resulting in ICERs of CAN$14,616 (€10,514) per life years gained and CAN$17,938 (€12,904) per QALY gained compared with usual care.[25] This was deemed cost-effective at a WTP threshold of CAN$50,000 per QALY gained.

Overall, the study was considered to be of moderate quality and only partially applicable due to a number of limitations. Firstly, the analyses did not account for the costs and effects on healthcare utilisation outside of hospital admissions (for example, ED attendance and GP visits). Secondly, the composition of the comparator (usual care) was unclear. Thirdly, the cost year in which costs were reported was not stated, making it unclear whether or not cost sources were inflated to a common year. Fourthly, the 5% discounting rate applied to costs and benefits is higher than the 4% discounting rate recommended by Irish guidelines.[23] The sensitivity analysis appeared to be insufficient and was not transparently reported. For example, the one-way sensitivity analysis was restricted to assessing a higher PRP cost per patient of CAN$2,863 (€2,060), the source of which was unclear, as opposed to assessing the plausible extremes of input parameters.[23, 46] Finally, the PRP evaluated had a mean duration of 3.9 weeks which is shorter than the inclusion criterion of a six weeks minimum duration employed in this review.[19] The study was included as the hypothetical PRP was based on a survey of Canadian PRPs which ranged from 1.7 to 6.1 weeks, and because the PRP was relatively intensive, with over 38 hours of treatment during the 3.9 weeks.

An Irish study by Gillespie et al.[41] conducted a CUA and cost-effectiveness analysis (CEA) alongside the PRINCE (Pulmonary Rehabilitation in Nurse-led Community Environments) RCT which compared a PRP with usual care in general practice.[47] The study adopted the perspective of the Health Service Executive (HSE) across a 22 week time horizon with costs reported in 2009 euro. Outcomes were measured using a disease-specific health-related quality of life (HRQoL) instrument, the Chronic Respiratory Questionnaire (CRQ), and a generic HRQoL instrument, the EQ-5D (Euro-QoL 5 Dimensions). They estimated an ICER of €472,000 (€514,256) per QALY gained and €850 (€926) per unit increase in total CRQ score, compared with usual care.[41] An ICER of €472,000 (€514,256) per QALY gained would not be considered cost-effective at the €45,000 per QALY gained WTP threshold generally employed in Ireland. The authors noted that the incremental gain in QALYs was not statistically significant and that, although the CRQ gain was statistically significant, the confidence intervals were wide and included differences that were pre-specified as clinically insignificant.[47]

The study was considered of moderate quality and partially applicable due to limitations. As acknowledged by the authors, the short time horizon (22 weeks) may not be long enough to capture the long-term costs and benefits of pulmonary rehabilitation.[48, 49] They also noted

that the EQ-5D may not have been sufficiently sensitive to detect meaningful improvements in HRQoL for COPD patients given the contradictory evidence of statistical significance in incremental gains in HRQoL when measuring with the CRQ and the EQ-5D (CRQ gain p<0.01; QALY gain p=0.63). The increase in healthcare utilisation following PRP participation, which contradicts the findings of other studies,[45, 50-53] was primarily driven by an increase in average COPD-related inpatient length of stay, and this may have been skewed by a small number of individuals.[47] It may also have been due to the novel approach adopted in the education component of the PRP and the once per week programme frequency of exercise sessions.[54] National and international guidelines recommend a minimum of two supervised exercise sessions per week, with accompanying unsupervised home sessions.[55, 56]

In addition to these limitations, the three-day training programme for practice nurses (who potentially had limited knowledge of COPD) may have been insufficient to provide them with the holistic skillset required to promote and motivate the behavioural changes that PRP participants must negotiate.[54] PRP education sessions typically benefit from a collaborative approach with the involvement of a multidisciplinary team encouraging participants' adherence to health-enhancing behaviours. However, education sessions in the PRINCE study were delivered solely by practice nurses. Finally, it was noted that the authors reported industry funding, but did not describe steps taken to address the potential conflict of interest.

Hoogendoorn et al.[42] also conducted a CUA and CEA alongside an RCT,[57] which compared a community-based PRP (INTERCOM – INTERdisciplinary COMmunity-based COPD management) with usual care (pharmacotherapy, smoking cessation information and nutritional advice) in the Netherlands. The authors employed both societal and third party payer perspectives across a two-year time horizon with costs reported in 2007 euro. The study included both disease-specific and generic HRQoL measures. Disease-specific outcomes were measured using the St George's Respiratory Questionnaire (SGRQ) while QALYs were elicited using the EQ-5D. From a third-party payer perspective, Hoogendoorn et al.[42] estimated ICERs of €7,086 (€7,450) per SGRQ point improvement and €25,309 (€26,610) per QALY gained. From a societal perspective, Hoogendoorn et al.[42] estimated ICERs of €9,078 (€9,545) per SGRQ point improvement and €32,425 (€34,092) per QALY gained. Results from both perspectives indicated that the PRP was cost-effective at their WTP threshold of €50,000 per QALY gained. Of note, the authors reported an increase of 0.84 (3.02 compared with 2.18) exacerbations per patient in those undergoing the programme over the two year period; however, this was not statistically significant.

This study was deemed to be of moderate quality and only partially applicable due to the short time horizon of only two years, the lack of discounting of costs and benefits, the presence of potential conflicts of interest (without an outline of actions to address these conflicts) and differences between the funding of the Irish and Dutch healthcare systems. The Dutch healthcare system is an insurance-based model, where it is compulsory for all residents

to have private health insurance, whereas in Ireland there is a mixture of private health insurance and also a government funded public healthcare system.[58, 59]

A Canadian study by Xie et al.[39] used a decision analytic model to evaluate a standardised PRP in outpatient hospital-based, community-based and home-based settings compared with usual care (no PRP). The CEA was conducted from the healthcare provider perspective over a one-year time horizon. The cost of the PRPs, reported in 2014 Canadian dollars, were estimated at CAN$1,635 (€1,138) per patient for outpatient hospital-based and community-based PRPs, and CAN$3,498 (€2,338) per patient for the home-based PRP, with all three PRPs showing a reduction in the number of hospitalisations (256 avoided per 1,000 patients). Xie et al.[39] reported that both outpatient hospital- and community-based PRPs dominated (that is, was less costly and more effective than) usual care with cost savings of CAN$1,098 (€764) per patient and reduced hospitalisations. The home-based PRP had an ICER of CAN$2,989 (€2,080) per hospitalisation avoided.

The study was deemed to be of moderate quality and only partially applicable due to several limitations. Firstly, the model was restricted to effects on rehospitalisation rates only and did not incorporate any of the additional benefits documented for PRPs, notably the increases in HRQoL and exercise capacity.[38, 60] Secondly, the CEA was conducted over a one-year time horizon due to the absence of long-term evidence of the effects of PRPs. This short time horizon prevents estimation of the long-term costs and benefits associated with PRPs.[48, 49] Thirdly, Xie et al.[39] simplified their costs to only include healthcare professional services, citing a UK study[61] which reported that equipment costs only contributed approximately 0.6% of the total cost of their PRP. As a result, the costs of outpatient hospital- and community-based programmes were identical. However, in the UK study[61][61] these two settings were demonstrated to have different costs, with the hospital-based programme costing approximately 88% as much as the community-based programme.[61] Finally, they assumed a standardised PRP across all settings, which the authors admitted is unrealistic as individualisation is a key element of PRPs, with home-based programmes generally being much shorter in length than outpatient PRPs.

Table 4.2: Summary of characteristics, methods and results of economic evaluations relevant to pulmonary rehabilitation programmes

Author, country (year)	Population and Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI)
Atsou, France (2016)[40]	**Population:** Adults with COPD (GOLD stages 2 to 4) **Intervention:** PRP (one course every 2 years across patient lifespan) **Comparator:** Usual care (no PRP)	**Analysis type:** Markov (CUA) **Perspective:** Societal **Time horizon:** Lifetime **Discount rate:** 3.5% (costs only)	**Currency & cost year:** 2015 € **Cost components:** Programme costs: physiotherapy, medical, nurse and admin costs Direct medical costs: medications, physician visits and consultations, laboratory tests and investigations, respiratory support, nursing sessions, physical therapy, hospitalisation Non-medical costs: medical transport and work stoppages **Clinical outcomes:** LYs and QALYs (EQ-5D converted from SGRQ score)	OWSA and PSA ICERs ranged from €7,210 to €52,750 in the OWSA The main driver of cost-effectiveness was the utility gained versus usual care. The probability of PR being cost-effective was 1.00 at a WTP threshold of €50,000 per QALY gained.	**Costs:** Cost of PRP: €1,583 Incremental cost: €14,102 Cost per patient over lifetime: €72,993 **Clinical outcomes:** Incremental QALYs gained: 0.802 No incremental difference in LYs gained **ICER:** €17,583 per QALY gained
Chandra, Canada (2012)[25]	**Population:** Adults with COPD GOLD stage 2 (40%)	**Analysis type:** Markov (CUA) **Perspective:**	**Currency & cost year:** Canadian $, cost year not reported **Cost components:**	OWSA and PSA The probability of being cost-effective was 0.94	**Costs:** Mean PRP cost: CAN$1,527 Incremental cost: CAN$626 **Clinical outcomes:**

Author, country (year)	Population and Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI)
	and 3 (60%) who have suffered an acute exacerbation (age: ≥ 68 years) **Intervention:** PRP in an outpatient setting **Comparator:** Usual care	Publicly funded health care system **Time horizon:** Lifetime **Discount rate:** 5%	Hospitalisation costs, maintenance costs and PRP running costs **Clinical outcomes:** LYs and QALYs (elicited from EQ-5D with Dutch and Spanish tariffs applied)	at the WTP threshold of $50,000 per QALY gained	Incremental LYs: 0.04 Incremental QALYs: 0.03 **ICERs:** CAN$14,616 per LY gained CAN$17,938 per QALY gained
Gillespie, Ireland (2013)[41]	**Population:** Adults with COPD GOLD stage 2 or 3 (*n*=350) **Intervention:** PRP in general practice (*n*=178) **Comparator:**	**Analysis type:** CEA and CUA alongside RCT **Perspective:** Healthcare provider (HSE) **Time horizon:** 22 weeks	**Currency & cost year:** 2009 € **Cost components:** Implementation costs: educator and patient recruitment; educator, administrator and patient time input; venue and equipment rental; educational materials and consumables; post;	Parametric bootstrapping The probability of being cost-effective was 0.994 at a WTP of €45,000 per CRQ point gained. The probability of being cost-	**Costs:** PRP cost: €564 per patient Incremental healthcare cost: €944 per patient (€489–1,400, *p*<0.01) **Clinical outcomes:** Incremental mean CRQ point gained: 1.11 (0.35–1.87, *p*<0.01)

Author, country (year)	Population and Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI)
	Usual care in general practice (*n*=172)	**Discount rate:** Not applied	packaging; telephone and travel expenses Healthcare utilisation: costs of GP, practice nurse, physiotherapist, dietician, public health nurse, home help and social worker consultations, outpatient services, accident and emergency visits, hospital admissions, medications and oxygen therapy. **Clinical outcomes:** CRQ Total score & QALYs (elicited from EQ-5D with UK tariffs)	effective was 0.007 at a WTP threshold of €45,000 per QALY gained.	Incremental QALYs gained: 0.002 (-0.006–0.011, *p*=0.63) **ICERs:** €850 per CRQ point gained €472,000 per QALY gained
Hoogendoorn, Netherlands (2010)[42]	**Population:** Adults with COPD GOLD stage 2 or 3 (*n*=199) **Intervention:** PRP (INTERCOM programme, *n*=102)	**Analysis type:** CEA and CUA alongside RCT **Perspective:** Societal and third party payer **Time horizon:**	**Currency & cost year:** 2007 € **Cost components:** Third party payer perspective: Healthcare professionals, prescribed medications, oxygen use, and other direct medical costs.	OWSA and PSA In the OWSA, ICERs ranged from €8,421 to €90,990 per QALY gained. The probability of being cost-effective was 0.67 at a WTP threshold	**Costs:** PRP costs: €1,520 per patient Incremental healthcare cost: €2,147 (-€1,091–5,649) **Clinical outcomes:** SGRQ score*:* 13% net improvement in INTERCOM

Author, country (year)	Population and Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI)
	Comparator: Usual care (pharmacotherapy, smoking cessation and nutritional advice, *n*=97)	2 years **Discount rate:** Not applied	Societal perspective: out-of-pocket patient costs and productivity loss. **Clinical outcomes:** SGRQ score, number of COPD exacerbations and QALYs (elicited from EQ-5D)	of €50,000 per QALY gained	group vs. 17% net deterioration in usual care Incremental exacerbations: 0.84 per patient (-0.07–1.78) Incremental QALYs gained: 0.08 (-0.01–0.18) **ICERs:** Societal perspective: €32,425 per QALY gained, €9,078 per SGRQ point gained Third party payer perspective: €25,309 per QALY gained, €7,086 per SGRQ point gained
Xie, Canada (2015)[39]	**Population:** COPD adults who were within 4 weeks of hospital discharge for an	**Model type:** CEA **Perspective:** Healthcare provider	**Currency & cost year:** 2014 Canadian $ **Cost components:** Healthcare professional services (salary plus benefits)	OWSA and PSA The probability of the hospital- and community-based PRPs being cost saving was 0.88.	**Costs:** PRP costs: Hospital-/community-based: CAN$1,635 Home-based: CAN$3,498

Author, country (year)	Population and Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI)
	acute exacerbation, with > 1 year life expectancy **Interventions:** Standardised PRP in hospital, community and home settings **Comparator:** Usual care	**Time horizon:** one year **Discount rate:** Not applied	and transportation (for home PRP only) **Clinical outcomes:** Number of hospitalisations avoided	The probability of the home-based PRP being cost saving was 0.14.	Incremental costs: Hospital-/community-based: saving of CAN$1,098 per patient Home-based: CAN$765 per patient **Clinical outcomes:** Hospitalisations avoided per 1,000 patients: 256 (same for all settings) **ICERs:** Hospital-/community-based: dominates usual care (lower costs and more effective) Home-based: CAN$2,989 per hospitalisation avoided

Key: CEA – cost-effectiveness analysis; CI – confidence interval; COPD – chronic obstructive pulmonary disease; CRQ - Chronic Respiratory Questionnaire; CUA – cost–utility analysis; EQ-5D – EuroQol 5-Dimensions instrument; GOLD - Global Initiative for Chronic Obstructive Lung Disease; HSE – Health Service Executive; ICER – incremental cost-effectiveness ratio; LY – life years; OWSA – one-way sensitivity analysis; PATH – Programs for Assessment of Technology in Health; PRP – pulmonary rehabilitation programme; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; RCT – randomised controlled trial; SGRQ – St George's Respiratory Questionnaire; WTP – willingness to pay.

4.4 Methodological quality and applicability

4.4.1 Methodological quality

The methodological quality of the included studies was assessed using the CHEC-list questionnaire,[21] the outcomes of this are presented in Table 4.3. Generally, the included studies were considered of moderate quality,[25, 39, 41, 42] with one study considered to be low quality.[40] The main reasons for downgrading quality were the lack of detail about the comparators or costs, insufficient time horizons or outcome measures, lack of generalisability, unstated conflicts of interest, and absence of ethical and or distributional discussions.

Table 4.3: CHEC-list quality assessment of pulmonary rehabilitation economic evaluations

Item	Atsou (2016)[40]	Chandra (2012)[25]	Gillespie (2013)[41]	Hoogendoorn (2010)[42]	Xie (2015)[39]
Is the study population clearly described?	+	+	●	+	+
Are competing alternatives clearly described?	+	−	+	+	+
Is a well-defined research question posed in answerable form?	+	+	+	+	+
Is the economic study design appropriate to the stated objective?	+	+	+	+	+
Is the chosen time horizon appropriate to include relevant costs and consequences?	+	+	−	−	−
Is the actual perspective chosen appropriate?	+	+	+	+	+
Are all important and relevant costs for each alternative identified?	−	+	+	+	−
Are all costs measured appropriately in physical units?	+	+	+	+	+
Are costs valued appropriately?	+	−	+	+	+
Are all important and relevant outcomes for each alternative identified?	+	+	+	+	−
Are all outcomes measured appropriately?	+	+	+	+	+
Are outcomes valued appropriately?	+	+	+	+	+
Is an incremental analysis of costs and outcomes of alternatives performed?	+	+	+	+	+
Are all future costs and outcomes discounted appropriately?	−	+	●	−	●
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	+	−	+	+	+
Do the conclusions follow from the data reported?	+	+	+	+	+
Does the study discuss the generalizability of the results to other settings and patient/ client groups?	−	+	−	+	+
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	+	+	−	−	+
Are ethical and distributional issues discussed appropriately?	−	−	−	−	−

4.4.2 Applicability

Applicability (based on relevance and credibility) was assessed using the International Society for Pharmacoeconomics (ISPOR) questionnaire,[22] the outcomes of the assessment are presented in Table 4.4.

All of the included studies were considered partially applicable. This was due to the absence of adequate internal or external validation, unstated conflicts of interest, absence of relevant outcomes, inadequate reporting and the lack of, or incorporation of a different discount rate than the 4% required by Irish national guidelines.[23] While not always the case, use of a lower discount rate for costs and benefits typically leads to lower ICERs (that is, an intervention becomes more cost-effective). However, most of the benefits attributed to the PRPs in these studies were limited to short time spans and, therefore, the ICERs would not be expected to be significantly impacted.

Table 4.4: Applicability of pulmonary rehabilitation economic evaluations

Item	Atsou (2016)[40]	Chandra (2012)[25]	Gillespie (2013)[41]	Hoogendoorn (2010)[42]	Xie (2015)[39]
Relevance					
Is the population relevant?	Yes	Yes	Yes	Yes	Yes
Are any critical interventions missing?	No	No	No	No	No
Are any relevant outcomes missing?	No	No	No	No	Yes
Is the context applicable?	Yes	Yes	Yes	No	Yes
Credibility					
Is external validation of the model sufficient?	No	No	No	No	No
Is internal verification of the model sufficient?	No	No	No	No	No
Does the model have sufficient face validity?	Yes	Yes	Yes	Yes	Yes
Is the design of the model adequate?	Yes	Yes	Yes	Yes	No
Are the data used in populating the model suitable?	Yes	Yes	Yes	Yes	Yes
Were the analyses adequate?	Yes	Yes	Yes	Yes	Yes
Was there adequate assessment of uncertainty?	Yes	Unclear	Yes	Yes	Yes
Was the reporting adequate?	No	No	Yes	Yes	Yes
Was interpretation fair and balanced?	Yes	Yes	Yes	Yes	Yes
Were there any potential conflicts of interest?	No	No	Yes	Yes	No
Were steps taken to address conflicts?	N/A	N/A	No	No	N/A

Key: N/A – not applicable

4.5 Discussion

There is evidence that PRPs lead to improvements in disease symptoms, exercise capacity, functional status, HRQoL, hospital readmissions and exacerbation rate in the short term.[38, 44, 45, 60, 62] However, further high-quality evidence is required to substantiate these benefits in the long term.

Four CUAs[25, 40-42] of PRPs were identified which reported conflicting cost-effectiveness results, with ICERs ranging between €12,904 and €514,256 per QALY gained. Although there is no explicit WTP threshold for non-pharmaceutical technologies in Ireland, a threshold of €45,000 per QALY gained is generally employed. Apart from the study by Gillespie et al.,[41] ICERs from the remaining three CUAs ranged between €12,904 and €34,092 per QALY gained, which would be considered cost-effective in Ireland. The final study,[39] which estimated disease-specific outcomes only, found that PRPs were cost-saving and more effective than usual care.

Variation in the results between the five included studies could have been due to the heterogeneity among the PRPs examined. The four key areas of variation were:

- programme duration, which ranged from four weeks[25] to four months[42]
- programme intensity, which varied in regards to session duration (from 30 minutes[42] to two hours),[41] number of sessions per week (ranging from once per week[41] to 5.5 times per week)[25] and number of healthcare professionals (HCPs) involved in the delivery (ranging from one[39] to nine HCPs).[25] One PRP[42] also offered a 20 month maintenance programme in addition to the four month PRP
- setting, which comprised outpatient hospital-,[25, 39] community-[39, 41, 42] and home-based settings,[39] or a combination of all three[40]
- cost components, with some studies incorporating many costs,[25, 40, 42] including implementation costs,[41] while another[39] estimated the cost of input from HCPs and transportation only.

A limitation of multifactorial interventions such as PRPs is the inability to determine the relative contribution of each of the different elements of the intervention to the improved outcomes reported. Furthermore, two of the studies[41, 42] were based on relatively small RCTs (*n*=350[41] and *n*=199).[42] Small sample sizes inevitably lead to imprecise effect estimates. In addition, due to the greater variability in cost data, studies powered to detect a clinical effect are often underpowered to generate stable cost estimates.

The outcome of the CUA by Gillespie et al. was an outlier when compared with the results of the other included studies. From the healthcare payer's perspective, they estimated a disease-specific ICER of €926 per CRQ point gained, whereas the generic ICER was €514,256

per QALY gained, compared with usual care. Gillespie et al. queried the sensitivity of the EQ-5D to detect meaningful improvements in HRQoL for COPD patients when compared with the statistically significant improvement in CRQ (EQ-5D gain p=0.63; CRQ gain p<0.01).[41] Other authors have also found that significant improvements in disease-specific HRQoL outcomes is not always reflected in QALY outcomes.[42, 61] However, the interpretation of the cost-effectiveness of disease-specific outcomes is complicated because the results are not directly comparable to interventions for other diseases and thus cannot be applied to commonly employed WTP thresholds.

There are a number of factors worth noting that may also have influenced the CUA outcome estimated by Gillespie et al.. Firstly, it incorporated a shorter time horizon (22 weeks) compared with the three international studies. Application of a longer time horizon may influence the cost-effectiveness results, as demonstrated by the sensitivity analysis conducted by Hoogendoorn et al., who reported an ICER of €34,092 per QALY gained for their base case of two years but €95,668 per QALY gained for a four month time horizon.[42] Secondly, Gillespie et al.'s study[41] was based on data from a single RCT[47] which, in contrast to other studies,[45, 50-53] reported an increase in healthcare utilisation following participation in a PRP. An editorial on the original RCT,[47, 54] commented that this may have been due to the novel approach adopted in the education component of the PRP and the once per week programme frequency of exercise sessions. National and international guidelines recommend a minimum of two supervised exercise sessions per week, with accompanying unsupervised home sessions.[55, 56] It was also commented that the three-day training programme for practice nurses (who potentially had limited knowledge about COPD) may have been insufficient to provide them with the holistic skillset required to promote and motivate the behavioural changes that PRP participants must negotiate.[54] PRP education sessions typically benefit from a collaborative approach with the involvement of a multidisciplinary team encouraging participants' adherence to health-enhancing behaviours. However, education sessions in the PRINCE study were delivered solely by practice nurses. Finally, the increase in healthcare utilisation was driven by an increase in average COPD-related inpatient length of stay and this may have been skewed by a small number of individuals.[47]

Three systematic reviews were identified in our search, but none met the inclusion criteria stipulated in our protocol.[33] However, one systematic review was assessed as high quality (see Appendix 8): the Irish study conducted by HIQA.[26] On the cost-effectiveness of PRPs, they concluded that all studies reported some degree of improvement in clinical outcome or utility, irrespective of disease severity. Based on the four better quality studies identified,[25, 41, 42, 63] there was limited evidence that pulmonary rehabilitation is cost-effective in patients with moderate to severe COPD. The results of the systematic review by HIQA were largely consistent with those of the current HRB-CICER systematic review.

4.6 Implications for future research

A key finding of this systematic review is the need for future research to clarify the cost-effectiveness of PRPs in Ireland. Many of the studies incorporated simplifying assumptions (for example, same costs and effects across settings or only including effects on hospitalisation) which limits the applicability of the results. Many of the studies considered short term time horizons due to the lack of available high-quality evidence of longer term effects. Drummond and Jefferson argue that this approach may introduce bias,[64] especially for treatments like PRPs where short time horizons do not capture the long-term costs and benefits, such as lifestyle modifications and better self-management, derived from the psychological and behavioural interventions associated with PRPs.[48, 49] The heterogeneity of PRPs (for example, in terms of setting, duration and components) in the included studies raises concerns on the applicability of their results to the Irish setting. Future studies should aim to design economic models which reflect the recommended PRP structure outlined in the HSE Pulmonary Rehabilitation Model of Care,[19] incorporate longer time horizons and more comprehensively capture treatment effects.

4.7 Conclusions

This systematic review identified five relevant studies of low to moderate quality. The cost-effectiveness evidence of PRPs is limited due to methodological issues, programme heterogeneity, restricted comparability of outcomes and a lack of evidence of long-term effectiveness. However, the majority of CUAs (three out of the four) identified in this systematic review indicated that pulmonary rehabilitation is cost-effective and one CEA reported the intervention to be cost-saving. The CUA which reported that pulmonary rehabilitation was not cost-effective employed a very short time horizon (22 weeks) and queried the sensitivity of the QALY as a measure of COPD HRQoL. When considering disease-specific outcome measures the clinical improvements were statistically significant in this study. Consequently, international evidence indicates that pulmonary rehabilitation is potentially cost-effective in patients with moderate to severe COPD; however, further Irish-specific cost-effectiveness analyses based on long-term effectiveness data are required to substantiate this finding.

5. COPD outreach

5.1 Description of the intervention

COPD outreach provides an early supported discharge (Hospital at Home programme) for patients who present with an uncomplicated acute exacerbation of COPD. An outreach service facilitates patients to be discharged, within 72 hours of presentation to the hospital under the care of an outreach team. During the supported discharge the patient is visited at home and their progress is monitored by the outreach team.

A home visit comprises a thorough assessment of spirometry, inhaler techniques, quality of life, offers support with new equipment (such as oxygen and nebulisers), education on COPD and medication, instructions on self-management and early intervention strategies. The core objective of a COPD outreach service is to deliver a high quality, professional, holistic patient focused service in the patient's home environment that attempts to improve the patient's quality of life, coping strategies and social functioning skills.[20]

This chapter focuses on the economic evidence to support the guideline's recommendation to include the involvement of the COPD outreach team at the earliest possible time during a COPD exacerbation when it is being treated in hospital.

5.2 Overview of included studies

Only one study met the inclusion criteria, a 2013 economic evaluation from the Netherlands. A summary of the study characteristics is presented in Table 5.1.

Table 5.1: Characteristics of interventions and comparators of included study

Author, country (year)	Intervention	Comparator
Goossens, Netherlands (2013)[65]	EAD comprising three days of inpatient care followed by four days of home care. Home care comprised one to three visits by community nurses, who observed the patient's recovery and counselled the patient and primary informal caregiver. The home visit assessed medication compliance and inhaler technique, breathing and coughing techniques, adherence to dietary advice (if applicable), support in ADL (such as washing and dressing) if necessary. If COPD symptoms worsened, patients could contact the respiratory hospital ward directly at any time.	Seven days of usual hospital in-patient care. This comprised pharmacological treatment (systemic corticosteroids, nebulised bronchodilators, subcutaneous thrombosis prophylaxis, stomach protection and, if necessary, oxygen therapy and or antibiotics) and non-pharmacological treatment (physiotherapy and, if necessary, dietary advice).

Key: ADL – activities of daily living; CCQ – Clinical COPD Questionnaire; CEA – cost-effectiveness analysis; CUA – cost–utility analysis; EAD – early assisted discharge; QALY – quality-adjusted life year; RCT – randomised controlled trial.

5.3 Summary of included studies

In accordance with the methods outlined in Chapter 2, all costs are presented as they were reported in the original studies with the adjusted 2019 Irish euro equivalent presented in parentheses.

Goossens et al.[65] conducted a cost-effectiveness analysis (CEA) and cost–utility analysis (CUA) alongside a randomised controlled trial (RCT) in the Netherlands to estimate the cost-effectiveness of an early assisted discharge (EAD) programme (that is, COPD outreach). The study adopted both societal and healthcare perspectives across a three month time horizon with costs reported in 2009 euro. Clinical outcomes were measured using both disease-specific and generic health-related quality of life (HRQoL) instruments, the Clinical COPD Questionnaire (CCQ) and the EQ-5D, respectively. Goossens et al.[65] reported that HRQoL worsened in the EAD trial arm. They found an increase of 0.041 in CCQ score (where a higher score indicates lower HRQoL) and a decrease of 0.005 in quality-adjusted life years (QALYs) relative to usual care. However, the changes in effects (measured by the CCQ and EQ-5D) were neither statistically nor clinically significant at three months follow-up. From a healthcare payer's perspective, EAD cost €168 (€174) less than usual hospital care. Goossens et al. reported incremental cost-effectiveness ratios (ICERs) of €4,000 (€4,151) saved per patient without an improvement in CCQ score and €31,111 (€32,287) saved per QALY lost.[65] In other words, EAD was less costly, but also less effective than usual care. From a societal perspective, the cost of EAD was an additional €880 (€913) per patient, meaning that usual hospital care was dominant (that is, less costly and more effective).

The study was of moderate quality and partially applicable due to several limitations. Firstly, the three month time horizon may be insufficient to capture the impact of COPD outreach on healthcare utilisation. Secondly, the initial treatment phase was limited to seven days in both arms which limits applicability to Ireland where patients remain under the care of the COPD outreach team for up to six weeks following hospital discharge.[20] Thirdly, the study was limited by the reasonably small sample size (*n*=139) which may have led to imprecise effect estimates. Furthermore, due to the greater variability in cost data, studies powered to detect a clinical effect are often underpowered to generate stable cost estimates. The study is also limited by differences between the Irish and Dutch healthcare systems. The funding of the Dutch healthcare system is based on an insurance model, where it is compulsory for all residents to have private health insurance, whereas in Ireland there is a mixture of private health insurance and government funded public healthcare.[58, 59] In addition, the healthcare utilisation, in terms of acute care hospital bed occupancy, differs considerably between the two countries. In 2016, the Netherlands had a bed occupancy of 59%, while in Ireland this rate was 94%.[66] This would be expected to impact the time allocated to inpatient care and

associated cost between the two countries. Finally, actions taken to address potential conflicts of interest from the funding supplied by two insurance companies were not outlined.

A summary of the characteristics, methods and results of the study by Goossens et al. is presented in Table 5.2.

Table 5.2: Summary of characteristics, methods and results of economic evaluations relevant to COPD outreach programmes

Author, country (year)	Population and Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI)
Goossens, Netherlands (2013)[65]	**Population:** Adults admitted to hospital for exacerbation of COPD (age: ≥ 40 years) (*n*=139) **Intervention:** 3 days of usual hospital care followed by 4 days of homecare **Comparator:** 7 days of usual hospital care	**Analysis type:** CEA and CUA alongside a RCT **Perspective:** Societal and healthcare payer **Time horizon:** 3 months **Discount rate:** N/A	**Currency & cost year:** 2009 € **Cost components:** Hospitalisations, ER visits, pulmonologist, specialist physicians, GP, respiratory nurse, homecare, dietician, physiotherapist and social worker visits, ambulance rides and medication use **Clinical outcomes:** Total CCQ score and QALYs (elicited from EQ-5D with Dutch tariff)	Scenario and PSA Scenario analysis: Health care perspective: ICERs ranged from €1,852 to €271,111 saved per QALY lost. Societal perspective: normal hospital care was dominant in all but one scenario, which reported an ICER of €77,037 saved per QALY lost. In the PSA, the base case probability of being cost saving was 0.612 from the healthcare perspective and 0.115 from the societal perspective.	**Costs:** Incremental cost: Healthcare perspective: -€168 (-€1,253–€922) Societal perspective: €880 (-€580–€2,268) **Clinical outcomes:** Incremental CCQ score: 0.041 (-0.41–0.48) Incremental QALYs: -0.005 (-0.021–0.0095) **ICERs:** Healthcare perspective: €4,000 saved per patient without an improvement in CCQ score and €31,111 saved per QALY lost. Societal perspective: Usual hospital care was dominant for both CCQ score and QALYs.

Key: CCQ – Clinical COPD Questionnaire; CEA – cost-effectiveness analysis; CI – confidence interval; COPD – chronic obstructive pulmonary disease; CUA – cost–utility analysis; EQ-5D – EuroQol 5-Dimensions instrument; ER – emergency room; GP – general practitioner; ICER – incremental cost-effectiveness ratio; N/A – not applicable; OWSA – one-way sensitivity analysis; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; RCT – randomised controlled trial.

5.4 Methodological quality and applicability

5.4.1 Methodological quality

The methodological quality of the included study was assessed using the CHEC-list questionnaire.[21] The outcome of the assessment is presented in Table 5.3.

The included study was considered to be of moderate quality,[65] mainly due to the short time horizon (three months), a lack of discussion regarding the generalisability of the results, ethical and or distributional issues and the presence of potential conflicts of interest.

Table 5.3: CHEC-list quality assessment of the COPD outreach study

Item	Goossens (2013)[65]
Is the study population clearly described?	+
Are competing alternatives clearly described?	+
Is a well-defined research question posed in answerable form?	+
Is the economic study design appropriate to the stated objective?	+
Is the chosen time horizon appropriate to include relevant costs and consequences?	–
Is the actual perspective chosen appropriate?	+
Are all important and relevant costs for each alternative identified?	+
Are all costs measured appropriately in physical units?	+
Are costs valued appropriately?	+
Are all important and relevant outcomes for each alternative identified?	+
Are all outcomes measured appropriately?	+
Are outcomes valued appropriately?	+
Is an incremental analysis of costs and outcomes of alternatives performed?	+
Are all future costs and outcomes discounted appropriately?	
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	+
Do the conclusions follow from the data reported?	+
Does the study discuss the generalizability of the results to other settings and patient/ client groups?	–
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	–
Are ethical and distributional issues discussed appropriately?	–

+ Yes Not applicable – No

5.4.2 Applicability

Applicability (based on relevance and credibility) was assessed using the International Society for Pharmacoeconomics (ISPOR) questionnaire.[22] The outcomes of the assessment are presented in Table 5.4.

The study was deemed only partially applicable [65] to the Irish healthcare system due to the short time horizon employed, unclear reporting of the model structure, a lack of internal verification or external validation and the presence of potential conflicts of interest without outlining the steps taken to address these.

Table 5.4: Applicability of the COPD outreach study

Item	Goossens (2013)[65]
Relevance	
Is the population relevant?	Yes
Are any critical interventions missing?	No
Are any relevant outcomes missing?	No
Is the context applicable?	No
Credibility	
Is external validation of the model sufficient?	No
Is internal verification of the model sufficient?	No
Does the model have sufficient face validity?	Yes
Is the design of the model adequate?	No
Are the data used in populating the model suitable?	Yes
Were the analyses adequate?	Yes
Was there adequate assessment of uncertainty?	Yes
Was the reporting adequate?	Yes
Was interpretation fair and balanced?	Yes
Were there any potential conflicts of interest?	Yes
Were steps taken to address conflicts?	No

5.5 Discussion

This systematic review identified one study which investigated the cost-effectiveness of a COPD outreach programme in the Netherlands. From a healthcare payer's perspective, COPD outreach was less costly, but also less effective than usual hospital care with an ICER of €31,227 saved per QALY lost. Interpreting this result is not straightforward. Cost-effectiveness is generally interpreted by employment of willingness to pay (WTP) thresholds. However, studies have shown that people's willingness to pay for health gains may not equate to their willingness to forego health.[67, 68] From a societal perspective, outreach was more costly and less effective than usual hospital care. The savings from reduced inpatient hospital costs were offset by the higher costs of community nursing and informal care. However, there is considerable uncertainty in the difference in costs and effects for both perspectives with neither statistically significant.

A 2012 Cochrane review by Wong et al. found that outreach nursing was associated with improvements in health-related quality of life (HRQoL) and mortality, but that there were insufficient data to determine the effect of home care interventions on lung function and exercise capacity.[4] A 2017 Cochrane review that compared early supported discharge with acute hospital inpatient care concluded that there was insufficient information to determine the effect on mortality and readmission in trials recruiting participants with COPD due to the variable effects reported.[69] Given the uncertain eveidence of the cost and effectiveness of outreach, the individual patient's preference may need to play a central role in deciding whether they receive COPD outreach or inpatient care.

Expansion of COPD outreach in Ireland is likely to release hospital capacity for inpatient care. A UK study by Beech et al. which investigated the economic consequences of early-assisted discharge (EAD) for stroke patients suggested that EAD should not be perceived as a means of generating financial savings but as a method of releasing inpatient beds to increase hospital capacity.[70] As the rate of acute care hospital bed occupancy in Ireland is high (94%),[66] this benefit of outreach programmes should be considered. However, given the equivocal nature of findings regarding the effectiveness of outreach programmes and the absence of definitive evidence of cost-effectiveness, the preferences of COPD patients should also be considered to ensure that holistic patient-centred care is delivered.

A limitation of this review is the strict eligibility criteria that were applied to studies examining the cost-effectiveness of COPD outreach programmes. This was done to ensure that only the cost-effectiveness of outreach programmes similar to those operating in Ireland were critically reviewed. Inclusion of dissimilar outreach programmes may skew the cost-effectiveness of the intervention. As discussed by Goossens et al.,[65] there appears to be broad consensus amongst older studies (pre 2008) that COPD outreach programmes are associated with cost-savings.[34, 71-73] However, these studies were not critically appraised in this systematic review.

5.6 Conclusions

There is a lack of international literature examining the cost-effectiveness of COPD outreach. Based on the findings of this systematic review, COPD outreach programmes are likely to generate cost savings from a healthcare payer's perspective. However, as the effectiveness of COPD outreach is uncertain, the cost-effectiveness is also uncertain.

6. Long-term oxygen therapy

6.1 Description of the intervention

Airflow limitation in COPD can cause low arterial blood oxygen levels, known as hypoxaemia, which can lead to short-term and long-term complications.[74] Hypoxaemia can be treated with long-term oxygen therapy (LTOT), defined as supplemental oxygen therapy that is used by patients for 15 to 24 hours each day.[75] It can help prevent long-term complications such as polycythaemia, pulmonary hypertension and neuropsychological problems while also relieving symptoms such as fatigue and breathlessness and improving mental health and sleep quality.[30, 74]

The selection criteria for receiving LTOT are:

- PaO_2 (pressure of arterial oxygen) at or below 7.3 kPa (55 mmHg) or SaO_2 (saturation of arterial oxygen) at or below 88%, with or without hypercapnia confirmed twice over a three-week period
- PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO_2 of 88% if there is evidence of pulmonary hypertension, peripheral oedema suggesting congestive cardiac failure, or polycythemia (haematocrit > 55%).[2, 75]

Typically, LTOT is delivered via an oxygen concentrator, a machine which concentrates oxygen from room air.[75, 76]

This chapter focuses on the economic evidence to support the guideline's recommendations to provide long-term oxygen therapy to patients with chronic stable hypoxemia with a PaO_2 less than 7.3 Kpa or a $Pa0_2$ between 7.3 and 8Kpa with signs of tissue hypoxia (haematocrit greater than 55%, pulmonary hypertension or cor pulmonale) and to recommend against the provision of oxygen for patients with moderate hypoxemia, nocturnal de-saturation, nocturnal or exercise-induced de-saturation in patients with COPD.

6.2 Overview of included studies

Two studies were included in the economic review of LTOT, both were modelled cost–utility analyses (CUAs). The first was a 2012 study from Canada,[25] while the second was a 2009 study from the USA.[77] A summary of the characteristics of the included studies is presented in Table 6.1.

Table 6.1: Characteristics of interventions and comparators of included studies

Author, country (year)	Intervention	Comparator
Chandra, Canada (2012)[25]	LTOT (continuous oxygen therapy for about 15 hours per day) in outpatient setting. Included home assessment, training, education and oxygen supply system.	Usual care (not defined)
Oba, USA (2009)[77]	LTOT (more than 16 hours per day) in community setting.	No oxygen therapy

Key: CUA – cost–utility analysis; LTOT – long-term oxygen therapy; QALY – quality-adjusted life years.

6.3 Summary of included studies

In accordance with the methods outlined in Chapter 2, all costs are presented as they were reported in the original studies with the adjusted 2019 Irish euro equivalent presented in parentheses. Where the cost year was not reported by the study's authors, it was assumed that the unit costs were from two years prior to study publication (based on the average difference between publication year and cost year reported in studies included within this review). A summary of the characteristics, methods and results of the included studies is presented in Table 6.2.

Chandra et al.[25] used a Markov model to compare LTOT with usual care in an outpatient setting. In their model, patients with severe hypoxaemia were assigned to GOLD stage 4. The CUA was conducted from the publicly funded Canadian healthcare system perspective, over a lifetime time horizon and applied a discount rate of 5% to costs and benefits. The average annual LTOT cost per patient was reported as CAN$2,261 (€1,627), based on data provided by the Ministry of Health and Long-Term Care. The effect of LTOT was based on a reduced mortality risk of 0.68 (95% CI: 0.46–1.0) compared with usual care, informed by a systematic review of clinical effectiveness.[74] The authors reported an incremental cost-effectiveness ratio (ICER) of CAN$38,993 (€28,051) per quality-adjusted life year (QALY) gained, compared with usual care, concluding that LTOT was cost-effective at a willingness to pay (WTP) of CAN$50,000 per QALY gained.

The study was deemed to be of moderate quality and only partially applicable due to a number of limitations. Firstly, there was a lack of clarity regarding the comparator (usual care). As the Markov model designed by Chandra et al. was used to investigate several treatment options (such as PRP and smoking cessation), it created uncertainty on what was deemed to be usual care. Secondly, the effectiveness of LTOT was defined by changes in mortality only, without consideration of changes in other health outcomes (such as rates of exacerbations of COPD and healthcare utilisation). Thirdly, utility and maintenance COPD costs were calculated based on GOLD severity stage rather than specific to COPD patients

with severe hypoxaemia, assigning all patients with severe hypoxaemia to GOLD stage 4. However, LTOT is prescribed on the basis of hypoxaemic state not on GOLD severity state and not all patients with severe hypoxaemia are classified as GOLD stage 4. Fourthly, limited detail was reported regarding the sensitivity analysis conducted, making it unclear whether this was sufficient or not. Finally, a discount rate of 5% was used, which is higher than the 4% currently required in Ireland.[23]

Oba conducted a CUA using a Markov model.[77] The author modelled the cost-effectiveness of LTOT compared with no oxygen therapy in two hypothetical cohorts of patients:

- patients with severe resting hypoxaemia who received continuous oxygen therapy (greater than 16 hours per day)
- patients with significant nocturnal desaturation (but without severe resting hypoxaemia) who received nocturnal oxygen therapy (nine hours per day).

The Markov model designed by Oba included three disease states based on forced expiratory volume (FEV_1) stages:

- stage 1 (FEV1 of >50% of predicted)
- stage 2 (FEV1 of 30–50% of predicted)
- stage 3 (FEV1 of <30% of predicted).

The US third-party payer perspective (that is, Medicare) was adopted across three- and five-year time horizons. Costs and benefits were discounted at 3%, with costs reported in 2007 US dollars. The estimated monthly cost of treatment per patient, based on 2007 Medicare reimbursement data, was $198 (€220). For the three-year time horizon, the author reported an ICER of $23,807 (€26,424) per QALY gained for continuous oxygen therapy compared with no oxygen therapy in the severe resting hypoxaemia cohort, indicating that it was cost-effective at a WTP threshold of $25,000 (€27,748) per QALY gained. The ICER decreased to $16,124 (€17,897) per QALY gained when estimated over a five-year time horizon. In contrast, the ICERs for nocturnal oxygen therapy in the nocturnal desaturation cohort were estimated at $477,929 (€530,469) and $306,356 (€340,034) per QALY gained compared with no oxygen therapy over a three- and a five-year time horizon, respectively.

The study was of moderate quality and partially applicable due to several limitations. Firstly, there was a lack of detail about the comparator (no oxygen therapy). Secondly, there was uncertainty regarding what costs were considered in the analysis due to a lack of detail provided. Thirdly, the clinical data used in the Markov model (including mortality rates, hospitalisation rates and disease progression) were derived from a literature review, with insufficient detail on quality assessment and the methodology of the primary studies (two of which were conducted in the 1980s). Fourthly, insufficient detail was provided in the

probabilistic sensitivity analysis to determine whether all parameters, in particular, the utility values, were assigned probability distributions. Fifthly, health state utility values were calculated based on FEV_1 states (GOLD stages 2 to 4 of COPD severity) rather than on hypoxaemia levels. These health state utilities may not be fully representative as LTOT is prescribed on the basis of hypoxaemic state not on GOLD severity state.[2, 75] Finally, differences between the US and Irish healthcare systems, the short time horizons employed and a discount rate of 3%, which is lower than the 4% currently required in Ireland,[23] all impacted on the applicability of the study.

Table 6.2: Summary of characteristics, methods and results of economic evaluations relevant to LTOT

Author, country (year)	Population and Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
Chandra, Canada (2012)[25]	**Population:** Adults with severe hypoxaemia (assigned to GOLD stage 4) (age: ≥ 58 years) **Intervention:** LTOT — continuous oxygen therapy for about 15 hours per day, in an outpatient setting **Comparator:** Usual care	**Analysis type:** Markov (CUA) **Perspective:** Publicly funded healthcare system **Time horizon:** Lifetime **Discount rate:** 5%	**Currency & cost year:** Canadian $, cost year not reported **Cost components:** Hospitalisation, maintenance and annual cost of LTOT (home assessment, 24 hour emergency services, maintenance and repair, training, education, oxygen supply system, disposables) **Clinical outcomes:** LYs and QALYs (elicited from EQ-5D with Dutch and Spanish tariffs)	PSA The probability of being cost-effective was 0.71 at the WTP threshold of $50,000 per QALY gained	**Costs:** Annual LTOT cost: $2,261 Incremental cost: $29,389 **Clinical outcomes:** Incremental LYs: 1.21 Incremental QALYs: 0.75 **ICERs:** $24,347 per LY gained $38,993 per QALY gained
Oba, USA (2009)[77]	**Population:** SRH cohort: Adults who have a FEV_1=0.69L and FEV_1 stage 2 (50%) or 3 (50%) (age: ≥ 63 years; 78% male)	**Analysis type:** Markov (CUA) **Perspective:**	**Currency & cost year:** 2007 US $ **Cost components:** Costs of oxygen therapy and stationary oxygen	OWSA and PSA For the five year time horizon, the OWSA resulted in ICERs ranging from $13,153	**Costs:** Monthly cost of LTOT: $198 Incremental cost: 3-year time horizon: $6,567 5-year time horizon: $9,517

Author, country (year)	Population and Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
	ND cohort: Adults who have an FEV_1=1.1L and FEV_1 stage 1 (15%), stage 2 (70%) or 3 (15%) (age: ≥ 63 years) **Intervention:** SRH cohort: LTOT — continuous oxygen therapy >16 hours per day ND cohort: LTOT — nocturnal oxygen therapy (9 hours per day) **Comparator:** No oxygen therapy	Third-party payer (Medicare) **Time horizon:** 3 and 5 years **Discount rate:** 3%	equipment with or without a portable system Concentrator running costs (including electricity) **Clinical outcomes:** QALYs (elicited from EQ-5D with US tariff)	to $24,658 per QALY gained. The 95% confidence ellipse was under the $50,000 per QALY gained WTP threshold	**Clinical outcomes:** Incremental QALY: 3-year time horizon: 0.28 5-year time horizon: 0.59 **ICERs:** SRH cohort: 3-year time horizon: $23,807 per QALY gained 5-year time horizon: $16,124 per QALY gained ND cohort: 3-year time horizon: $477,929 per QALY gained 5-year time horizon: $306,356 per QALY gained

Key: CI – confidence interval; COPD – chronic obstructive pulmonary disease; CUA – cost–utility analysis; EQ-5D – EuroQol 5-Dimensions instrument; FEV_1 – forced expiratory volume in one second; GOLD – Global Initiative for Chronic Obstructive Lung Disease; ICER – incremental cost-effectiveness ratio; LTOT – long-term oxygen therapy; LY – life year; ND – nocturnal desaturation; OWSA – one-way sensitivity analysis; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; SRH – severe resting hypoxaemia; WTP – willingness to pay.

6.4 Methodological quality and applicability

6.4.1 Methodological quality

The methodological quality of the included studies was assessed using the CHEC-list questionnaire,[21] the outcomes of this are presented in Table 6.3. The two included studies investigating LTOT were considered to be of moderate quality, mainly due to the lack of detail about the comparator and costs, insufficient and inappropriately valued outcome measures, inappropriate time horizon and perspective, insufficient testing of uncertainty and the absence of ethical and or distributional discussions.

Table 6.3: CHEC-list quality assessment of LTOT studies

Item	Chandra (2012)[25]	Oba (2009)[77]
Is the study population clearly described?	+	+
Are competing alternatives clearly described?	–	–
Is a well-defined research question posed in answerable form?	+	+
Is the economic study design appropriate to the stated objective?	+	+
Is the chosen time horizon appropriate to include relevant costs and consequences?	+	–
Is the actual perspective chosen appropriate?	+	–
Are all important and relevant costs for each alternative identified?	+	–
Are all costs measured appropriately in physical units?	+	+
Are costs valued appropriately?	–	+
Are all important and relevant outcomes for each alternative identified?	–	–
Are all outcomes measured appropriately?	+	+
Are outcomes valued appropriately?	–	–
Is an incremental analysis of costs and outcomes of alternatives performed?	+	+
Are all future costs and outcomes discounted appropriately?	+	+
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	–	–
Do the conclusions follow from the data reported?	+	+
Does the study discuss the generalizability of the results to other settings and patient/ client groups?	+	+
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	+	+
Are ethical and distributional issues discussed appropriately?	–	–

+ Yes Not applicable – No

6.4.2 Applicability

Applicability (based on relevance and credibility) was assessed using the International Society for Pharmacoeconomics (ISPOR) questionnaire.[22] The outcomes of the assessment are presented in Table 6.4. Both studies were deemed only partially applicable to the Irish healthcare service due to the absence of essential outcome measures (such as exacerbations and healthcare utilisation), lack of external validation and dissimilar healthcare context.

Table 6.4: Applicability of LTOT studies

Item	Chandra (2012)[25]	Oba (2009)[77]
Relevance		
Is the population relevant?	Yes	Yes
Are any critical interventions missing?	No	No
Are any relevant outcomes missing?	Yes	Yes
Is the context applicable?	Yes	No
Credibility		
Is external validation of the model sufficient?	No	Yes
Is internal verification of the model sufficient?	No	No
Does the model have sufficient face validity?	Yes	Yes
Is the design of the model adequate?	Yes	Yes
Are the data used in populating the model suitable?	Yes	Unclear
Were the analyses adequate?	Yes	Yes
Was there adequate assessment of uncertainty?	No	Yes
Was the reporting adequate?	No	No
Was interpretation fair and balanced?	Yes	Yes
Were there any potential conflicts of interest?	No	No
Were steps taken to address conflicts?	N/A	N/A

Key: N/A – not applicable.

6.5 Discussion

LTOT has been an important treatment option for hypoxaemic COPD patients for almost 40 years, based on two landmark trials.[78-80] The 2016 Long-term Oxygen Treatment Trial[81, 82] compared continuous oxygen therapy with no oxygen therapy in COPD patients with resting or exercise-induced moderate desaturation. The trial found no difference in terms of mortality, hospitalisation, nor sustained benefit in HRQoL.[81, 82] Accordingly, this national clinical guideline recommends provision of LTOT only to patients with chronic stable hypoxaemia with a PaO_2 less than 7.3 Kpa or a $Pa0_2$ between 7.3 and 8Kpa with signs of tissue hypoxia (haematocrit greater than 55%, pulmonary hypertension or cor pulmonale).

This systematic review identified two economic evaluations of LTOT, both of which reported that LTOT was cost-effective with ICERs of €17,897and €28,051 per QALY gained compared with no LTOT and usual care, respectively. These findings support the recommendations of this guideline to prescribe LTOT to patients with chronic stable hypoxaemia with a PaO_2 less

than 7.3 Kpa or a $Pa0_2$ between 7.3 and 8Kpa with signs of tissue hypoxia. The study by Oba[77] also supports the recommendation that oxygen should not be provided to patients with moderate hypoxemia, nocturnal de-saturation, or nocturnal or exercise-induced de-saturation. However, it should be noted that both studies were deemed to be only of moderate quality and partially applicable to the Irish context due to methodological limitations and transferability issues. Consequently, these studies should be interpreted with caution.

6.6 Conclusions

There is a lack of literature examining the cost-effectiveness of LTOT. Based on the two relevant papers identified in this systematic review, LTOT in patients with severe hypoxaemia is likely to be cost-effective. However, these studies contained methodological and transferability issues and, consequently, Irish-specific cost-effectiveness analyses would be required to validate these findings in the Irish healthcare setting.

7. Long-acting bronchodilators and inhaled corticosteroids

7.1 Description of the intervention

Pharmacological therapy for COPD can improve symptoms and exercise tolerance, reduce the frequency and severity of acute exacerbations and improve quality of life.[83-88] Bronchodilators and inhaled corticosteroids (ICS) are important therapy groups for COPD. Bronchodilators widen the airways by relaxing airway smooth muscle tone,[83, 89] while ICS reduce both pulmonary and systemic inflammation,[90, 91] leading to improved expiratory flow.

Long-acting beta$_2$-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are the inhaled bronchodilator drug classes most commonly used for maintenance treatment of COPD, which may be used as monotherapy or in combination.[83, 92, 93] There is indirect evidence that combination therapy is more effective than monotherapy at improving lung function, symptoms, health-related quality of life (HRQoL), exacerbation rates and safety outcomes.[94, 95] Fixed-dose single inhaler combinations of these agents are now available that offer greater convenience at a reduced price while remaining as effective as separate inhaler combinations.[96-98]

ICS may be combined with a LABA to more effectively improve lung function and health status, and reduce exacerbations than either mono-component alone.[83, 99, 100] The further addition of a LAMA (known as triple therapy) results in further improvement.[101-105] However, the use of ICS on their own is not recommended for treatment of patients with COPD due to increased risk of side effects, such as pneumonia.[83] This guideline recommends against offering ICS as first line therapy.

A 2018 report by the Medicines Management Programme (MMP) identified 42 licensed inhalers reimbursed for the treatment of COPD in Ireland.[106] Total PCRS expenditure in 2017 on inhalers used in obstructive airways disease was €91.9 million, of which over €73 million was in those aged over 45 years.[106] Approximately €42.3 million of this was spent on LABA/ICS combinations.[106] The recommended escalation strategy from the MMP for Inhaled Medicines for COPD[106] comprises progression from LAMA or LABA monotherapy to LAMA and LABA combination therapy to LAMA and LABA/ICS triple therapy. The ELLIPTA treatment pathway* (which is agent-specific to promote compliance, lower costs and assumes equal effectiveness) is the preferred pathway.

Consistent with the MMP approach, this guideline recommends a stepwise progression for

* The ELLIPTA pathway involves: Stage 1: LAMA (umeclidinium) or LABA (formoterol); Stage 2: LAMA/LABA (umeclidinium/vilanterol); Stage 3: ICS/LAMA/LABA (fluticasone, umeclidinium/vilanterol).

long-acting bronchodilators from monotherapy (LAMA (recommended first line therapy) or LABA only) to combination therapy (LAMA and LABA) in patients with stable COPD with continued respiratory symptoms (such as persistent dyspnoea) or a history of exacerbations. The guideline recommends that the addition of ICS may be reasonable for COPD patients already on combination therapy who have persistent dyspnoea or frequent exacerbations.
This chapter focuses on two review questions:

- What is the cost-effectiveness of inhaled LABA and LAMA combination therapy compared with LABA or LAMA monotherapy in adults with stable COPD?
- In adults with confirmed COPD who have frequent exacerbations, what is the cost-effectiveness of adding an ICS to inhaled LABA and LAMA combination therapy?

In this chapter, the use of two inhalers in combination is represented by a 'plus' between the medications (for example, LAMA + LABA) and the use of a fixed-dose single inhaler combination is represented by a 'forward slash' between the medications (for example, LAMA/LABA). A list of LAMA, LABA, ICS, LAMA/LABA, ICS/LABA and triple therapy (LAMA/LABA/ICS) inhalers licensed and reimbursed in Ireland is presented in Table 7.1.[106, 107]

Table 7.1: LAMA, LABA, ICS, LAMA/LABA, ICS/LABA and triple therapy inhalers available in Ireland as of 20 July 2018*

Drug (generic name)	Brand name(s)	Labelled strength	Cost per device (€)**	Cost per day(€)***	Year licensed+
Long-acting muscarinic antagonist (LAMAs) inhalers					
Aclidinium	Eklira Genuair®	322µg	33.22	1.11	2012
Glycopyrronium	Seebri Breezhaler®	44µg	33.29	1.11	2012
Tiotropium	Braltus®	10µg	31.24	1.04	2016
	Spiriva® Handihaler	18µg	33.40	1.11	2002
	Spiriva® Respimat	2.5µg	32.14	1.07	2007
Umeclidinium	Incruse® Ellipta	55µg	31.34	1.04	2014
Long-acting beta$_2$-agonist (LABA) inhalers					
Formoterol	Foradil® Aerolizer	12µg	22.42	0.75	1996
	Oxis® Turbohaler	6µg	16.55	1.10	2002
		12µg	20.11	0.67	2002
Indacaterol	Onbrez® Breezhaler	150µg	31.53	1.05	2009
		300µg	31.24	1.04	2009
Olodaterol	Striverdi Respimat®	2.5µg	28.20	0.94	2013
Salmeterol	Salmeterol Neolab®	25µg	26.37	0.88	2011
	Serevent® Evohaler	25µg	23.91	0.80	2006
	Serevent® Diskus	50µg	24.03	0.80	1997
Fixed-dose combination LAMA/LABA inhalers					
Aclidinium/formoterol	Brimica® Genuair	340/12µg	45.36	1.51	2014
Glycopyrronium/indacaterol	Ultibro® Breezhaler	43/85µg	47.31	1.58	2013
Tiotropium/olodaterol	Spiolto® Respimat	2.5/2.5µg	44.82	1.49	2015
Umeclidinium/vilanterol	Anoro® Ellipta	55/22µg	43.15	1.44	2014
Inhaled corticosteroids (ICS)					
Budesonide	Pulmicort® Turbohaler	400µg	12.84	0.51	2000
Fluticasone proprionate	Flixotide® Evohaler	250µg (120 dose)	27.36	0.91	1999

Drug (generic name)	Brand name(s)	Labelled strength	Cost per device (€)**	Cost per day(€)***	Year licensed[+]
	Flixotide® Diskus	500µg	29.78	0.99	1996
Fixed-dose combination ICS/LABA inhalers					
Budesonide/formoterol	Bufomix® Easyhaler[++]	160/4.5µg	31.86	1.06	2014
		320/9µg	31.86	1.06	2014
	DuoResp® Spiromax	160/4.5µg	37.58	1.25	2014
		320/9µg	36.85	1.23	2014
	Symbicort® Turbohaler[++]	200/6µg	38.62	1.29	2001
		400/12µg	36.67	1.22	2003
Fluticasone propionate/salmeterol	Aerivio® Spiromax	500/50µg	33.85	1.13	2016
	AirFluSal® Forspiro	500/50µg	41.41	1.38	2014
	Seretide® Diskus	500/50µg	38.23	1.28	1999
Fluticasone furoate/vilanterol	Relvar® Ellipta	92/22µg	32.59	1.09	2013
Fixed-dose combination ICS/LAMA/LABA inhalers					
Fluticasone furoate/ umeclidinium/vilanterol	Trelegy® Ellipta	92/55/22µg	59.35	1.98	2017

Key: ICS – inhaled corticosteroid; LABA – long-acting beta$_2$-agonist; LAMA – long-acting muscarinic antagonist

* Table adapted from the Medicines Management Programme (MMP) Inhaled Medicines for Chronic Obstructive Pulmonary Disease: Prescribing and Cost Guidance report.[106]

** Reimbursement cost as listed in the MMP report,[106] sourced from the HSE Primary Care Reimbursement Service (PCRS) website.[107] Where multiple preparations of the same device are listed, the least expensive was selected. The prices listed exclude mark-up and dispensing fees that private/Drugs Payment Scheme patients may be charged.

*** Based on recommended daily dosage.[108] The cost per day of monocomponents with variable recommended dosage is estimated as equivalent to the fixed-dose combination dosage, calculated from the MMP list price per actuation using the recommended daily dosage provided by the summary of product characteristics (SPC).[106, 109, 110]

[+]Year first licensed in Ireland or the EU according to Health Products Regulatory Authority[108] or European Medicines Agency[111] websites.

7.2 Overview of included studies

Nine economic evaluations[112-120] were included in the economic review. Seven focused solely on long-acting bronchodilators,[112, 114, 116-120] while two also investigated the addition of an ICS.[113, 115] Of the nine economic evaluations, two were from the UK,[113, 116] and one each was from Canada,[115] Italy,[118] the Netherlands,[119] Scotland,[117] Spain,[114] Taiwan[112] and the USA.[120] The studies were published between 2008 and 2018. One study was conducted alongside a randomised control trial (RCT) (*n*=449), and the remaining eight studies were modelled cost–utility analyses (CUAs). A summary of the interventions and comparators of the included studies is presented in Table 7.2.

Five systematic reviews[28, 29, 31, 32, 121] were identified during the search. However, none of these reviews met the inclusion criteria stipulated in our protocol.[33] A brief summary of these systematic reviews is presented in Appendix 7, and the results of the quality assessment of systematic reviews presented in Appendix 8.

Table 7.2: Characteristics of interventions and comparators of the included studies

Study, country (year)	Intervention (strength; dose)	Comparator(s) (strength; dose)
Chan, Taiwan (2018)[112]	LAMA/LABA: GLY/IND (strength; dose not reported)	LAMA: TIO* (strength; dose not reported)
Hertel, UK (2012)[113]	LABDs review question: LAMA + LABA: TIO + LABA (costs of SAL; effects based on SAL and FORM) (strength; dose not reported) ICS review question: LAMA + ICS/LABA: TIO + ICS/LABA (cost of FLU/SAL; effects based on BUD/FORM and FLU/SAL) (strength; dose not reported)	LABDs: ▪ LABA (costs of SAL; effects based on SAL and FORM) ▪ LAMA (TIO) (strength; dose not reported) ICS: LAMA + LABA: TIO + LABA (costs of SAL; effects based on SAL and FORM) (strength; dose not reported)
Miravitlles, Spain (2016)[114]	LAMA/LABA: UMEC/VIL (55/22µg; 1 puff once daily)	LAMA: TIO (18µg; 1 puff once daily)
Najafzadeh, Canada (2008)[115]	LABDs review question: LAMA + LABA: TIO (18µg; 1 puff once daily) + SAL (25µg; 2 puffs twice daily) ICS review question: LAMA + ICS/LABA: TIO (18µg; 1 puff once daily) + FLU/SAL (250/25µg/puff; 2 puffs twice daily)	LABDs review question: LAMA: TIO (18µg; 1 puff once daily) + placebo (twice daily) – in separate inhaler combination (considered equivalent to LAMA in this review) ICS review question: LAMA + LABA: TIO (18µg; 1 puff once daily) + SAL (25µg; 2 puffs twice daily)
Punekar, UK (2015)[116]	LAMA/LABA: UMEC/VIL (55/22µg; 1 puff once daily)	LAMA: TIO (18µg; 1 puff once daily)
Ramos, Scotland (2016)[117]	LAMA/LABA: ACL/FORM (340/12µg; 1 puff once daily)	LAMA: ACL (322µg; 2 puffs once daily)
Selya-Hammer, Italy (2016)[118]	LAMA/LABA: TIO/OLO (2.5/2.5µg; 2 puffs once daily)	LAMA: TIO (2.5µg; 2 puffs once daily)
Van Boven, Netherlands (2016)[119]	LAMA/LABA: TIO/OLO (2.5/2.5µg; 2 puffs once daily)	LAMA: TIO (2.5µg; 2 puffs once daily)
Wilson, USA (2017)[120]	LAMA/LABA: UMEC/VIL (55/22µg; 1 puff once daily)	LAMA: TIO* (18µg; 1 puff once daily)

Key: ACL – aclidinium; BUD – budesonide; FLU – fluticasone propionate; FORM – formoterol; GLY – glycopyrronium; ICS – inhaled corticosteroids; IND – indacaterol; LABA – long-acting beta2-agonist; LABD – long-acting bronchodilator; LAMA – long-acting muscarinic antagonist; OLO – olodaterol; SAL – salmeterol; TIO – tiotropium; UMEC – umeclidinium; VIL – vilanterol.

*The analysis included additional comparators, but only strategies relevant to this systematic review's inclusion criteria are presented.

7.3 Summary of included studies

In accordance with the methods outlined in Chapter 2, all costs are presented as they were reported in the original studies with the adjusted 2019 Irish euro equivalent presented in parentheses. Where the cost year was not reported by the study's authors, it was assumed that the unit costs were from two years prior to study publication (based on the average difference between publication year and cost year reported in studies included within this review).

In this section, the economic evaluations are summarised according to the intervention under evaluation (that is, long-acting bronchodilators or ICS). The economic evaluations of long-acting bronchodilators are further subdivided according to the comparison under evaluation:

- LAMA/LABA versus LAMA
- LAMA + LABA versus LAMA or LABA.

A summary of the characteristics, methods and results of the included studies is presented in Table 7.3.

7.3.1 Long-acting bronchodilators

LAMA/LABA versus LAMA

Seven studies[112, 114, 116-120] compared a LAMA/LABA fixed-dose combination inhaler with a LAMA inhaler (recommended as first-line maintenance therapy in patients with stable COPD).[83, 122] All seven studies included modelled CUAs from the perspective of the healthcare payer. The time horizons ranged between three years[114] and lifetime,[112, 116] with five studies[112, 116, 118-120] employing time horizons longer than 15 years. One study, by Van Boven et al.,[119] applied a discount rate of 4% to costs and 1.5% to benefits. All other studies applied the same rate to both costs and benefits: discount rates of either 3%[112, 114, 118, 120] or 3.5%[116, 117] were used. The price of the fixed-dose LABA/LAMA combination inhaler ranged from £33 (€42)[117] to $315 (€275)[120] per month.

The COPD population included in the models varied: one study included patients with mild to very severe COPD (GOLD stages 1 to 4),[112] four studies included patients with moderate to very severe COPD (GOLD stages 2 to 4),[114, 118-120] one study included patients with moderate to severe COPD (GOLD stages 2 to 3),[117] and the COPD severity of those included was unclear in one study.[116]

The specific LAMA and LABA agents used in the combination- and mono-therapy strategies modelled varied: tiotropium monotherapy was the most common comparator used in the cost-effectiveness analyses (CEAs) and was compared to umeclidinium/vilanterol (*n*=3

studies),[114, 116, 120] tiotropium/olodaterol (*n*=2 studies)[118, 119] and glycopyrronium/indacaterol (*n*=1 study),[112] one study compared aclidinium/formoterol with aclidinium monotherapy.[117]

All seven studies[112, 114, 116-120] estimated an improvement in FEV_1 and a reduction in the number of exacerbations for combination therapy compared with monotherapy. Clinical effectiveness input data were derived from clinical trials ranging in length from 24 weeks[116, 117, 120] to 64 weeks.[112] One study modelled a decreased exacerbation rate of 0.61 compared with 0.91 for monotherapy.[112] The majority of studies included multiple trials (two or three) to inform their treatment effect,[116-120] but two studies relied on a single trial.[112, 114] The other six studies incorporated reduced exacerbation frequency by modelling that patients spent longer in health states associated with a lower disease severity (for example, spending longer in GOLD stage 2 before progressing to GOLD stage 3).[112, 114, 116-120] All seven studies included drug (LAMA/LABA or LAMA maintenance therapy) and exacerbation costs (costs of hospital and or primary care). COPD maintenance costs (such as other medications, GP visits, spirometry, flu vaccination or oxygen therapy) were included for all studies except for one.[116]

All seven studies[112, 114, 116-120] found that LAMA/LABA combination therapy was cost-effective compared with LAMA monotherapy. Six studies[112, 114, 116-119] estimated incremental cost-effectiveness ratios (ICERs) ranging from £2,088 (€2,882)[116] to €21,475 (€26,942)[114] per quality-adjusted life year (QALY) gained. The remaining study found that LAMA/LABA dominated (that is, was less costly and more effective than) LAMA monotherapy.[120] All of these results would be considered cost-effective in Ireland when employing a willingness to pay (WTP) threshold of €45,000 per QALY gained.

LAMA + LABA versus LAMA or LABA

Two studies investigated the cost-effectiveness of using LAMA + LABA dual therapy (separate inhalers) compared with LAMA monotherapy.[113, 115] One of these studies, Hertel et al., also compared LAMA + LABA with LABA monotherapy.[113] One study was a modelled CUA,[113] the other comprised a CUA alongside an RCT.[115] Both studies were conducted from the perspective of the healthcare payer. One-year[115] and lifetime[113] time horizons were employed. Discounting was applied by Hertel et al. to costs and benefits at a rate of 3.5%.[113] The COPD population included patients with GOLD stages 2 to 3[115] and patients with GOLD stages 3 and 4.[113]

Hertel et al.[113] compared the cost-effectiveness of tiotropium and the average effect of two LABAs (formoterol and salmeterol) with both tiotropium monotherapy and LABA monotherapy (based on the average LABA effect). Najafzadeh et al. compared tiotropium + salmeterol with tiotropium (+ placebo).[115] The price of LABA + LAMA was £62 (€88)[113] and CAN$122 (€97)[115] per month. Najafzadeh et al. conducted an economic evaluation alongside

an RCT,[115] directly measuring the number of exacerbations and HRQoL using the St George's Respiratory Questionnaire (SGRQ), which was converted to QALYs using Meguro's algorithm.[123] Hertel et al.[113] estimated the number of exacerbations by employing a relative risk ratio of exacerbations for each treatment based on a mixed treatment comparison study[124] and HRQoL by multiplying the time spent in each health state by different utility and disutility weights.[125, 126] Both studies included drug, maintenance and exacerbation costs (including hospital and community care costs).[113, 115]

The results of Hertel et al.[113] indicated that LAMA + LABA was cost-effective with an ICER of £15,700 (€22,401) per QALY gained compared with LAMA, and £5,617 (€8,014) per QALY gained compared with LABA. These ICERs would be considered cost-effective at a WTP threshold of €45,000 per QALY.

Najafzadeh et al. reported that LAMA + LABA combination therapy was dominated by (that is, more costly and less effective than) LAMA monotherapy.[115] However, it was noted that the QALY difference observed between treatments was not statistically significant (0.0052; 95% confidence interval (CI): -0.0088–0.0032). Interpretation of the results of subsequent economic evaluations can be complicated, and the focus should in this instance be on the cost findings rather than on the effectiveness data. Najafzadeh et al. reported an incremental cost of CAN$123 (€97) per patient on LABA + LAMA therapy over the one-year time horizon.[115] However, this estimate was subject to critical variation depending on the assumptions used in its calculation, with sensitivity analysis reporting that LAMA + LABA combination therapy was actually less costly than LAMA monotherapy when limited to those who completed treatment, those with GOLD stage 3 COPD or when non-COPD hospitalisation costs were included.

7.3.2 Inhaled corticosteroids

The cost-effectiveness of triple therapy (LAMA + fixed-dose ICS/LABA combination) relative to dual therapy (LAMA + LABA) was investigated in two studies.[113, 115] One found that the triple therapy combination was cost-effective with an ICER of £3,455 (€4,930) per QALY gained,[113] the other presented insufficient results to calculate an ICER.[115]

Disease-specific ICERs were calculable for both studies, with the cost per exacerbation avoided for triple therapy compared with dual combination therapy calculated as CAN$3,650 (€2,889)[115] and £416 (€594),[113] respectively. The interpretation of disease-specific ICERs is complicated by the absence of an accepted WTP threshold for determining cost-effectiveness.

Table 7.3: Summary of characteristics, methods and results of economic evaluations relevant to LABDs and ICS

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
Chan, Taiwan (2018)[112]	**Population:** Simulated cohort of COPD patients (age: ≥ 40 years) **Intervention:** GLY/IND (LAMA/LABA) **Comparator:*** TIO (LAMA)	**Analysis type:** Patient-level simulation (CEA and CUA) **Perspective:** Third party payer (Taiwan NHIA) **Time horizon:** 1, 3, 5, 10 years, and lifetime **Discount rate:** 3%	**Currency & cost year:** US$, no year reported **Cost components:** COPD maintenance (medications, outpatient care, examinations, and other costs), exacerbation (outpatient clinic, hospitalisation) and drug costs (GLY/IND = $2.02 per day, equating to $61.44 per month; TIO = $1.67 per day, $50.80 per month) **Clinical outcomes:** Exacerbations, LYs, QALYs	OWSA and PSA Key drivers were: FEV_1 treatment benefit, exacerbation rate ratio, and proportion of very severe COPD patients. Probability of being cost-effective was 0.98 at a WTP threshold of $20,000.	(For lifetime time horizon) **Cost:** Incremental cost: $463 **Incremental outcomes:** Exacerbations avoided: 0.66 LYs gained: 0.12 QALYs gained: 0.08 **ICERs:** $5,899 per QALY gained
Hertel, UK (2012)[113]	**Population:** GOLD stages 3 and 4 (mean age: 64 years); ICS-tolerant and intolerant patients **Intervention:** <u>LABDs:</u> LAMA (TIO) + LABA (FORM or SAL) <u>ICS:</u> LAMA (TIO) + ICS/LABA (BUD/	**Analysis type:** Markov (CUA) **Perspective:** UK NHS **Time horizon:** Lifetime (30 years) **Discount rate:** 3.5%	**Currency & cost year:** £, no year reported **Cost components:** Maintenance, drug (LAMA = £32.33 per month; LABA = £29.67 per month; ICS/LABA = £41.49 per month) and exacerbation (community- and hospital-treated) **Clinical outcomes:** Exacerbations, LYs, QALYs	OWSA and PSA (but results were not presented for comparisons of LAMA + LABA with LAMA or LABA; or LAMA + ICS/LABA with LAMA + LABA)	**Costs:** Total cost per patient: LAMA: £21,500 LABA: £21,477 LAMA + LABA: £21,814 LAMA + ICS/LABA: £22,816 **Clinical outcomes:** Total QALYs: LAMA: 5.17 LABA: 5.13 LAMA + LABA: 5.19 LAMA + ICS/LABA: 5.48

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
	FORM or FLU/SAL) **Comparators:*** <u>LABDs:</u> LAMA (TIO); LABA (FORM or SAL) <u>ICS:</u> LAMA (TIO) + LABA (FORM or SAL)				**ICERs:**** <u>LAMA + LABA versus LAMA:</u> £15,700 per QALY gained <u>LAMA + LABA versus LABA:</u> £5,617 per QALY gained <u>LAMA + ICS/LABA versus LAMA + LABA:</u> £3,455 per QALY gained £416 per exacerbation avoided
Miravitlles, Spain (2016)[114]	**Population:** GOLD stages 2 to 4 with the presence of dyspnoea (mMRC score ≥2) and a low risk of exacerbations **Intervention:** UMEC/VI (LAMA/LABA) **Comparator:** TIO (LAMA)	**Analysis type:** Linked risk-equation disease progression model (CUA) **Perspective:** Spanish NHS **Time horizon:** 3 years **Discount rate:** 3%	**Currency & cost year:** 2015 € **Cost components:** Drug (UMEC/VI = €70.25 per month; TIO = €49.06 per month), exacerbations (moderate - oral corticosteroids and/or ABs; severe - hospitalisation) and maintenance costs **Clinical outcomes:** QALYs (elicited from EQ-5D with Spanish tariffs)	OWSA, PSA and scenario analysis ICERs ranged from €8,955 to €47,428 per QALY gained in the deterministic analyses. Key drivers: utility value, treatment efficacy, effect duration and time horizon. Probability of being cost-effective was 0.80 at a WTP threshold of €30,000.	**Costs:** Total UMEC/VI cost: €6,215 Incremental cost: €590 **Clinical outcomes:** Incremental QALYs gained: 0.027 **ICER:** €21,475 per QALY gained
Najafzadeh, Canada (2008)[115]	**Population:** GOLD stages 2 and 3 (age: > 35 years, *n*=449)	**Analysis type:** CEA and CUA alongside an RCT **Perspective:**	**Currency & cost year:** 2006 CAN $ **Cost components:** Drug (TIO = $2.25 per capsule,	Scenario and PSA Substantial variation reported in the ICERs estimated in the scenario analysis. Several	**Costs (95% CI):** TIO + placebo: $2,678 ($1,950-$3,536) TIO + SAL: $2,801 (£2,306-$3,362)

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
	Intervention: LABDs: TIO + SAL (LAMA + LABA) ICS: TIO + FLU/SAL (LAMA + ICS/LABA) **Comparator:*** LABDs: TIO (LAMA) + placebo ICS: TIO + SAL (LAMA + LABA)	Canadian healthcare payer **Time horizon:** 1 year **Discount rate:** Not applied	equating to $68.44 per month; SAL = $0.44 per puff, $53.53 per month; FLU/SAL = $1.16 per puff, $141.13 per month exacerbation related medications, nursing and respiratory care visits at home, physician and ED visits, and hospital or ICU admissions. **Clinical outcomes:** Exacerbations, QALYs (based on SGRQ scores)	scenarios resulted in TIO + SAL being dominated by TIO + placebo. Other scenarios (such as only including data from those that completed treatment) resulted in TIO + SAL dominating TIO + placebo. TIO + SAL was excluded from the PSA as it was dominated by TIO + placebo in the base case.	TIO + FLU/SAL: $4,042 (£3,228-$4,994) **Clinical outcomes (95% CI):** LABDs: Incremental QALYs lost (adjusted for baseline): 0.0052 (0.0088 lost - 0.0032 gained) ICS: Exacerbations per year: TIO + SAL: 1.69 (1.47-1.94) TIO + FLU/SAL: 1.35 (1.16-1.55) **ICER:** LABDs: TIO + SAL dominated by TIO + placebo ICS: $3,650 per exacerbation avoided
Punekar, UK (2015)[116]	**Population:** COPD patients with starting FEV_1 47.7% predicted (mean age: 63.3 years) **Intervention:** UMEC/VI	**Analysis type:** Linked risk-equation disease progression model (CEA and CUA) **Perspective:** UK NHS	**Currency & cost year:** 2011-2012 £ **Cost components:** Hospitalisation (ICU, general ward, COPD-related admission, ED visit, outpatient visit), physician (home and office visits), and drug (UMEC/VI same price as TIO =	Scenario and PSA Deterministic results ranged from UMEC/VI dominating TIO to an ICER of £17,541, per QALY gained. Reducing the time horizon improved the cost-effectiveness.	**Costs:** Incremental cost: £372 **Clinical outcomes:** Incremental QALYs gained: 0.18 **ICER:** £2,088 per QALY gained

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
	(LAMA/LABA) **Comparator:** TIO (LAMA)	**Time horizon:** 1, 5 and lifetime (40 years) **Discount rate:** 3.5%	£33.50 per 30 days) **Clinical outcomes:** Exacerbations, LYs, QALYs	Probability of being cost effective was 0.85 at a WTP threshold of £20,000. This fell to 0.73 and 0.23 at prices of £36.85 and £62.76 for UMEC/VI respectively.	
Ramos, Scotland (2016)[117]	**Population:** GOLD stages 2 and 3 (mean age: 63.5 years) that are current or ex-cigarette smokers **Intervention:** ACL/FORM (LAMA/LABA) **Comparator:** ACL (LAMA)	**Analysis type:** Markov (CUA) **Perspective:** Scottish NHS **Time horizon:** 5 years **Discount rate:** 3.5%	**Currency & cost year:** 2014 £ **Cost components:** Drug (ACL/FORM = £32.97 per month; ACL = £29.02 per month), management (GP and outpatient visits, spirometry, flu vaccination, oxygen therapy), and event costs (community- and hospital-treated exacerbations, and pneumonia) **Clinical outcomes:** QALYs (elicited from EQ-5D with UK tariffs)	OWSA, scenario and PSA ACL/FORM dominated ACL in all scenario analyses. Key drivers were: baseline FEV_1 values; exacerbation risk; and lung-function improvement from treatment. Probability of being cost effective was 0.79 at a WTP threshold of £20,000 per QALY gained.	**Costs:** Incremental cost: £41 **Clinical outcomes:** Incremental QALYs gained: 0.014 **ICER:** £2,976 per QALY gained
Selya-Hammer, Italy (2016)[118]	**Population:** GOLD stages 2 to 4 (mean age: 65 years, *n*=2,062) **Intervention:** TIO/OLO (LAMA/LABA)	**Analysis type:** Patient-level simulation (CUA) **Perspective:** Italian NHS **Time horizon:**	**Currency & cost year:** 2015 € **Cost components:** Drug costs (TIO = €31.23 per month; TIO/OLO = €43.95 per month), other medications, routine management, treatment of	OWSA† and PSA ICERs ranged from £2,905 to £9,621 per QALY gained in the OWSA. Risk of severe exacerbation was the most influential parameter. ICER increased to £18,180 when evaluated over a 10 year time	**Costs:** Incremental cost: €1,167 **Clinical outcomes:** Incremental QALYs gained: 0.16 **ICER:** €7,518 per QALY gained

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
	Comparator: TIO (LAMA)	15 years **Discount rate:** 3%	exacerbations **Clinical outcomes:** LYs, exacerbation-free months per patient per year, annual severe and non-severe exacerbations, QALYs	horizon. Probability of being cost-effective was 0.95 at a WTP threshold of €20,000 per QALY gained.	
Van Boven, Netherlands (2016)[119]	**Population:** GOLD stages 2 to 4 (mean age: 64 years, *n*=2,062) **Intervention:** TIO/OLO (LAMA/LABA) **Comparator:** TIO (LAMA)	**Analysis type:** Patient-level simulation (CUA) **Perspective:** Dutch healthcare payer's perspective **Time horizon:** 15 years **Discount rate:** Costs: 4% Benefits: 1.5%	**Currency & cost year:** 2014 € **Cost components:** Drug costs (TIO/OLO = €56.30 per pack (30 days); TIO = €41.27 per pack (30 days)), hospitalisation, and primary care visits **Clinical outcomes:** LYs, exacerbation-free months per patient per year, annual severe and non-severe exacerbations, QALYs	OWSA and PSA OWSA results ranged from TIO/OLO dominating TIO to an ICER of €13,150 per QALY gained. The time horizon was the most influential parameter on the ICER. Probability of being cost effective was 0.61 at a WTP threshold of €20,000 per QALY gained.	**Costs:** Incremental cost: €508 **Clinical outcomes:** Incremental exacerbation-free months per year: 0.04 Incremental LYs: 0.057 Incremental QALYs: 0.0726 **ICER:** €7,004 per QALY gained
Wilson, USA (2017)[120]	**Population:** GOLD stages 2 to 4 (age: ≥ 40 years) that are current or ex-cigarette smokers **Intervention:** UMEC/VI (LAMA/LABA)	**Analysis type:** Markov (CUA) **Perspective:** Third-party payer in the USA **Time horizon:** Lifetime (20 years)	**Currency & cost year:** 2015 US$ **Cost components:** Drug costs (UMEC/VI = $297.81 per month; TIO = $315.68 per month), exacerbation costs (inpatient, ED outpatient, home visits and skilled nursing facility services),	OWSA and PSA UMEC/VI was dominant compared with TIO throughout the OWSA. Probability of being cost-effective was 0.95 at a WTP threshold of $50,000 per	**Costs:** Total cost per patient: $82,344 Incremental saving: $6,478 **Clinical outcomes:** Incremental exacerbations avoided: 0.157 Incremental LYs: 0.156 Incremental QALYs: 0.109

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
	Comparator:* TIO (LAMA)	**Discount rate:** 3%	maintenance and AE costs **Clinical outcomes:** Exacerbations, LYs, QALYs	QALY gained.	**ICER:** UMEC/VI dominated TIO

Key: AB – antibiotic; ACL – aclidinium; AE – adverse event; CEA – cost-effectiveness analysis; CI – confidence interval; COPD – chronic obstructive pulmonary disease; CUA – cost–utility analysis; ED – emergency department; EQ-5D – EuroQol 5-Dimensions instrument; FEV_1 – forced expiratory volume in one second; FORM – formoterol; GLY/IND – glycopyrronium/indacaterol; GP – general practitioner; ICER – incremental cost-effectiveness ratio; ICS – inhaled corticosteroids; ICU – intensive care unit; LABA – long-acting $beta_2$ agonist; LABD – long-acting bronchodilator; LAMA – long-acting muscarinic antagonist; LY – life years; NHIA – National Health Insurance Administration; NHS – National Health Service; OWSA – one-way sensitivity analysis; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; RCT – randomised controlled trial; SAL – salmeterol; SGRQ – St George's Respiratory Questionnaire; TIO – tiotropium; TIO/OLO – tiotropium/olodaterol; UMEC/VI – umeclidinium/vilanterol; WTP – willingness to pay.

* The analysis included additional comparators, but only strategies relevant to this systematic review's inclusion criteria are presented here.

** HRB-CICER calculated the ICERs according to the base case results presented by Hertel et al.[113] and may be subject to rounding errors.

† Selya-Hammer et al.[118] reported results of the one way sensitivity analysis in pound sterling. The rest of the article was reported in 2015 euro. Results have been reported here as they were in the original article.

7.4 Methodological quality and applicability

7.4.1 Methodological quality

Of the nine economic evaluations identified, two[113, 120] were deemed to be of low quality, four[112, 115-117] of moderate quality and three[114, 118, 119] of high quality. Eight of the included studies[112-114, 116-120] were modelled CUAs. The other study was conducted alongside an RCT.[115] The methodological quality was assessed using the CHEC-list questionnaire,[21] and the outcomes of this are presented in Table 7.5.

Methodological limitations common across all of the included studies were:

- a lack of discussion regarding generalisability of the results to other settings
- a lack of discussion regarding ethical and distributional issues
- evidence of potential conflicts of interest from the receipt of funding (usually from pharmaceutical companies) which were not adequately addressed.

Other limitations included:

- two studies[114, 117] were considered to have insufficient time horizons (three and five years) and one study[120] was uncertain (as it reported a lifetime time horizon but only modelled 20 years with a starting age of 40 years)
- three studies inappropriately valued costs (such as not reporting the cost year and source of valuation for each cost parameter)[112, 113, 120]
- five studies[113, 117-120] inappropriately valued outcomes (such as failing to report the method of valuation and using utilities which were not systematically identified)
- one study[116] did not include all relevant costs (as it did not include maintenance COPD costs)
- one study[115] did not measure outcomes appropriately (as it converted utilities from the SGRQ to QALYs using a mapping algorithm[123] which had not been independently validated).

Table 7.5: CHEC-list[21] quality assessment of LABD and ICS economic evaluations

Item	Chan (2018)[112]	Hertel (2012)[113]	Miravitlles (2016)[114]	Najafzadeh (2008)[115]	Punekar (2015)[116]	Ramos (2016)[117]	Selya-Hammer (2016)[118]	Van Boven (2016)[119]	Wilson (2017)[120]
Is the study population clearly described?	+	+	+	+	+	+	+	+	+
Are competing alternatives clearly described?	+	+	+	+	+	+	+	+	+
Is a well-defined research question posed in answerable form?	+	+	+	+	+	+	+	+	+
Is the economic study design appropriate to the stated objective?	+	+	+	+	+	+	+	+	+
Is the chosen time horizon appropriate to include relevant costs and consequences?	+	+	–	●	+	–	+	+	Unclear
Is the actual perspective chosen appropriate?	+	+	+	+	+	+	+	+	+
Are all important and relevant costs for each alternative identified?	+	+	+	+	–	+	+	+	+
Are all costs measured appropriately in physical units?	+	+	+	+	+	+	+	+	+
Are costs valued appropriately?	–	–	+	+	+	+	+	+	–
Are all important and relevant outcomes for each alternative identified?	+	+	+	+	+	+	+	+	+
Are all outcomes measured appropriately?	+	+	+	–	+	+	+	+	+
Are outcomes valued appropriately?	+	–	+	+	+	–	–	–	–
Is an incremental analysis of costs and outcomes of alternatives performed?	+	+	+	+	+	+	+	+	+
Are all future costs and outcomes discounted appropriately?	+	+	+	●	+	+	+	+	+
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	+	+	+	+	+	+	+	+	+
Do the conclusions follow from the data reported?	+	+	+	+	+	+	+	+	+
Does the study discuss the generalizability of the results to other settings and patient/ client groups?	–	–	–	–	–	–	–	–	–
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	–*	–	–	+*	–	–	–	–	–
Are ethical and distributional issues discussed appropriately?	–	–	–	–	–	–	–	–	–

+ Yes ● Not applicable – No

*No competing interests declared, but funding was disclosed from entities that may potentially represent a conflict of interest.

7.4.2 Applicability

Applicability (based on relevance and credibility) was assessed using the International Society for Pharmacoeconomics (ISPOR) questionnaire.[22] The outcomes of this assessment are presented in Table 7.6.

Eight studies were partially applicable.[112-119] One study was deemed not applicable due to significant issues in relation to medication price differentials (compared with the Irish healthcare system), model validation, data used to calculate exacerbation rates and utility, inadequate reporting, the presence of industry funding that was not appropriately addressed, and a lack of credibility due to assumptions underpinning the model.[120]

Downgrading of applicability was due to the following limitations:

- five studies did not include external validation[113-117]
- six studies did not include internal verification[112, 113, 115-117, 119]
- the model of one study was populated with unsuitable data (due to concerns regarding the methods for valuing the outcome and the effects of treatment switching which were not accounted for in the incremental analysis)[115]
- two studies did not adequately assess uncertainty for the comparisons relevant to this systematic review (as the primary focus of their studies were other comparisons)[113, 115]
- the reporting of three studies was inadequate (for example, reporting insufficient information in relation to cost sources or sensitivity analysis).[112, 115, 119]

Additionally, all of the studies were subject to the following limitations:

- using a different discount rate for costs and benefits to that required by Irish national guidelines (4%)
- not incorporating the impact of treatment compliance on costs or outcomes
- not incorporating treatment switching appropriately (one study[113] modelled treatment switching from first- to second-line regimens after one year, but this switch was not informed by disease progression, treatment response or exacerbation rates)
- potential conflicts of interest (usually funding from pharmaceutical companies) that were not appropriately addressed.

Table 7.6: Applicability of LABDs and ICS economic evaluations

Item	Chan (2018)[112]	Hertel (2012)[113]	Miravitlles (2016)[114]	Najafzadeh (2008)[115]	Punekar (2015)[116]	Ramos (2016)[117]	Selya-Hammer (2016)[118]	Van Boven (2016)[119]	Wilson (2017)[120]
Relevance									
Is the population relevant?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are any critical interventions missing?	No	No	No	No	No	No	No	No	No
Are any relevant outcomes missing?	No	No	No	No	No	No	No	No	No
Is the context applicable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Credibility									
Is external validation of the model sufficient?	Yes	No	No	No	No*	No	Yes	Yes	No
Is internal verification of the model sufficient?	No	No	Yes	No	No*	No	Yes	No	No
Does the model have sufficient face validity?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the design of the model adequate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are the data used in populating the model suitable?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Were the analyses adequate?	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Was there adequate assessment of uncertainty?	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Was the reporting adequate?	No	Yes	Yes	No	Yes	Yes	Yes	No	No
Was interpretation fair and balanced?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were there any potential conflicts of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were steps taken to address conflicts?	No	No	No	No	No	No	No	No	No

*Conduct of validation was stated, but insufficient details were reported.

7.5 Discussion

Nine economic evaluations were included in the systematic review.[112-120] Of these, seven were of moderate to high quality, all of which were partially applicable to the Irish healthcare setting.[112, 114-119] The six modelled studies reported adjusted ICERs for combination therapy ranging from €2,882 to €26,942 per QALY gained compared with monotherapy.[112, 114, 116-119] These results would be considered cost-effective at a WTP threshold of €45,000 per QALY gained. One study, conducted alongside an RCT, indicated that combination therapy was more costly and less effective than monotherapy.[115] However, this was an older study (from 2008), included the more expensive LAMA + LABA combination in two separate inhalers, was conducted over a short (one year) time horizon, the difference in effectiveness was small and not statistically significant. Consequently, the majority of evidence suggests that combination therapy is cost-effective compared with monotherapy. Notably, the comparison with LABA monotherapy was assessed in only one low-quality study.[113]

Two of the included studies also investigated the cost-effectiveness of triple therapy compared with dual therapy, although this was not the primary analysis of either study.[113, 115] One of the studies [113] presented sufficient results to calculate an ICER for QALYs gained, indicating that triple therapy would be cost-effective at a WTP threshold of €45,000 with an adjusted ICER of €4,930 per QALY gained compared with dual therapy. However, this study was deemed to be of low quality, meaning there was insufficient evidence to make an assessment on the cost-effectiveness of triple therapy compared with dual therapy.

A 2019 guideline update was published by NICE following the completion of this systematic review.[127] The evidence update contained a de novo CUA that compared the cost-effectiveness of alternative escalation strategies:

- starting treatment with LABA and stepping up to LABA/ICS
- starting treatment with LABA and stepping up to LAMA/LABA
- starting treatment with LAMA and stepping up to LABA/ICS
- starting treatment with LAMA and stepping up to LAMA/LABA
- starting treatment with LABA/ICS (without first prescribing monotherapy)
- starting treatment with LAMA/LABA (without first prescribing monotherapy).[128, 129]

The CUA found that initiating treatment with a LAMA/LABA combination therapy was the most cost-effective strategy, with an estimated ICER of £3,653 (€4,356) per QALY gained compared with transitioning from LAMA to LAMA/LABA combination therapy. The CUA would not meet the inclusion criteria of the current systematic review as it did not directly compare the cost-effectiveness of progressing from monotherapy to combination therapy against monotherapy only. However, the cost-effectiveness of initiating treatment with combination therapy may be relevant in the future.

The NICE guideline update also contained a de novo CUA comparing triple therapy (LAMA/ LABA/ICS) with:

- LAMA/LABA
- LABA/ICS.[130]

The CUA comprised a Markov model which simulated the natural progression of COPD in patients, initially distributed across GOLD stages 1-4 (mild: 19.3%, moderate: 55.6%, severe: 23.6% and very severe: 1.5%), that continue to suffer exacerbations or breathless on dual therapy.[128, 130] In each three-month model cycle, patients could experience a hospitalised exacerbation, a non-hospitalised exacerbation, or an adverse event. Compared with LABA/LAMA, an ICER of £5,182 (€6,028) per QALY gained was estimated for triple therapy. The results were generally robust to sensitivity analysis, however, the probability of being cost-effective decreased from 89.6% to 38.6% when triple therapy was delivered in two separate inhalers.

The outcomes of NICE's CUAs are broadly consistent with the findings of this systematic review. However, it should be noted that there is a smaller price difference between LAMA/LABA and LAMA in the UK than in Ireland. For example, in the ELLIPTA pathway changing from umeclidinium to umeclidinium/vilanterol results in a 38% cost increase in Ireland compared to a 18% cost increase in the UK. As such the findings of these models may not be directly applicable in the Irish context.

7.6 Implications for future research

Based on the limitations of the studies included in this systematic review, future economic evaluations would benefit from including treatment switching and adherence. Given that management of COPD involves stepwise escalation strategies according to disease progression, future models would benefit from estimating the impact of switching and adherence on costs and clinical outcomes. As the CUA by NICE found that initiating treatment with LAMA/LABA combination therapy was more cost-effective than stepwise progression from monotherapy,[128] it may be worthwhile investigating this finding in the Irish context particularly given the pricing differentials between the UK and Ireland. An Irish-specific CUA (ideally modelling the impact of switching, adherence, adverse events and mortality) would be required.

7.7 Conclusions

This systematic review identified nine relevant studies of varying quality. The majority of studies (seven of the eight partially applicable studies) found that treatment with combination therapy was cost-effective when compared with monotherapy. Accordingly, the evidence suggests that stepwise progression from first-line LAMA or LABA monotherapy to

LAMA and LABA combination therapy, when symptoms are no longer controlled by monotherapy, is likely to be cost-effective. Although a number of transferability issues were identified, this finding is likely to be applicable to the Irish healthcare setting.

Insufficient evidence was identified to make a conclusion on the cost-effectiveness of triple therapy compared with dual combination therapy. Further research is required to determine the cost-effectiveness of both stepwise progression to triple therapy and whether treatment should initially be with combination therapy.

8. Prophylactic use of macrolide antibiotics

8.1 Description of the intervention

Macrolides are broad spectrum antibiotics which are used to treat or prevent a wide variety of bacterial infections.[131] They work by stopping protein growth through the inhibition of bacterial protein synthesis, and they also have anti-inflammatory and immunomodulatory properties.[132] When taking these medications (or any medication) to prevent disease, it is known as prophylaxis.[133] Common antibiotics included in this class are azithromycin, clarithromycin and erythromycin.[131]

In COPD, the prophylactic use of macrolides involves regular dosing with one of these antibiotics on either a continuous (that is, daily), intermittent (for example three times per week) or pulsed (for example five consecutive days every eight weeks) schedule and has been demonstrated to reduce COPD-related exacerbations.[134] The exact mechanism by which macrolides reduce COPD-related exacerbations is unclear; however, proposed mechanisms include their anti-bacterial, anti-inflammatory, mucous secretion inhibiting and anti-viral effects.[135-137]

This chapter focuses on the economic evidence to support the guideline's recommendation that the addition of azithromycin may be considered for one year for patients who have severe COPD, are non-smokers and have had two treated exacerbations. This needs to be done in conjunction with respiratory specialist advice and surveillance for bacterial resistance and side effects such as impaired hearing and cardiac arrhythmias.

8.2 Overview of included studies

Only one study was identified as being relevant to the economic review of prophylactic macrolide antibiotic use: a 2013 budget impact analysis (BIA) from Belgium conducted alongside a systematic review of the long-term-effectiveness and safety of macrolides.[138] A summary of the study characteristics is presented in Table 8.1.

Table 8.1: Characteristics of the intervention and comparator of the included study

Author, country (year)	Intervention	Comparator
Simoens, Belgium (2013)[138]	Generic azithromycin 250mg one capsule once daily for one year, in addition to usual care.	Usual care: COPD medications such as inhaled bronchodilators and ICS, basic education about COPD, and regular clinical appointments.*

Key: COPD – chronic obstructive pulmonary disease; ICS – inhaled corticosteroids.

*This was not discussed by Simoens et al.,[138] but was outlined in the underpinning trial and its protocol.[139]

8.3 Summary of included studies

In accordance with the methods outlined in Chapter 2, all costs are presented as they were in the original study with the adjusted 2019 Irish euro equivalent presented in parenthesis.

Simoens et al.[138] estimated the one-year budget impact of prophylactic azithromycin therapy compared with usual care to prevent COPD exacerbations in Belgium. The target population included COPD patients in GOLD stage 2-4, estimated using European COPD prevalence data applied to the Belgian population.[140-142] Costs were reported in 2012 euro and reflected a third-party payer's reimbursement (including patient co-payments). Only hospitalisation (from COPD exacerbations) and treatment costs, based on Belgian sources and inclusive of co-payments,[143, 144] were included in the analysis. Treatment effect was incorporated as a reduction in the mean number of exacerbation-related hospitalisations per patient (0.15, 0.11 and 0.29 fewer for GOLD stages 2, 3 and 4, respectively) based on the results of a multi-centre double-blind randomised control trial (RCT) (n=1,142).[139]

The estimated additional treatment cost per annum with azithromycin was €595 million (€668 million). However, treatment would be associated with hospital savings of €950 million (€1.07 billion), resulting in an annual net budgetary saving of €355 million (€398 million), equivalent to a saving of €354 (€397) per person. In the sensitivity analysis, the overall budget impact ranged from an annual net budgetary cost of €120 (€135) million to a budgetary saving of €830 (€931) million. The reduction in exacerbation-related hospitalisations was the key driver of budget impact.

A summary of the characteristics, methods and results of the study by Simoens et al.[138] is presented in Table 8.2.

Table 8.2: Summary of characteristics, methods and results of included study

Author, country (year)	Population & Interventions	Analysis details	Costs	Analysis of uncertainty	Results
Simoens, Belgium (2013)[138]	**Population:** COPD patients: GOLD stage 2 (those who experience many exacerbations under usual care) (*n*=848,333); GOLD stage 3 (*n*=132,208); GOLD stage 4 (*n*=22,035) **Intervention:** Prophylactic azithromycin treatment **Comparator:** Usual Care	**Analysis type:** BIA **Perspective:** Third party payer including patient co-payment **Time horizon:** 1 year **Discount rate:** N/A	**Currency & cost year:** 2012 € **Cost components:** Hospitalisation related to COPD exacerbation (medications, hospital stay, diagnostic and laboratory tests and patient co-payments) and annual cost of azithromycin treatment.	OWSA and scenario analyses BIAs ranged between a budgetary saving of €830 million to a budgetary cost of €120 million, with the absolute number of exacerbation-related hospitalisations avoided with azithromycin treatment identified as the key driver.	**Costs:** COPD exacerbation hospitalisation: €6,413 Annual treatment: €594 Additional expenditure over 1 year: €595 million Hospital savings over 1 year: €950 million **Budget impact:** Budgetary savings of €355 million per year

Key: BIA – budget impact analysis; COPD – chronic obstructive pulmonary disease; GOLD – Global Initiative for Chronic Obstructive Lung Disease; N/A – not applicable; OWSA – one-way sensitivity analysis.

8.4 Methodological quality and applicability

8.4.1 Methodological quality

The included study was assessed to be of low quality.[138] Quality was assessed using the CHEC-list questionnaire, [21] the outcomes of the assessment are presented in Table 8.3.

The methodological limitations identified in the study included:

- an insufficient time horizon (one year), which would not adequately capture all relevant costs and consequences
- not all important costs and outcomes relevant to the stated perspective (societal) were included. For example, out-of-pocket patient expenses, productivity losses, adverse events, possible changes in resistance patterns associated with long-term antibiotic treatment or the impact of changes in the number of physician visits related to increased adverse event surveillance (such as hearing impairment and cardiac arrhythmias) and reduced non-hospital COPD exacerbations
- inadequate assessment of uncertainty – not all important variables were assessed (for example, unit cost of hospitalisation) and an arbitrary range (±50%) for the number of hospitalisations avoided was used instead of one informed by the initial study
- the presence of a potential conflict of interest from pharmaceutical industry funding was not adequately addressed
- a lack of discussion regarding ethical and distributional issues.

Table 8.3: CHEC-list[21] quality assessment of included study

Item	Simoens (2013)[138]
Is the study population clearly described?	+
Are competing alternatives clearly described?	+
Is a well-defined research question posed in answerable form?	+
Is the economic study design appropriate to the stated objective?	+
Is the chosen time horizon appropriate to include relevant costs and consequences?	–
Is the actual perspective chosen appropriate?	–
Are all important and relevant costs for each alternative identified?	–
Are all costs measured appropriately in physical units?	+
Are costs valued appropriately?	+
Are all important and relevant outcomes for each alternative identified?	–
Are all outcomes measured appropriately?	+
Are outcomes valued appropriately?	+
Is an incremental analysis of costs and outcomes of alternatives performed?	+
Are all future costs and outcomes discounted appropriately?	
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	–
Do the conclusions follow from the data reported?	+
Does the study discuss the generalizability of the results to other settings and patient/ client groups?	+
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	–
Are ethical and distributional issues discussed appropriately?	–

+ Yes Not applicable – No

8.4.2 Applicability

Applicability (based on relevance and credibility) was assessed using the International Society for Pharmacoeconomics (ISPOR) questionnaire.[22] The outcomes of the assessment are presented in Table 8.4.

The included study was deemed not applicable to the Irish healthcare system due to major credibility limitations.[138] Along with the limitations identified in the quality assessment, the following additional limitations were noted:

- an inadequate model with insufficient face validity, due to the lack of relevant costs

and outcomes and the short (one year) time horizon

- data which may have been unsuitable for populating the model.

The primary source of the clinical effectiveness of azithromycin prophylaxis used by Simeons et al. was from an RCT, published in 2011, which reported the frequency of acute COPD exacerbations.[139] Simeons et al. used only data pertaining to exacerbations that required hospitalisation, which were not determined to be statistically significant in the RCT. A 2018 Cochrane review concluded that while prophylactic treatment with macrolide antibiotics is effective at reducing COPD related exacerbations, delaying the time to first exacerbation and improving health-related quality of life (HRQoL), it is not associated with a significant reduction in hospitalisations.[134]

Table 8.4: Applicability of included study

Item	Simoens (2013)[138]
Relevance	
Is the population relevant?	Yes
Are any critical interventions missing?	No
Are any relevant outcomes missing?	Yes
Is the context applicable?	Yes
Credibility	
Is external validation of the model sufficient?	N/A
Is internal validation of the model sufficient?	N/A
Does the model have sufficient face validity?	No
Is the design of the model adequate?	No
Are the data used in populating the model suitable?	Unclear
Were the analyses adequate?	Yes
Was the adequate assessment of uncertainty?	No
Was the reporting adequate?	Yes
Was interpretation fair and balanced?	Yes
Were there any potential conflicts of interest?	Yes
Were steps taken to address conflicts?	Yes

Key: N/A – not applicable.

8.5 Discussion

The guideline recommends the consideration of azithromycin prophylactic treatment for one year in patients with severe COPD who have been treated for two exacerbations and are non-smokers. The systematic review identified one study[138] which was relevant to assessing the economic impact of prophylactic macrolide antibiotic use. The identified study[138] reported that prophylactic oral azithromycin 250mg once daily was a cost saving treatment which would result in an estimated budgetary saving of €398 million in Belgium over a one-year time horizon. However, this study contained several methodological and applicability limitations

and was, therefore, deemed not applicable to informing the recommendations of this guideline.

When considering the cost-effectiveness of prophylactic macrolide use, careful consideration needs to be given to the dosing schedule and population being treated. The GDG's recommendation of treatment in non-smokers only is supported by the trial which demonstrated a lack of effectiveness in current smokers.[139, 145] This limited evidence also indicates that older age groups and milder GOLD severity stages 2-3 may be associated with better treatment response.[139, 145]

A possible limitation of this systematic review may have been the focus on azithromycin studies only. This was due to the guideline's explicit recommendation to use azithromycin, due to the best available clinical evidence existing for this particular antibiotic.[83] However, as demonstrated by the 2018 Cochrane review,[134] other antibiotics, such as clarithromycin, doxycycline, erythromycin, roxithromycin and moxifloxacin, have also been trialled as prophylactic treatment for preventing COPD-related exacerbations.

The results of an RCT which investigated the effectiveness and safety of prophylactic azithromycin treatment was published in May 2019.[146] A secondary analysis focusing on the cost-effectiveness was also planned.[147] The results of this cost-effectiveness analysis may provide better evidence on the cost-effectiveness of azithromycin prophylactic treatment.

8.6 Conclusions

This systematic review identified one relevant study; however, this study contained several limitations and was deemed not applicable to informing this guideline. Consequently, until further evidence becomes available, the decision to prescribe prophylactic macrolide antibiotics should focus on the clinical benefits associated with treatment and the patient groups who will benefit most while considering the possible adverse events and changes in antibiotic resistance patterns.

9. Lung volume reduction surgery, endobronchial valve and coil treatment

9.1 Description of the intervention

Lung volume reduction surgery (LVRS) is a surgical procedure in which (diseased or damaged) parts of the lungs are surgically removed to reduce hyperinflation and improve the mechanical efficiency of respiratory muscles.[83, 148] Lung hyperinflation (where the lungs are overinflated due to a reduction in elasticity or trapped gas, and interfering with discharge of air)[149] leads to breathlessness and is associated with reduced physical activity and survival.[150] LVRS has been shown to offer relief as a palliative treatment in selected patients with poor baseline exercise capacity and upper lobe-predominant emphysema where the worst affected areas of lung tissue are targeted by resection.[151, 152] However, its invasive and irreversible nature along with its strict patient selection criteria has led to the development of other bronchoscopic procedures, including endobronchial valve therapy (EBV) and endobronchial coil treatment (ECT).[153, 154]

EBV therapy is a minimally invasive and reversible treatment comparable to LVRS.[155] EBV therapy is intended to cause atelectasis (closure) of the worst affected part of the lung by using endobronchial valves to obstruct the airways supplying the target lobe. By doing so, EBV therapy impacts the function of the rest of the lung in a similar way to LVRS.[152] EBV therapy can only be successful in patients without interlobar collateral ventilation (that is, ventilation of alveolar structures through channels that bypass the normal airways),[156] which is estimated to be only 33% of patients with severe emphysema.[157] Additionally, placing one-way valves to block all airways into the target lobe can be technically challenging.[157] ECT reduces hyperinflation (independently of the presence of collateral ventilation) by placing non-blocking shape-memory nitinol coils into subsegmental airways of the lung.[154, 158] The nitinol coils are implanted into the airway of the most severely damaged lobe to bend parenchyma (tissue), enhance lung recoil and re-establish small airway tethering.[154, 159]

This chapter focuses on the economic evidence to support the guideline's recommendations to provide LVRS for carefully selected patients with upper lobe emphysema and low post rehabilitation exercise capacity as well as the guideline's recommendation of bullectomy in selected patients.

Based on these clinical recommendations, the economic review question included in the registered protocol was to investigate the cost-effectiveness of LVRS only.[33] However, it was agreed with the Guideline Development Group to deviate from the protocol and expand the review question to include the minimally invasive lung volume reduction techniques EBV therapy and ECT.

9.2 Overview of included studies

Five studies were included in the systematic review of LVRS. Of these, one economic evaluation examined the cost-effectiveness of LVRS,[160] two examined the cost-effectiveness of EBV therapy,[155, 161] and two investigated the cost-effectiveness of ECT.[154, 158] Of these, two studies were from France,[154, 158] with one each from the US,[160] Germany[155] and the Netherlands.[161] The comparator in each study was usual care. In two studies the usual care group received the intervention after a delay of six months[161] or one year.[158] The studies were published between 2008 and 2018. All of the studies included economic evaluations alongside randomised control trials (RCTs). No eligible systematic reviews of cost-effectiveness were identified for inclusion. A summary of the characteristics of the included studies is presented in Table 9.1.

Table 9.1: Characteristics of interventions and comparators of included studies

Study, country (year)	Intervention	Comparator
Bulsei, France (2018)[158]	ECT: patients received usual care and coil treatment (under general anaesthesia using fluoroscopy to guide placement). Contralateral treatment was completed one to three months after the first coil treatment. ECT was delivered with shape-memory nitinol coils of either 100mm or 125mm. Approximately 10 coils per targeted lobe were inserted.	Usual care: patients received rehabilitation, inhaled bronchodilator therapy, and influenza and pneumococcal vaccination (with or without ICS and or oxygen therapy) according to the degree of severity and rate of exacerbations. Patients received ECT after one year.
Deslée, France (2016)[154]	ECT: patients received usual care and coil treatment (under general anaesthesia using fluoroscopy to guide placement). Contralateral treatment was completed one to three months after the first coil treatment. ECT was delivered with shape-memory nitinol coils of either 100mm or 125mm. Approximately 10 coils per targeted lobe were inserted.	Usual care: patients received rehabilitation, inhaled bronchodilator therapy, influenza and pneumococcal vaccination (with or without ICS and or oxygen therapy) according to the degree of severity and rate of exacerbations.

Study, country (year)	Intervention	Comparator
Hartman, Netherlands (2018)[161]	EBV treatment: the target lobar airway was temporarily occluded by a balloon catheter to assess collateral ventilation. Under general anaesthesia or conscious sedation, Zephyr endobronchial valves were placed in all (sub)segments of the target lobe.	Usual care (according to 2007 GOLD guidelines).[162] Patients received EBV treatment after six months.
Pietzsch, Germany (2014)[155]	EBV treatment: patients received usual care and EBV implantation (under general anaesthesia and on a ventilator, or under moderate sedation with unassisted breathing). Zephyr EBVs were placed unilaterally at the lobar, segmental, or sub-segmental levels depending on the anatomy of the patient.	Usual care: pre-randomisation patients received pulmonary rehabilitation, education and smoking cessation support, pharmacological treatments including bronchodilators, influenza and pneumococcal vaccinations, and oxygen therapy as required. Post-randomisation patients received usual care (according to GOLD guidelines) and exercise at a minimum frequency of three times per week.
Ramsey, USA (2008)[160]	LVRS: patients underwent bilateral stapled wedge resection through a median sternotomy or video-assisted thoracic surgery. Patients also received standard medical therapy.	Usual care including pulmonary rehabilitation

Key: EBV – endobronchial valve; ECT – endobronchial coil treatment; GOLD – Global Initiative for Chronic Obstructive Lung Disease; ICS – inhaled corticosteroid; LVRS – lung volume reduction surgery.

9.3 Summary of included studies

In accordance with the methods outlined in Chapter 2, all costs are presented as they were in the original studies with the adjusted 2019 Irish euro equivalent presented in parenthesis. Where the cost year was not reported by the study's authors, it was assumed that the unit costs were from two years prior to study publication (based on the average cost year reported in studies included within this review). A summary of the characteristics, methods and results of the included studies is presented in Table 9.2.

9.3.1 Lung volume reduction surgery (LVRS)

Ramsey et al.[160] examined the cost-effectiveness of LVRS plus usual care compared with usual care alone based on the five-year follow-up of a multicentre RCT in patients with severe emphysema (n=1,066).[151] Patients in the intervention group were randomised between two surgical approaches:

- LVRS via sternotomy
- LVRS via video-assisted thoracoscopic surgery.

The cost–utility analysis (CUA) was conducted from the US societal perspective over three-, five- and ten-year time horizons. A discount rate of 3% was applied to costs and benefits. Quality-adjusted life years (QALYs) were calculated based on the Quality of Wellbeing[163] responses collected from trial participants.[151] Across all patients in the RCT, the incremental cost-effectiveness ratios (ICERs) were $54,000 (€62,587) (when projected over a ten-year time horizon) and $140,000 (€162,264) (at five-year follow-up) per QALY gained compared with usual care. The authors concluded that LVRS was not cost-effective based on the observed RCT data, but speculated that it would be in the long term.

Ramsey et al. also reported ICERs for three subgroups defined by the baseline characteristics of the presence of upper lobe predominance in emphysema distribution and exercise capacity.[160] The costs per QALY gained compared with usual care in the subgroup analysis were:

- $48,000 (€55,633) when projected over a 10-year time horizon and $77,000 (€89,245) at follow-up in patients with upper-lobe predominat emphysema and low exercise capacity
- $40,000 (€46,361) when projected over a 10-year time horizon and $170,000 (€197,035) at follow-up in patients with upper-lobe predominant emphysema with high exercise capacity
- $87,000 (€100,835) when projected over a 10-year time horizon and $225,000 (€260,781) at follow-up in patients with non-upper-lobe predominant emphysema with low exercise capacity.

9.3.2 Endobronchial valve (EBV) therapy

Two studies investigated the cost-effectiveness of EBV therapy, both concluding that EBV therapy was cost-effective compared with usual care.[155, 161]

Pietzsch et al.[155] developed a Markov model to conduct a CUA alongside a multicentre prospective RCT (*n*=73),[164] to investigate the cost-effectiveness of EBV therapy compared with usual care in patients with severe emphysema. The CUA was conducted from the German Statutory Health Insurance (direct healthcare payer) perspective over five- and 10-

year time horizons, with a 3% discount rate applied to costs and benefits. The CUA employed a two-tiered approach where one year of follow-up data was supplemented by model projections of clinical events and health-related quality of life (HRQoL) based on disease staging and progression for the remaining years. During year one, the incidence of clinical events was higher in the EBV therapy group; however, clinically meaningful improvements in HRQoL and disease progression were achieved by the end of year one that resulted in longer survival in subsequent years. EBV therapy was cost-effective over the ten-year time horizon at a WTP threshold of €50,000 per QALY with an estimated ICER of €25,142 (€28,113) per QALY gained compared with usual care.

Hartman et al.[161] evaluated the cost-effectiveness of EBV treatment compared with usual care in patients with severe emphysema based on six-month follow-up data from an RCT (*n*=68) in the Netherlands.[165] After six months, the control group received EBV treatment. A two-tiered approach was employed where the cost-effectiveness of EBV treatment was calculated based on six-month follow-up data and then projected across five- and 10-year time horizons using a Markov model. The CUA was conducted from the Dutch hospital perspective (direct payer/health insurance) with a 4% discount rate applied to costs and benefits. QALYs were estimated by mapping the St George's Respiratory Questionnaire (SGRQ) to the EQ-5D. The ICERs compared with usual care were:

- €42,775 (€44,395) per QALY gained over a five-year time horizon
- €25,827 (€26,805) per QALY gained over a 10-year time horizon.

9.3.3 Endobronchial coil treatment (ECT)

Two studies[154, 158] investigated the cost-effectiveness of ECT, one[158] an update of the other.[154] Both studies concluded that ECT was not cost-effective compared with usual care or with ECT delayed by one year.

Deslée et al.[154] examined the cost-effectiveness of ECT compared with usual care in patients with severe bilateral emphysema in a prospective CUA alongside an RCT (n=100) in France.[166] The CUA was conducted over a one-year time horizon from the perspective of the French healthcare payer. They estimated an ICER of $782,598 (€828,782) per QALY gained compared with usual care at one-year follow-up. These results were reflected in the sensitivity analysis, where the probability of being cost-effective at a WTP threshold of $500,000 per QALY gained was approximately 0.1. The authors reported in the discussion that the ICER would improve to $270,000 (€285,934) per QALY gained compared with usual care when assessed over a three-year time horizon (assuming benefits are maintained), but this was not included in the CUA.

Bulsei et al.[158] updated the CUA by Deslée et al.[154] based on two years of follow-up data from the same trial[166] to evaluate the cost-effectiveness of ECT compared with usual care in

patients with bilateral severe emphysema. After one year, patients in the usual care (control) group received ECT. The CUA was conducted from the perspective of the French healthcare payer over a two-year time horizon with a 4% discounting rate applied to costs and benefits. The two-year follow-up data demonstrated that there was an improvement in HRQoL in both trial arms following ECT but that HRQoL significantly decreased during the first year in the control group (0.023 mean QALYs lost at one-year follow-up). By the end of year two, HRQoL in the control group had not improved to the level of the intervention. This finding may indicate that early ECT leads to better HRQoL outcomes. Bulsei et al. estimated an ICER of €75,978 (€80,462) per QALY gained compared with usual care (that is, delayed ECT).[158] Sensitivity analysis indicated that there was a 0.5 probability of ECT being cost-effective at a WTP threshold of €83,200 (€88,110).

Table 9.2: Summary of characteristics, methods and results of economic evaluations relevant to LVRS, EBV therapy and ECT

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI – unless stated otherwise)
Bulsei, France (2018)[158]	**Population:** Patients with (bilateral) severe emphysema who attended a PRP in the previous 12 months (*n*=100, mean age: 62 years, FEV_1<50%, RV<220%) **Intervention:** ECT (bilateral or unilateral) **Comparator:** Usual care (received ECT after 1 year)	**Analysis type:** CUA alongside RCT **Perspective:** Healthcare payer **Time horizon:** 2 years **Discount rate:** 4%	**Currency & cost year:** 2016 € **Cost components:** Procedure and hospital costs (medical devices, staff, OR, hospital stay, rehospitalisation, consultation, transport, oxygen, monitoring tests and imaging) **Clinical outcomes:** QALYs (elicited from EQ-5D-5L with French tariffs), number and length of hospitalisations	Non-parametric bootstrapping The likelihood of being cost-effective was 0.5 at a WTP threshold of €83,200 per QALY gained.	**Costs:** Mean total cost per patient: €40,376 (SD: €21,173) Incremental cost: €9,655 **Clinical outcomes:** Incremental QALYs gained: 0.127 **ICERs:** €75,978 per QALY gained
Deslée, France (2016)[154]	**Population:** Patients with (bilateral) severe emphysema following PRP	**Analysis type:** CUA alongside RCT **Perspective:**	**Currency & cost year:** 2014 US $ **Cost components:**	Parametric tests and non-parametric bootstrapping	**Costs:** Mean cost per patient: $53,821 (SD: $10,475) Incremental cost: $47,908 ($47,879–48,073, *p*<0.001)

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI – unless stated otherwise)
	participation in previous year (*n*=100, mean age: 62 years, FEV_1<50%, RV<220%) **Intervention:** ECT (bilateral or unilateral) **Comparator:** Usual care (inhaled therapies and oxygen)	Healthcare payer **Time horizon:** 1 year **Discount rate:** Not applicable	Procedure and hospital costs (medical devices, staff, OR, hospital stay, rehospitalisation, consultation, transport, oxygen, monitoring tests and imaging) **Clinical outcomes:** QALYs (elicited from EQ-5D-5L with French tariffs) SGRQ score, exercise capacity, mMRC dyspnoea score, pulmonary function and adverse events	The likelihood of being cost-effective was 0.1 at a WTP of $500,000 per QALY gained.	**Clinical outcomes:** Incremental QALYs gained: 0.061 (0.061–0.064)* **ICER:** $782,598 ($663,496–1,327,212) per QALY gained
Hartman, Netherlands (2018)[161]	**Population:** Patients with severe emphysema (GOLD stage 2 to 4, mean age: 50 years) **Intervention:**	**Analysis type:** CEA and CUA alongside RCT with Markov model projection **Perspective:**	**Currency & cost year:** 2016 € **Cost components:** Direct medical (treatment) costs and clinical events (exacerbations, pneumonia and re-bronchoscopy)	Non-parametric bootstrapping	**Costs:** Mean EBV cost: €13,197 per patient at 6 months Incremental costs: €16,721 (€16,675–16,766) per patient at 6 months €1,952,104 total cost at 5 years €2,067,498 total cost at 10 years

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI – unless stated otherwise)
	EBV therapy (*n*=34) **Comparator:** Standard medical care and EBV therapy after 6 months (*n*=34)	Hospital (Dutch health insurance) **Time horizon:** 6 months, 5 and 10 years **Discount rate:** 4%	**Clinical outcomes:** QALYs (mapped from SGRQ to EQ-5D), LYs, exercise capacity and mortality		**Clinical outcomes:** Incremental QALYs gained: 0.12 (0.01-0.24) at 6 months; 47 at 5 years; 85 at 10 years Incremental SGRQ score: 0.16 (0.07–0.24) at 6 months; 45 at 5 years; 80 at 10 years **ICERs:**** 6 months follow-up: €205,129 (€203,547–206,709) per QALY gained at 6 months €42,775 per QALY gained at 5 years €25,827 per QALY gained at 10 years
Pietzsch, Germany (2014)[155]	**Population:** Patients with severe emphysema (complete fissure and high heterogeneity,	**Analysis type:** CUA alongside RCT with Markov projection **Perspective:**	**Currency & cost year:** 2014 € **Cost components:** Treatment costs (including EBV implantation and clinical	DSA and scenario analysis Using an average of 4 valves per procedure (versus 3.08) increased	**Costs:** Incremental cost: €10,299 at 5 years €10,425 at 10 years **Clinical outcomes:** Incremental QALYs gained:

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI – unless stated otherwise)
	mean age: 62 years)*** **Intervention:** EBV therapy (*n*=37) **Comparator:** Usual care (*n*=36)	German Statutory Health Insurance (direct healthcare payer) **Time horizon:** 5 and 10 years **Discount rate:** 3%	events) and add-on payments (valves used) **Clinical outcomes:** QALYs (mapped from SGRQ), clinical events and mortality.	the 5- and 10-year ICERs to €53,367 and €28,920 per QALY gained respectively.	0.22 at 5 years 0.41 at 10 years **ICERs:** €46,322 per QALY gained at 5 years €25,142 per QALY gained at 10 years

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results (95% CI – unless stated otherwise)
Ramsey, USA (2008)[160]	**Population:** Patients with severe emphysema following PRP participation (mean age: 67 years) **Intervention:** LVRS plus usual care (*n*=531) **Comparator:** Usual care (*n*=535)	**Analysis type:** CUA alongside RCT with Markov projection **Perspective:** Societal **Time horizon:** 3, 5 and 10 years **Discount rate:** 3%	**Currency & cost year:** US $, cost year not reported **Cost components:** Direct medical care (pre-operative evaluation, operation, and all emphysema-related care post-surgery), non-medical care related to LVRS (such as travel to and from the clinic), and productivity loss (caregiver and patient recovery time) **Clinical outcomes:** QALYs (measured by QWB questionnaire)	Insufficient detail reported	**ICERs:†** $190,000 per QALY gained at 3 years (observed data) $140,000 per QALY gained at 5 years (observed data) $54,000 per QALY gained at 10 years (projected based on 5-year follow-up)

Key: CEA – cost-effectiveness analysis; CI – confidence interval; CUA – cost–utility analysis; DSA – deterministic sensitivity analysis; EBV – endobronchial valve; ECT – endobronchial coil treatment; EQ-5D – EuroQol 5-Dimensions; EQ-5D-5L – EuroQol 5-Dimensions 5-Levels; FEV_1 – Forced expiratory volume; GOLD – Global Initiative for Chronic Obstructive Lung Disease; ICER – incremental cost-effectiveness ratio; LVRS – lung volume reduction surgery; mMRC – modified Medical Research Council; OR – operating room, PRP – pulmonary rehabilitation programme; QALY – quality-adjusted life year; QWB – Quality of Well-Being; RCT – randomised controlled trial; RV – residual volume; SD – standard deviation; SGRQ – Saint George's Respiratory Questionnaire; WTP – willingness to pay.

* CI noted to include estimate as lower limit, but reported exactly as in Deslée et al.[154]

** ICERs estimated according to EQ-5D score have been excluded. Hartman et al.[161] reported that the ICERs estimated according to EQ-5D scores were unreliable due a significant difference at baseline. The QALY gains presented here were estimated by mapping the SGRQ to the EQ-5D.

*** Complete fissure is considered a proxy for collateral ventilation.
† Ramsey et al.[160] also reported ICERs according to three subgroups based on emphysema lobar distribution and exercise capacity. The ICERs reported here are based on all eligible patients assessed in the RCT.

9.4 Methodological quality and applicability

9.4.1 Methodological quality

Five economic evaluations were identified: one evaluating LVRS,[160] and two analysing EBV therapy[155, 161] and ECT,[154, 158] respectively. All of the studies included economic evaluations alongside RCTs. Three of the studies also included model projections to longer term time horizons based on the most recent follow-up data from the RCTs.[155, 160, 161] Of these, one was deemed to be of high quality,[154] two were of moderate quality[155, 158] and two were of low quality.[160, 161] The methodological quality was assessed using the CHEC-list questionnaire,[21] and the outcomes of this are presented in Table 9.3.

Common methodological limitations included:

- three studies lacked detail on the intervention and or comparators[155, 160, 161]
- four studies were considered to have insufficient time horizons (such as only one or two years) to account for all the relevant costs and outcomes expected over a patient lifetime[154, 155, 158, 161]
- three studies had inappropriately measured and valued costs (such as primarily using tariff-based costs or not listing sources).[155, 160, 161] In one study,[158] it was unclear if valuation was appropriate (as detailed costs had been presented in an earlier study; however, it was reported that these costs had decreased and insufficient detail was presented)
- three studies[155, 158, 161] did not subject all important inputs to appropriate methods for dealing with uncertainty (such as probabilistic sensitivity analysis). In one study, the reporting made it unclear if appropriate sensitivity analysis was conducted[160]
- four studies had evidence of potential conflicts of interest from association with or receipt of funding from commercial entities which were not adequately addressed[154, 155, 158, 161]
- four studies had a lack of discussion on the generalisability of findings to other settings and patient groups[154, 155, 158, 160]
- all studies lacked a discussion regarding ethical and distributional issues.[154, 155, 158, 160, 161]

Other limitations which were applicable to individual papers included:

- exclusion of relevant costs (COPD management costs)[161]
- not identifying all relevant outcomes (healthcare utilisation)[160]
- inappropriately valued outcomes (assigning health-state utility weights that were not systematically identified).[155]

Table 9.3: CHEC-list quality assessment of included studies

Item	Bulsei (2018)[158]	Deslée (2016)[154]	Hartman (2018)[161]	Pietzsch (2014)[155]	Ramsey (2008)[160]
Is the study population clearly described?	+	+	+	+	–
Are competing alternatives clearly described?	+	+	–	–	–
Is a well-defined research question posed in answerable form?	+	+	+	+	+
Is the economic study design appropriate to the stated objective?	+	+	+	+	+
Is the chosen time horizon appropriate to include relevant costs and consequences?	–	–	–	–	+
Is the actual perspective chosen appropriate?	+	+	+	+	+
Are all important and relevant costs for each alternative identified?	+	+	–	+	+
Are all costs measured appropriately in physical units?	+	+	–	+	–
Are costs valued appropriately?	Unclear	+	+	–	–
Are all important and relevant outcomes for each alternative identified?	+	+	+	+	–
Are all outcomes measured appropriately?	+	+	+	+	+
Are outcomes valued appropriately?	+	+	+	–	+
Is an incremental analysis of costs and outcomes of alternatives performed?	+	+	+	+	+
Are all future costs and outcomes discounted appropriately?	+	Not applicable	+	+	+
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	–	+	–	–	Unclear
Do the conclusions follow from the data reported?	+	+	+	+	+
Does the study discuss the generalizability of the results to other settings and patient/ client groups?	–	–	+	–	–
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	–	–	–	–	+
Are ethical and distributional issues discussed appropriately?	–	–	–	–	–

+ Yes Not applicable – No

9.4.2 Applicability

Applicability (based on relevance and credibility) was assessed using the International Society for Pharmacoeconomics (ISPOR) questionnaire,[22] the outcomes of this assessment are presented in Table 9.4.

No Irish studies were identified. All of the studies were considered partially applicable due to a number of limitations. In summary:

- one study did not include all relevant outcomes[160]
- four of the five studies were subject to competing interests (Deslée et al.[154] reported that the funders had no involvement in the design, collection of data, conduct of analysis, preparation of and decision to submit the manuscript)[154, 155, 158, 161]
- three studies did not demonstrate sufficient assessment of uncertainty,[155, 158, 161] and this was unclear in one study[160]
- reporting was inadequate in three studies[158, 160, 161]
- face validity was insufficient in one study[161] and unclear in another[160]
- whether the model was adequately designed was unclear in two studies,[158, 160] with the suitability of the data used in populating the model also unclear in one[160]
- interpretation was considered biased in favour of the intervention in one study[154]
- two studies[155, 160] applied discounting to costs and benefits at a different rate to that required by Irish national guidelines (4%)[167]
- no study adequately reported internal verification or external validation of the models.

Table 9.4: Applicability of included studies

Item	Bulsei (2018)[158]	Deslée (2016)[154]	Hartman (2018)[161]	Pietzsch (2014)[155]	Ramsey (2008)[160]
Relevance					
Is the population relevant?	Yes	Yes	Yes	Yes	Yes
Are any critical interventions missing?	No	No	No	No	No
Are any relevant outcomes missing?	No	No	No	No	Yes
Is the context applicable?	Yes	Yes	Yes	Yes	Yes
Credibility					
Is external validation of the model sufficient?	No	No	No	No	No
Is internal verification of the model sufficient?	No	No	No	No	No
Does the model have sufficient face validity?	Yes	Yes	No	Yes	Unclear
Is the design of the model adequate?	Unclear	Yes	Yes	Yes	Unclear
Are the data used in populating the model suitable?	Yes	Yes	Yes	Yes	Unclear
Were the analyses adequate?	Yes	Yes	Yes	Yes	Yes
Was there adequate assessment of uncertainty?	No	Yes	No	No	Unclear
Was the reporting adequate?	No	Yes	No	Yes	No
Was interpretation fair and balanced?	Yes	No	Yes	Yes	Yes
Were there any potential conflicts of interest?	Yes	Yes	Yes	Yes	No
Were steps taken to address conflicts?	Yes	Yes	Yes	No	N/A

Key: N/A – not applicable

9.5 Discussion

Lung volume reduction surgery (LVRS) is an established palliative treatment for severe emphysema which reduces hyperinflation by resection of severely damaged lung tissue.[83] Minimally invasive techniques to reduce lung volume (including endobronchial valve (EBV) therapy and endobronchial coil treatment (ECT)) have also been developed. This systematic review identified five economic evaluations: one assessing the cost-effectiveness of LVRS, [160] two analysing EBV[155, 161] and two analysing ECT.[154, 158] All of the studies included economic evaluations alongside RCTs. Three[155, 160, 161] of the studies also included model projections to longer term time horizons based on the most recent follow-up data from the RCTs. All five of the included studies were considered partially applicable to the Irish setting.

The only included study[160] that evaluated the cost-effectiveness of LVRS was considered low quality, thus the results should be viewed with caution. The authors estimated ICERs over several time horizons, but given that studies of long-term outcomes of LVRS have reported five-year survival rates of 71%[168] and 80%,[169] and estimated 10-year survival rates of approximately[†] 64%[170] and 44%,[171] the results for the 10-year time horizon are most relevant. Ramsey et al. reported an adjusted ICER of €62,587 per QALY gained for LVRS compared with usual care in patients with severe emphysema,[160] which would not be considered cost-effective at the €45,000 WTP threshold commonly employed in Ireland. The study suggested cost-effectiveness could be improved by limiting LVRS to those with upper lobe emphysema, which is consistent with the recommendation of this guideline that recommends LVRS for use only in carefully selected patients with upper lobe emphysema and low post rehabilitation exercise capacity. However, even in these subgroups, the results reported by Ramsey et al.[160] would not be considered cost-effective in Ireland.

Following our search, a systematic review[172] by NICE was published in December 2018. NICE's review included one additional study from 2006 by Miller et al.[173] that assessed the cost-effectiveness of LVRS (excluded from the current systematic review, which included studies published from 2008 to 2018). The study was conducted from the perspective of the Canadian healthcare system over a two-year time horizon. Miller et al.[173] estimated an ICER of €107,850 per QALY gained compared with usual care in patients with advanced emphysema. The ICER would not be considered cost-effective at the €45,000 WTP threshold.

The cost-effectiveness of EBV therapy was assessed in two studies, both deemed partially

[†]Approximate estimated survival rates obtained from the Kaplan-Meier curves, using WebPlotDigitizer web application (https://automeris.io/WebPlotDigitizer/).

applicable, with one of moderate quality[155] and the other of low quality.[161] The estimated adjusted ICERs were €28,113 and €26,805‡ per QALY gained, respectively, when compared with usual care in patients with severe emphysema over a 10-year time horizon. These ICERs would be considered cost-effective at the €45,000 WTP threshold.

Two studies,[154, 158] both partially applicable, assessed the cost-effectiveness of ECT alongside an RCT in France.[166] The first study,[154] which was of high quality, reported an adjusted ICER of €828,782 per QALY gained compared with usual care over a one-year time horizon, while the second study,[158] which was of moderate quality, reported an adjusted ICER of €80,462 per QALY gained over a two-year time horizon. Neither of these ICERs would be considered cost-effective at the €45,000 WTP threshold. The contrast in the ICERs between one- and two-years follow-up reflects a greater incremental HRQoL gain in the intervention arm compared to the control in the second year of the RCT and indicates the uncertainty around the longer-term cost-effectiveness of this treatment. This guideline does not explicitly recommend either EBV therapy or ECT, however, the limited cost-effectiveness evidence indicates that EBV therapy warrants consideration while longer-term cost-effectiveness studies of ECT are required before conclusions about this treatment can be made.

The RCT[166] which formed the basis for the two ECT studies[154, 158] intends to follow both patient groups for five years post treatment. The release of the five-year follow up data will demonstrate whether the observed effects are sustained in the longer term, making the cost-effectiveness of ECT clearer. Additionally, a UK clinical trial investigating the relative effectiveness and value of LVRS and EBV is scheduled.[174]

9.6 Conclusions

Five economic evaluations assessing the cost-effectiveness of LVRS, ECT and EBV therapy published between 2008 and 2018 were identified by this systematic review. No eligible Irish studies were identified for inclusion.

Limited evidence, based on a single low-quality study, found that while cost-effectiveness is improved by restricting LVRS to patients with upper-lobe emphysema and particularly those with high exercise capacity, it is not cost-effective at a WTP threshold of €45,000 per QALY gained. Two studies,[155, 161] of low to moderate quality and partial applicability, indicated that EBV therapy is likely to be cost-effective in patients with severe emphysema. Two studies,[154, 158] of high to moderate quality with partial applicability, indicated that ECT was not cost-effective. However, the two ECT studies[154, 158] were based on short-term time horizons of less than two years. This COPD guideline does not explicitly recommend for or against EBV

‡When QALYs were estimated by mapping the SGRQ to the EQ-5D.

therapy or ECT; however, the evidence identified by this systematic review suggests that EBV therapy warrants consideration and longer term studies of ECT are required.

10. Non-invasive ventilation

10.1 Description of the intervention

Acute respiratory failure, a condition in which there is insufficient oxygen or too much carbon dioxide in the blood, can be a complication in severe exacerbations of COPD. This causes the pH of the blood to decrease, which is known as respiratory acidosis. This clinical state is classified as acute hypercapnic respiratory failure and may be life threatening. It is characterised by symptoms of confusion, sleepiness, rapid breathing, use of accessory breathing muscles or possible loss of consciousness.[175-179] Non-invasive ventilation (NIV) helps a person to breathe more deeply by pushing air into the lungs.[83, 180-182] This is most commonly done via a mask covering the nose or face, referred to as non-invasive positive pressure ventilation (NPPV).[83] NIV can be used during acute respiratory failure as an alternative to invasive mechanical intubation (which occurs via an oro-tracheal tube or tracheostomy), to improve the oxygen, carbon dioxide and pH levels in the blood, rest the breathing muscles and reduce the feeling of breathlessness.[83, 182, 183] These effects have been shown to result in reduced mortality and intubation rates; decreased complications (such as ventilator associated pneumonia); and shorter length of hospital stay (LOS).[83, 183, 184]

This chapter focuses on the economic evidence to support the guideline's recommendation to provide early use of NIV in patients with acute exacerbations of COPD who develop acute respiratory failure associated with respiratory acidosis ($PaCO_2$ greater than 6 kPa and an arterial pH less than 7.35).

10.2 Overview of included studies

Two studies were included in the economic review of NIV: both were modelled cost–utility analyses (CUAs). One study was from Canada (published in 2012),[25] and the other from India (published in 2015).[185] A summary of the interventions and comparators of the included studies is presented in Table 10.1.

Table 10.1: Characteristics of interventions and comparators of the included studies

Study, country (year)	Intervention	Comparator
Chandra, Canada (2012)[25]	Inpatient based NPPV plus usual medical care.	Usual medical care*: medical treatment, which could include supplemental oxygen, bronchodilators, corticosteroids, antibiotics, diuretics and or respiratory stimulators.
Patel, India (2015)[185]	Ward based NIV plus standard treatment	Standard treatment alone**: which could include oxygen via a nasal cannula, beta2-agonists, anticholinergics, prednisolone, diuretics, correction of electrolyte imbalance and use of antibiotics.

Key: NIV – non-invasive ventilation; NPPV – non-invasive positive pressure ventilation.

*This was not defined by Chandra et al.,[25] but was discussed in the associated systematic review.[184]
**This was not defined by Patel et al.,[185] but was discussed in the two RCTs used to inform their model.[186, 187]

10.3 Summary of included studies

In accordance with the methods outlined in Chapter 2, all costs are presented as they were in the original studies with the adjusted 2019 Irish euro equivalent presented in parenthesis. Where the cost year was not reported by the study's authors, it was assumed that the unit costs were from two years prior to study publication (based on the average cost year reported in studies included within this review). A summary of the characteristics, methods and results of the included studies is presented in Table 10.2.

Chandra et al. developed a Markov model to compare NPPV plus usual medical care with usual medical care alone in patients with acute respiratory failure (due to an acute exacerbation in severe COPD) in an inpatient setting.[25] The CUA was conducted from the perspective of the publicly funded Canadian healthcare system over a lifetime time horizon. Discounting was applied to costs and benefits at a rate of 5%. Clinical effectiveness inputs were derived from a systematic review of randomised control trials (RCTs).[188] Pooled analysis of the results gave an estimated reduced hospital length of stay (LOS) of 2.68 days (95% CI: 0.94–4.41 days; n=11 RCTs) and a 47% reduction in the risk of inpatient mortality (relative risk of 0.53 (95% CI: 0.35–0.81); n=9 RCTs) compared with usual medical care alone. Chandra et al. reported that NPPV plus usual medical care dominated (that is, was less costly and more effective than) usual medical care alone after estimating an incremental cost saving of CAN$2,746 (€1,975) and an incremental gain of 0.13 QALYs per patient.

Patel et al. used a decision tree (CUA) to compare NIV plus standard treatment with standard treatment alone in COPD-related respiratory failure patients in India.[185] The study was conducted from a societal perspective over a lifetime time horizon, with discounting applied to costs and benefits at rates of both 3% and 5%. Costs were reported in 2012 US dollars, but reflect the Indian setting and were obtained from Indian sources.[189] LOS and probability of death were estimated at 9.63 (95% CI: 8.22-11.04) days and 0.101 (95% CI: 0.077–0.131),

respectively, in the intervention group compared with 13.33 (95% CI: 8.64-18.02) days and 0.278 (95% CI: 0.24-0.32) in the comparator group. These estimates were based on two RCTs from India.[187, 190] QALYs were assumed to be equivalent post-hospital discharge.[191] NIV plus standard treatment was reported as cost-effective at a willingness to pay (WTP) threshold of US$4,467 (€4,195) per QALY gained with an estimated incremental cost-effectiveness ratio (ICER) of US$61 (€57) per QALY gained compared with standard treatment alone (for both discount rates).

Table 10.2: Summary of characteristics, methods and results of economic evaluations relevant to NIV

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
Chandra, Canada (2012)[25]	**Population:** GOLD stage 3, who have suffered an acute exacerbation (age: ≥ 65 years) **Intervention:** NPPV plus usual medical care **Comparator:** Usual medical care alone	**Analysis type:** Markov (CUA) **Perspective:** Publicly funded health care system **Time horizon:** Lifetime **Discount rate:** 5%	**Currency & cost year:** Canadian $, cost year not reported **Cost components:** Lifetime exacerbation and maintenance costs and hospitalisation costs (nursing care, operating room, intensive care unit, diagnostic imaging, pharmacy, and laboratory tests) **Clinical outcomes:** LYs and QALYs (elicited from EQ-5D with Dutch and Spanish tariffs)	PSA The probability of being cost-effective was 1 at the WTP threshold of $50,000 per QALY gained	**Costs:** Incremental saving per patient: $2,746 **Clinical outcomes:** Incremental LYs: 0.19 Incremental QALYs: 0.13 **ICERs:** Dominates (that is, less expensive and more effective) in both LYs gained and QALY gained
Patel, India (2015)[185]	**Population:** COPD-related respiratory failure patients in India	**Analysis type:** Decision tree (CUA) **Perspective:**	**Currency & cost year:** 2012 US $ **Cost components:** Cost of ward hospitalisation, NIV treatment and chronic	OWSA, TWSA and PSA ICERs ranged between approximately $20 to	**Costs:*** Standard treatment: $486 NIV: $575 Incremental cost: $89 **Clinical outcomes:***

Author, country (year)	Population & Interventions	Analysis details	Costs and clinical outcomes	Analysis of uncertainty	Results
	Intervention: Ward-based NIV plus standard treatment **Comparator:** Standard treatment	Societal **Time horizon:** Lifetime **Discount rate:** 3% and 5%	costs for moderate to severe COPD **Clinical outcomes:** QALYs (elicited from EQ-5D with Finnish tariffs)	$105 per QALY gained in the OWSA. Key drivers were: LOS, annual COPD cost per patient, cost of NIV treatment and cost of hospitalisation. The probability of NIV being cost-effective was 1 at a WTP threshold of $4,467 per QALY gained.	Standard treatment QALYs: 6.0 NIV QALYs: 7.47 Incremental QALYs gain: 1.47 **ICER:** $61 per QALY gained

Key: COPD – chronic obstructive pulmonary disease; CUA – cost–utility analysis; EQ-5D – EuroQol 5-Dimensions instrument; GOLD – Global Initiative for Chronic Obstructive Lung Disease; ICER – incremental cost-effectiveness ratio; LY – life years; NIV – non-invasive ventilation; NPPV – non-invasive positive pressure ventilation; OWSA – one-way sensitivity analysis; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; TWSA – two way sensitivity analysis; WTP – willingness to pay.

*Cost and clinical outcomes presented here are discounted at a rate of 5%. Costs and benefits were also discounted at a rate of 3%, but are not presented here as the ICER reported was the same as that for the 5% discount rate.

10.4 Methodological quality and applicability

10.4.1 Methodological quality

The methodological quality of the included studies was assessed using the CHEC-list questionnaire,[21] the outcomes of which are presented in Table 10.3. One was deemed to be of low quality[185] and the other of moderate quality.[25] Methodological limitations common to both studies included:

- not including all important and relevant costs (for example, ventilator acquisition or procedure costs)[25, 185]
- valuing costs inappropriately (Chandra et al.[25] valued the intervention based on diagnosis and principal procedure codes,[192] whereas the comparator was based on a comprehensive study[193] which may have included costs not captured in procedure codes (such as ambulance transport, one month supply of medications post discharge and outpatient visits); Patel et al.[185] used the estimated cost of patients following treatment guidelines recommended by a national report[189] instead of the actual cost of COPD estimated by the same report (₹1,320 instead of ₹32,685 – Indian rupees))
- a lack of discussion regarding ethical and distributional issues.

Additional methodological limitations for the study by Patel et al.[185] included:

- valuing outcomes inappropriately for example ~~as~~ the source of utility estimates during hospital stay was unclear
- a lack of discussion on the generalisability of findings to other settings and patient groups.

Chandra et al.[25] did not subject all important variables to appropriate methods for dealing with uncertainty as one-way sensitivity analysis was not reported.

Table 10.3: CHEC-list quality assessment of non-invasive ventilation economic evaluations

Item	Chandra (2012)[25]	Patel (2015)[185]
Is the study population clearly described?	+	+
Are competing alternatives clearly described?	+	+
Is a well-defined research question posed in answerable form?	+	+
Is the economic study design appropriate to the stated objective?	+	+
Is the chosen time horizon appropriate to include relevant costs and consequences?	+	+
Is the actual perspective chosen appropriate?	+	+
Are all important and relevant costs for each alternative identified?	–	–
Are all costs measured appropriately in physical units?	+	+
Are costs valued appropriately?	–	–
Are all important and relevant outcomes for each alternative identified?	+	+
Are all outcomes measured appropriately?	+	+
Are outcomes valued appropriately?	+	–
Is an incremental analysis of costs and outcomes of alternatives performed?	+	+
Are all future costs and outcomes discounted appropriately?	+	+
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	–	+
Do the conclusions follow from the data reported?	+	+
Does the study discuss the generalizability of the results to other settings and patient/ client groups?	+	–
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	+	+
Are ethical and distributional issues discussed appropriately?	–	–

+ Yes Not applicable – No

10.4.2 Applicability

Applicability (based on relevance and credibility) was assessed using the International Society for Pharmacoeconomics (ISPOR) questionnaire,[22] and the outcomes of this assessment are presented in Table 10.4.

The study by Patel et al.[185] was not applicable due to major differences in relation to the context (as the Indian healthcare costs were much lower than in Ireland and emergency treatment in an ICU following treatment failure was assumed to not be possible).

The study by Chandra et al.[25] was considered partially applicable, but contained the following limitations:

- the absence of adequate external validation and internal verification

- inadequate assessment of uncertainty (one-way sensitivity analysis was not reported)
- a discount rate to costs and benefits different to that required by Irish national guidelines (4%).[167]

Table 10.4: Applicability of non-invasive ventilation economic evaluations

Item	Chandra (2012)[25]	Patel (2015)[185]
Relevance		
Is the population relevant?	Yes	Yes
Are any critical interventions missing?	No	No
Are any relevant outcomes missing?	No	No
Is the context applicable?	Yes	No
Credibility		
Is external validation of the model sufficient?	No	No
Is internal verification of the model sufficient?	No	No
Does the model have sufficient face validity?	Yes	No
Is the design of the model adequate?	Yes	Yes
Are the data used in populating the model suitable?	Yes	No
Were the analyses adequate?	Yes	Yes
Was the adequate assessment of uncertainty?	No	Yes
Was the reporting adequate?	Yes	Yes
Was interpretation fair and balanced?	Yes	Yes
Were there any potential conflicts of interest?	No	No
Were steps taken to address conflicts?	N/A	N/A

Key: N/A – not applicable

10.5 Discussion

This systematic review identified two modelled CUAs which investigated the cost-effectiveness of NIV for treatment of respiratory failure in patients with acute exacerbations of COPD.[25, 185] Both studies reported that NIV was cost-effective compared with standard treatment. Patel et al.[185] reported an ICER of €57 per quality-adjusted life year (QALY) gained, while Chandra et al.[25] found that NIV was dominant (that is, NIV was less costly and more effective). Both ICERs would be considered cost-effective, at a willingness-to-pay (WTP) threshold of €45,000 per QALY gained, which is commonly employed for non-pharamceutical technologies in Ireland.

The study by Patel et al.[185] was considered not applicable due to differences between the Indian (where the costs are considerably less and the majority of hospitals do not have an ICU) and Irish healthcare settings. The findings of the study by Chandra et al.,[25] which was

considered partially applicable and of moderate quality, support the guideline recommendation for early use of NIV in patients with acute exacerbations of COPD who develop acute respiratory failure associated with respiratory acidosis.

The findings from Chandra et al.[25] are also consistent with earlier cost-effectiveness analyses,[194-196] which found NIV treatment to be cost-effective compared with standard treatment. However, in accordance with the eligibility criteria of our systematic review, only studies published from 2008 onwards were included and critically appraised; therefore,the quality and applicability of these earlier studies is unclear.

10.6 Conclusions

There is a lack of recent international literature examining the cost-effectiveness of NIV in patients with acute exacerbations of COPD. This may be due to the well-documented clinical benefits of NIV[83, 183, 184] and the favourable findings of cost-effectiveness studies in the early 2000s.[194-196] This systematic review identified two studies published since 2008,[25, 185] only one of which was of at least moderate quality and partially applicable to the Irish context.[25] The study found that the addition of NIV to usual medical care was both cost saving and more effective than usual medical care alone for patients with acute exacerbations of COPD who develop acute respiratory failure associated with respiratory acidosis. While based on very limited recent economic evidence, it is plausible that NIV could be cost-effective in Ireland for this indication.

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Appendix 1: Clinical recommendations

Table A1: Clinical recommendations

No.	Recommendation
1	We recommend prescribing inhaled short-acting beta$_2$-agonists (SABAs) to patients with confirmed COPD where rescue therapy is needed. (Grade A)
2	▪ We recommend offering long-acting bronchodilators to patients with confirmed stable COPD who continue to have respiratory symptoms (for example, dyspnoea or cough). (Grade A) ▪ We recommend offering inhaled long-acting muscarinic agents (LAMAs) as first line maintenance therapy in patients with confirmed stable COPD who have continued respiratory symptoms (for example, dyspnoea or cough) or who have a history of exacerbations with COPD. (Grade A) ▪ In patients with confirmed stable COPD who are on inhaled LAMAs or inhaled long-acting beta$_2$ agonists (LABAs) alone and have persistent dyspnoea on mono therapy we would recommend combination therapy with both LAMAs and LABAs. (Grade A)
3	▪ We recommend against offering an inhaled cortical steroid (ICS) in symptomatic patients with confirmed stable COPD as first line therapy. (Grade A) ▪ In patients with confirmed COPD who are on combination therapy with LAMAs and LABAs and have persistent dyspnoea or frequent COPD exacerbations, we suggest that the addition of an ICS may be reasonable (Grade B)
4	We recommend that each patient that is commenced on an inhaler device would be provided with instructions and a demonstration of proper inhalation technique prior to using the device and that such technique is checked on a regular basis subsequently. Inhaler technique and adherence to therapy should be assessed before concluding that current therapy is insufficient and a change in therapy considered. (Expert Opinion)
5	In select patients with the chronic bronchitic phenotype of COPD with severe to very severe air flow obstruction and history of exacerbations, a phosphodiesterase-4 (PDE-4) inhibitor may be reasonable add on to therapy with a LAMA and LABA and possibly ICS. This recommendation is dependent on reimbursement approval by HSE. (Grade B)
6	In certain selected patients, the addition of a theophylline may be reasonable (Grade B)
7	In patients who have severe COPD with two treated exacerbations and are non-smokers, the addition of azithromycin may be considered for one year (Grade A). This needs to be done in conjunction with respiratory specialist advice with surveillance for bacterial resistance and side effects such as impaired hearing and

No.	Recommendation
	cardiac arrhythmias. (Grade A)
8	We cannot support the use of mucolytic and antioxidants in routine practice for management of patients with COPD.
9	We cannot recommend a role for leukotriene receptor antagonists in the management of patients with COPD.
10	We recommend that AATD augmentation therapy might be considered in young patients who are never or ex-smokers with an FEV_1 of 35-60% predicted with continued and progressive disease. This recommendation is dependent on reimbursement approval by HSE. (Grade B)
11	We recommend smoking cessation measures for the prevention of COPD, to include advice on smoking cessation, nicotine replacement therapy and pharmacotherapy. (Grade A) At the moment, the effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain.
12	We recommend the provision of annual influenza vaccination. (Grade A)
13	We recommend the provision of the pneumococcal vaccination. (Grade B)
14	▪ We recommend the provision of pulmonary rehabilitation to stable patients with exercise limitation despite pharmacological treatment. (Grade A) ▪ We recommend the provision of pulmonary rehabilitation to patients who have recently been hospitalised for an acute exacerbation of COPD. (Grade B)
15	▪ We recommend the provision of long-term provision oxygen therapy to patients with chronic stable hypoxemia with a PaO_2 less than 7.3 Kpa or a $Pa0_2$ between 7.3 and 8Kpa with signs of tissue hypoxia (haematocrit greater than 55%, pulmonary hypertension or cor pulmonale). (Grade A) ▪ We do not recommend the provision of oxygen for patients with moderate hypoxemia, nocturnal de-saturation and exercise induced de-saturation in patients with COPD. (Grade A)
16	Nutritional support should be considered in all malnourished patients with COPD. (Grade B)
17	▪ We recommend lung volume reduction surgery for carefully selected patients with upper lobe emphysema and low post rehabilitation exercise capacity. (Grade A) ▪ In selected patients, bullectomy can also be recommended. (Grade C)
18	We recommend that appropriately selected patients with very severe COPD be considered for lung transplantation surgery. (Grade C)
19	In stable diagnosed COPD patients, decline in FEV_1 can be tracked by spirometry performed every two years. (Expert Opinion)
20	For advanced COPD care and palliation, patients should be referred to a palliative

No.	Recommendation
	care specialist as appropriate. (Expert Opinion)
21	We recommend the initiation of short acting acute bronchodilator therapy (salbutamol plus or minus ipratropium) for patients with an exacerbation of COPD (Grade C)
22	We recommend a course of systemic steroids (prednisone equivalent of 40mgs for five days) to be administered orally to all patients. Therapy should not be administrated for more than this. (Grade A)
23	We recommend antibiotic use for patients with exacerbations of COPD associated with increased dyspnoea and associated increased sputum purulent or volume. First line antibiotic choices should include doxycycline, amoxicillin or a macrolide. We recommend reserving broader spectrum antibiotics such as quinolones for specific indications. (Grade B)
24	We recommend the early use of non-invasive ventilation in patients with acute exacerbations of COPD who develop acute respiratory failure associated with respiratory acidosis, that is, a $PaCO_2$ greater than 6KPa and an arterial pH less than 7.35. (Grade A)
25	We recommend the involvement of the COPD outreach team at the earliest possible time during a COPD exacerbation when it is being treated in hospital (Expert Opinion)
26	We recommend that Respiratory Physiotherapists are key in delivering COPD outreach, NIV, oxygen assessment and pulmonary rehabilitation to patients who have exacerbations of COPD (Expert Opinion)
27	We do not recommend the use of theophylline in acute exacerbations of COPD. (Grade B)
28	▪ We recommend that patients discharged home from hospitalisation on oxygen therapy are evaluated for the need for long-term oxygen therapy 30–90 days after discharge. Long-term oxygen therapy (LTOT) should not be continued if patients do not meet the criteria. (Expert Opinion) ▪ We recommend against routinely offering of ambulatory LTOT for patients with chronic stable isolated exercise hypoxemia. (Grade A) ▪ Once the causes of nocturnal hypoxia have been evaluated, we do not recommend routinely offering oxygen therapy for the treatment of isolated nocturnal hypoxia. (Grade A)
29	We recommend that an admission and discharge bundle be applied to all patients admitted acutely with an exacerbation of COPD. (Expert Opinion)

Appendix 2: Search terms

The search terms for the economic search were adapted from the clinical search undertaken in the systematic review of pulmonary rehabilitation by Wuytack et al.[17] and combined with modified SIGN economic filters.[18] The search terms for the Medline and Embase databases are presented below.

Table A2.1: Clinical search terms

Medline (via Ovid)	
1.	Pulmonary Disease, Chronic Obstructive.sh.
2.	Bronchitis, Chronic.sh.
3.	Lung Diseases, Obstructive.sh.
4.	emphysema*.ti. or emphysema*.ab.
5.	(chronic* adj3 bronchiti*).af.
6.	(obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).ti. or (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).ab.
7.	copd.ti. or copd.ab. or coad.ti. or coad.ab. or cobd.ti. or cobd.ab. or aecopd.ti. or aecopd.ab.
8.	1 or 2 or 3 or 4 or 5 or 6 or 7
9.	..l/ 8 en=y and hu=y
Embase	
1.	'chronic obstructive lung disease'/exp OR 'chronic obstructive lung disease'
2.	'chronic bronchitis'/exp
3.	'chronic lung disease'/exp
4.	emphysema:ti,ab
5.	(chronic* NEAR/3 bronchiti*):ab,ti
6.	(obstruct* NEAR/3 (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)):ti,ab
7.	copd:ti,ab OR coad:ti,ab OR cobd:ti,ab OR aecopd:ti,ab
8.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
9.	#8 AND 'human'/de AND ('article'/it OR 'article in press'/it OR 'conference paper'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it) AND [english]/lim

Table A2.2: Economic filters

Medline (via Ovid)	
1.	ECONOMICS/
2.	"Costs and Cost Analysis"/
3.	"Cost Allocation"/
4.	Cost-Benefit Analysis/
5.	"Cost Control"/
6.	"Cost Savings"/
7.	"Cost of Illness"/
8.	"Cost Sharing"/
9.	"Deductibles and Coinsurance"/
10.	Medical Savings Accounts/

Medline (via Ovid)	
11.	Health Care Costs/
12.	Direct Service Costs/
13.	Drug Costs/
14.	Employer Health Costs/
15.	Hospital Costs/
16.	Health Expenditures/
17.	Capital Expenditures/
18.	"Value of Life"/
19.	exp economics, hospital/
20.	exp economics, medical/
21.	Economics, Nursing/
22.	Economics, Pharmaceutical/
23.	exp "fees"/ and "charges "/
24.	exp budgets/
25.	(low adj cost).mp
26.	(high adj cost).mp.
27.	(health?care adj cost?).mp.
28.	fiscal.ti. or fiscal.ab. or funding.ti. or funding.ab. or financial.ti. or financial.ab. or finance.ti. or finance.ab.
29.	(cost adj estimate$).mp
30.	(cost adj variable).mp
31.	(unit adj cost$).mp.
32.	economic$.ti. or economic$.ab. or pharmacoeconomic$.ti. or pharmacoeconomic$.ab. or price$.ti. or price$.ab. or pricing.ti. or pricing.ab.
33.	Or/1-32
34.	..l/ 33 en=y and hu=y

Embase	
1.	'Health economics'/exp
2.	Socioeconomics/
3.	'Cost benefit analysis'/
4.	'Cost effectiveness analysis'/
5.	'Cost minimi?ation analysis'/
6.	'Cost of illness'/
7.	'Cost control'/
8.	'Economic aspect'/
9.	'Financial management'/
10.	'Health care cost'/
11.	'Health care financing'/
12.	'hospital cost'/
13.	(fiscal or financial or finance or funding):ti,ab.

Embase	
14.	((cost NEXT/1 variable*) OR (cost NEXT/1 estimate*) OR (unit NEXT/1 cost*)):ab,ti
15.	or/1-14
16.	#15 AND 'human'/de AND ('article'/it OR 'article in press'/it OR 'conference paper'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'review'/it) AND [english]/lim

Appendix 3: Grey literature search

The following electronic sources were searched for economic evaluations relevant to the research questions of this systematic review:

- Centre for Health Economics and Policy Analysis (CHEPA) ; Available from http://www.chepa.org/
- Cost Effectiveness Analysis Registry; Available from http://healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx
- HTAi vortal; Available from https://www.htai.org/index.php?id=579
- Google Scholar and Google; Available from https://scholar.google.com/, https://www.google.ie
- Health Service Executive (HSE); Available from https://www.hse.ie/eng/
- Health Information and Quality Authority (HIQA); Available from https://www.hiqa.ie/
- Health Research Board (HRB) Ireland; Available from http://www.hrb.ie/home/
- Institute of Health Economics (Alberta Canada); Available from https://www.ihe.ca/
- Lenus; Available from http://www.lenus.ie/hse/
- National Coordinating Centre for Health Technology Assessment (NCCHTA) ; Available from https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/
- National Centre for Pharmacoeconomics (NCPE); Available from http://www.ncpe.ie/
- National Institute for Health and Clinical Excellence (NICE); Available from https://www.nice.org.uk/
- NHS Evidence database (UK); Available from https://www.evidence.nhs.uk/
- Open Grey; Available from http://www.opengrey.eu/
- World Health Organization (WHO); Available from http://www.who.int/en/

Appendix 4: Systematic review appraisal checklist

Table A4: Systematic review appraisal checklist

Checklist item	Yes/No/Unclear
Is a well-defined research question posed? Is the economic importance of the question clear?	
Did the research questions and inclusion criteria for the review include the components of PICO?	
Did the review contain an explicit statement that the review methods were established prior to the conduct of the review? Did the report justify any significant deviations from the protocol?	
Did the review authors explain their selection of the study designs for inclusion in the review?	
Did the review authors conduct a comprehensive literature search?	
Did the review authors perform study selection in duplicate?	
Did the review authors perform data extraction in duplicate?	
Did the review authors provide a list of excluded studies and justify the exclusions?	
Did the review authors describe the included studies in adequate detail? Were the characteristics of included studies presented sufficiently?	
Did the review authors use a satisfactory technique for assessing the quality individual studies that were included in the review? Where studies are considered low quality, were the reasons clear?	
Did the review consider the transferability of the included studies? Is the generalisability of the included studies discussed?	
Did the review authors account for the quality of the primary studies when interpreting/discussing the results of the review? Was the scientific quality of the included studies used appropriately?	
Did the review authors provide a satisfactory explanation for, and discussion of, variation observed in the results of the review? Have the authors explicitly discussed the impact of different decision rules across jurisdictions when making comparisons on the basis of incremental costs and effects?	
Did the review authors discuss the methods employed in the included studies for dealing with uncertainty? Did the authors report the key drivers of uncertainty from the included studies?	
Does the review provide information of relevance to policymakers?	
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	

Appendix 5: Protocol deviations

The methods used during the course of this systematic review deviated from the registered protocol as follows:

- An economic review question was included in the protocol to investigate the cost-effectiveness of lung volume reduction surgery only. However, due to the identification of potentially relevant studies during the screening stage, it was agreed with the GDG to deviate from the protocol and include studies that assessed minimally invasive lung volume reduction techniques (endobronchial valve therapy and endobronchial coil treatment). Additionally, the comparator for this review question was expanded from 'no surgery' to 'no surgery or delayed surgery'.
- The protocol stated that where systematic reviews of economic evaluations were identified, these would be appraised rather than the original economic evaluations and that economic evaluations would be excluded where a systematic review was identified. This was amended to reflect that systematic reviews needed to be of high quality and contain more than one study for potential inclusion.[33]

Appendix 6: Excluded studies

Table A6.1: Systematic reviews excluded from narrative synthesis (see Appendix 7)

No.	Reference
1.	Einarson TR, Bereza BG, Nielsen TA, Van Laer J, Hemels ME. Systematic review of models used in economic analyses in moderate-to-severe asthma and COPD. Journal of Medical Economics. 2016;19(4):319-55.
2.	Health Information and Quality Authority. Health technology assessment of chronic disease self-management support interventions. HIQA, 2015.
3.	Mauskopf JA, Baker CL, Monz BU, Juniper MD. Cost effectiveness of tiotropium for chronic obstructive pulmonary disease: a systematic review of the evidence. Journal of Medical Economics. 2010;13(3):403-17.
4.	National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre; 2010. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English.
5.	Roine E, Roine RP, Räsänen P, Vuori I, Sintonen H, Saarto T. Cost-effectiveness of interventions based on physical exercise in the treatment of various diseases: A systematic literature review. International Journal of Technology Assessment in Health Care. 2009;25(4):427-54.
6.	Rutten-van Molken MP, Goossens LM. Cost effectiveness of pharmacological maintenance treatment for chronic obstructive pulmonary disease: a review of the evidence and methodological issues. Pharmacoeconomics. 2012;30(4):271-302.
7.	van der Schans S, Goossens LM, Boland MR, Kocks JW, Postma MJ, van Boven JF, et al. Systematic Review and Quality Appraisal of Cost-Effectiveness Analyses of Pharmacologic Maintenance Treatment for Chronic Obstructive Pulmonary Disease: Methodological Considerations and Recommendations. Pharmacoeconomics. 2017;35(1):43-63.
8.	Chandra, K., et al. (2012). "Cost-effectiveness of interventions for chronic obstructive pulmonary disease (COPD) using an Ontario policy model." Ontario Health Technology Assessment Series 12(12): 1-61.

Table A6.2: Costing studies excluded due to availability of economic evaluations

No.	Reference
1.	Aimonino Ricauda N, Tibaldi V, Leff B, Scarafiotti C, Marinello R, Zanocchi M, et al. Substitutive "hospital at home" versus inpatient care for elderly patients with exacerbations of chronic obstructive pulmonary disease: a prospective randomized, controlled trial. Journal of the American Geriatrics Society. 2008;56(3):493-500.
2.	Kozma CM, Paris AL, Plauschinat CA, Slaton T, Mackowiak JI. Comparison of resource use by COPD patients on inhaled therapies with long-acting bronchodilators: a database study. BMC Pulmonary Medicine. 2011;11:61.
3.	Rasekaba TM, Williams E, Hsu-Hage B. Can a chronic disease management pulmonary rehabilitation program for COPD reduce acute rural hospital utilization? Chronic Respiratory Disease. 2009;6(3):157-63.
4.	Wong EM, Lo SM, Ng YC, Lee LL, Yuen TM, Chan JT, et al. Cost-effectiveness of 'Program We Care' for patients with chronic obstructive pulmonary disease: A case-control study. International emergency nursing. 2016;27:37-41.

Table A6.3: Studies excluded due to study design (for example, no economic analysis)

No.	Reference
1.	Akwe J, Steinbach S, Murphy JJ. A Review of the Non Pharmacologic Management of Chronic Obstructive Pulmonary Disease. American Journal of Pulmonary and Respiratory Medicine. 2016;1(1):11-27.
2.	Al Moamary MS. Health care utilization among chronic obstructive pulmonary disease patients and the effect of pulmonary rehabilitation. Medical Principles and Practice. 2010;19(5):373-8.
3.	Bakeer M, Abdelgawad TT, El-Metwaly R, El-Morsi A, El-Badrawy MK, El-Sharawy S. Low cost biological lung volume reduction therapy for advanced emphysema. International Journal of COPD. 2016;11:1793-800.
4.	Blough DK, Ramsey S, Sullivan SD, Yusen R. The impact of using different imputation methods for missing quality of life scores on the estimation of the cost-effectiveness of lung-volume-reduction surgery. Health Economics. 2009;18(1):91-101.
5.	Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax. 2013;68(SUPPL. 2):ii1-ii30.
6.	Brennan V, Cahill T, Byrne N, Breen DP. Oxygen Therapy in the Elderly: When Nasal Cannula Is Not Enough. Current Geriatrics Reports. 2016;5(4):283-8.
7.	Breunig IM, Shaya FT, Scharf SM. Delivering cost-effective care for COPD in the USA: recent progress and current challenges. Expert Review of Pharmacoeconomics & Outcomes Research. 2012;12(6):725-31.
8.	Chen YJ, Makin C, Bollu VK, Navaie M, Celli BR. Exacerbations, health services utilization, and costs in commercially-insured COPD patients treated with nebulized long-acting beta2-agonists. Journal of Medical Economics. 2016;19(1):11-20.
9.	Donner CF, Virchow JC, Lusuardi M. Pharmacoeconomics in COPD and inappropriateness of diagnostics, management and treatment. Respiratory Medicine. 2011;105(6):828-37.
10.	D'Urzo AD, Maleki-Yazdi MR, McIvor RA. Evolving therapies in chronic obstructive pulmonary disease. Clinical Practice. 2014;11(3):307-25.
11.	Eaton T, Young P, Ferguson W, Moodie L, Zeng I, O'Kane F, et al. Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. Respirology. 2009;14(2):230-8.
12.	Echevarria C, Brewin K, Horobin H, Bryant A, Corbett S, Steer J, et al. Early Supported Discharge/Hospital At Home For Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Review and Meta-Analysis. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2016;13(4):523-33.
13.	Evans R, Brutsche M, Busca R, Deslee G, de Soyza A, Fellrath JM, et al. Quantifying patient centered outcomes associated with the use of bilateral endobronchial coil treatment in patients with severe emphysema. Current Medical Research and Opinion. 2018:1-6.
14.	Hobbs K, Brown D. Consider adding this drug to fight COPD that's severe. Journal of Family Practice. 2012;61(7):414-6.
15.	Lindenauer PK, Stefan MS, Shieh MS, Pekow PS, Rothberg MB, Hill NS. Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease. JAMA Internal Medicine. 2014;174(12):1982-93.
16.	Matsumura T, Takarada K, Oki Y, Fujimoto Y, Kaneko H, Ohira M, et al. Long-term Effect of Home Nursing Intervention on Cost and Healthcare Utilization for Patients with Chronic Obstructive Pulmonary Disease: A Retrospective Observational Study. Rehabilitation Nursing Journal. 2015;40(6):384-9.
17.	National Clinical Guideline Centre. Chronic obstructive pulmonary disease: Evidence Update February 2012. 5 ed. NICE; 2012.
18.	National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease: beclometasone/formoterol (Fostair). Evidence summary. NICE, 2014 16 September 2014. Report No.: ESNM47.

No.	Reference
19.	National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease: umeclidinium/vilanterol combination inhaler (Anoro Ellipta). Evidence summary. NICE, 2014 6 November 2014. Report No.: ESNM49.
20.	National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease: tiotropium/olodaterol (Spiolto Respimat). Evidence summary. NICE, 2016 10 May 2016. Report No.: ESNM7.
21.	OHTAS COPD Working Group. Prophylactic Antibiotics for Individuals With Chronic Obstructive Pulmonary Disease (COPD): A Rapid Review. Ontario Health Technology Assessment Series. 2015.
22.	Parikh R, Shah TG, Tandon R. COPD exacerbation care bundle improves standard of care, length of stay, and readmission rates. International Journal of Copd. 2016;11:577-83.
23.	Patel N, DeCamp M, Criner GJ. Lung transplantation and lung volume reduction surgery versus transplantation in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society. 2008;5(4):447-53.
24.	Peng L, Ren PW, Liu XT, Zhang C, Zuo HX, Kang DY, et al. Use of noninvasive ventilation at the pulmonary infection control window for acute respiratory failure in AECOPD patients A systematic review and meta-analysis based on GRADE approach. Medicine (United States). 2016;95(24).
24.	Shah AA, D'Amico TA. Lung volume reduction surgery for the management of refractory dyspnea in chronic obstructive pulmonary disease. Current Opinion in Supportive & Palliative Care. 2009;3(2):107-11.
26.	Wise J. Coils implanted into lungs show promise for emphysema. BMJ (Online). 2016;352.
27.	Zafari Z, Bryan S, Sin DD, Conte T, Khakban R, Sadatsafavi M. A Systematic Review of Health Economics Simulation Models of Chronic Obstructive Pulmonary Disease. Value in Health. 2017;20(1):152-62.
28.	Zahid I, Sharif S, Routledge T, Scarci M. Is lung volume reduction surgery effective in the treatment of advanced emphysema? Interactive Cardiovascular and Thoracic Surgery. 2011;12(3):480-6.

Table A6.4: Studies excluded due to full text unavailability (including letters, commentaries, editorials, abstracts, protocols and conference papers)

No.	Reference
1.	Broder MS, Raimundo K, Ngai KM, Chang E, Griffin NM, Heaney LG. Cost and health care utilization in patients with asthma and high oral corticosteroid use. Annals of Allergy, Asthma, & Immunology. 2017;118(5):638-9.
2.	Grouse L. Cost-effective medicine vs. the medical-industrial complex. Journal of Thoracic Disease. 2014;6(9):E203-E6.
3.	Holland AE, Mahal A, Hill CJ, Lee AL, Burge AT, Moore R, et al. Benefits and costs of home-based pulmonary rehabilitation in chronic obstructive pulmonary disease - a multi-centre randomised controlled equivalence trial. BMC Pulmonary Medicine. 2013;13:57.
4.	Hopkinson N. Pulmonary rehabilitation for COPD. Tanaffos. 2017;16:S7-S8.
5.	Hopkinson NS. Lung volume reduction in advanced emphysema. Tanaffos. 2017;16:S9-S11.
6.	Murphy PB, Brueggenjuergen B, Reinhold T, Fusfeld L, Gu Q, Goss T, et al. Cost-Effectiveness of Home Oxygen Therapy-Home Mechanical Ventilation (HOT-HMV) for the Treatment of Chronic Obstructive Pulmonary Disease (COPD) with Chronic Hypercapnic Respiratory Failure Following an Acute Exacerbation of COPD in the United Kingdom (UK). A102 Determinants of outcomes and high-value care in COPD 2018. p. A2517-A.
7.	Neyt M, Devriese S, Thiry N, Van den Bruel A. Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions. BMC Pulmonary Medicine. 2010;10:47.
8.	Pomares Amigó X, Montón Soler C. Preventing COPD exacerbations: Budget impact of a respiratory day hospital and long-term azithromycin therapy. Respiratory Medicine. 2014;108(7):1064.
9.	Utens CM, Goossens LM, Smeenk FW, van Schayck OC, van Litsenburg W, Janssen A, et al. Effectiveness and cost-effectiveness of early assisted discharge for chronic obstructive pulmonary disease exacerbations: the design of a randomised controlled trial. BMC Public Health. 2010;10:618.

10.	van Agteren JE, Hnin K, Grosser D, Carson KV, Smith BJ. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2017;2017(2).
11.	van Agteren JEM, Carson KV, Tiong LU, Smith BJ. Lung volume reduction surgery for diffuse emphysema. Cochrane Database of Systematic Reviews. 2016;2016(10).

Table A6.5: Studies excluded due to English language restriction

No.	Reference
1.	Álvarez FV, Zabaleta RM, Solves JJM, Corbella EC, Díaz Lobato S, González-Torralba F, et al. What not to do in COPD. Methodological analysis. Revista de Patologia Respiratoria. 2016;19(3):76-82.
2.	Boland M, Kruis A, Tsiachristas A, Assendelft P, Gussekloo J, Blom C, et al. Is integrated COPD care cost-effective? Huisarts en Wetenschap. 2016;59(8):343-5.
3.	Braceras L, Elizondo I. Cost minimization and budget impact analyses in the Basque Country for the treatment of moderate-to-severe chronic obstructive pulmonary disease using aclidinium bromide instead of tiotropium bromide. Pharmacoeconomics - Spanish Research Articles. 2015;12(2):39-45.
4.	Mayoralas Alises S, Huerta A, Parrondo J. Healthcare costs avoided with fluticasone furoate/vilanterol due to the reduction in the rate of exacerbations in patients with chronic obstructive pulmonary disease. Pharmacoeconomics:Spanish Research Articles. 2016;13(3):97-104.

Table A6.6: Studies excluded due to cost-effectiveness results reported elsewhere

No.	Reference
1.	Degani N, Brener S, Chambers A, Franek J, Kaulback K, McMartin K, et al. Optimizing chronic disease management in the community (outpatient) setting (OCDM): An evidentiary framework. Ontario Health Technology Assessment Series. 2013;13(3):1-78.
2.	McCurdy BR, Bornstein M, Franek J, Kaulback K, Sehatzadeh S, Sikich N, et al. Chronic Obstructive Pulmonary Disease (COPD) Evidentiary Framework. Ontario Health Technology Assessment Series. 2012;12(2):1-97.
3.	McCurdy BR. Noninvasive positive pressure ventilation for acute respiratory failure patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ontario Health Technology Assessment Series. 2012;12(8):1-102.
4.	McCurdy BR. Hospital-at-home programs for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ontario Health Technology Assessment Series. 2012;12(10):1-65.
5.	OHTAS COPD Working Group. Noninvasive positive pressure ventilation for chronic respiratory failure patients with stable chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ontario Health Technology Assessment Series. 2012;12(9):1-51.
6.	OHTAS COPD Working Group. Long-term oxygen therapy for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. Ontario Health Technology Assessment Series. 2012;12(7):1-64.
7.	OHTAS COPD Working Group. Pulmonary rehabilitation for patients with chronic pulmonary disease (COPD): an evidence-based analysis. Ontario Health Technology Assessment Series. 2012;12(6):1-75.

Table A6.7: Studies excluded due to ineligible intervention or comparator

No.	Reference
1.	Abroug F, Ouanes-Besbes L, Hammouda Z, Benabidallah S, Dachraoui F, Ouanes I, et al. Noninvasive ventilation with helium–oxygen mixture in hypercapnic COPD exacerbation: aggregate meta-analysis of randomized controlled trials. Annals of Intensive Care. 2017;7(1).

No.	Reference
2.	Achelrod D, Welte T, Schreyogg J, Stargardt T. Costs and outcomes of the German disease management programme (DMP) for chronic obstructive pulmonary disease (COPD)-A large population-based cohort study. Health Policy. 2016;120(9):1029-39.
3.	Aikenhead A, Knai C, Lobstein T. Effectiveness and cost-effectiveness of paediatric bariatric surgery: A systematic review. Clinical Obesity. 2011;1(1):12-25.
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Appendix 7: Summary of systematic reviews

Systematic reviews of economic evaluations were appraised to identify high-quality reviews which could be used to summarise the existing literature.

A7.1 Pulmonary rehabilitation programmes

Three systematic reviews assessing the cost-effectiveness of pulmonary rehabilitation programmes (PRPs) published during the search period (1 January 2008 to 19 June 2018) — by Chandra et al.,[25] the Health Information and Quality Authority (HIQA)[26] and Roine et al.[27] — were identified. Following critical appraisal (see Appendix 8), the HIQA review was the only review of sufficiently high quality to be included.

The systematic review by HIQA was conducted as part of a national health technology assessment (HTA) examining the clinical and cost-effectiveness of self-management support interventions across a range of chronic diseases which included COPD (amongst others such as diabetes and asthma). The review identified six relevant studies. Four of these studies had been identified in our search,[25, 41, 42, 45] and two were published prior to 2008.[52, 63] Upon further investigation, the two additional studies did not meet the eligibility for our systematic review due to a pre- and post-intervention costing design,[52] and a study population that comprised adults with chronic disabling pulmonary pathologies as well as adults with COPD.[63] As the HIQA review was based on a mixture of included and excluded studies coupled with the fact that we had identified two additional studies for inclusion,[39, 40] it was deemed more appropriate to report the primary economic evaluations identified by our search.

A7.2 Long-acting bronchodilators and inhaled corticosteroids

Five systematic reviews assessing the cost-effectiveness of long-term bronchodilators published during our search period (1 January 2008 to 19 June 2018) — by Einarson et al.,[28] Mauskopf et al.,[29] the National Clinical Guideline Centre (NCGC) of the National Institute for Health and Care Excellence (NICE),[30] Rutten-van Molken et al.[31] and Van der Schans et al.[32] — were identified. Following critical appraisal (see Appendix 8), it was found that the review by Einarson et al. was the only review of sufficient quality for inclusion.

Einarson et al. conducted a systematic review to summarise the types and outcomes of economic models used to analyse the cost-effectiveness of drugs treating moderate-to-severe asthma and COPD. However, following further investigation of the review,[28] only one included study was applicable to our systematic review.[115] Therefore, it was more appropriate to report the primary economic evaluations identified by our search.

Appendix 8: Methodological quality of systematic reviews

Table A8.1: Risk of bias of systematic reviews of cost-effectiveness of pulmonary rehabilitation programmes

Item	Chandra (2012)[25]	HIQA (2015)[197]	Roine (2009)[27]
Is a well-defined research question posed? Is the economic importance of the question clear?	Yes	Yes	No
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	No
Did the review contain an explicit statement that the review methods were established prior to the conduct of the review? Did the report justify any significant deviations from the protocol?	No	No	No
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
Did the review authors conduct a comprehensive literature search?	Yes	Yes	Yes
Did the review authors perform study selection in duplicate?	Unclear	Yes	Yes
Did the review authors perform data extraction in duplicate?	Unclear	Yes	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No
Did the review authors describe the included studies in adequate detail? Were the characteristics of included studies presented sufficiently?	No	Yes	No
Did the review authors use a satisfactory technique for assessing the quality individual studies that were included in the review? Where studies are considered low quality, were the reasons clear?	Unclear	Yes	Yes
Did the review consider the transferability of the included studies? Is the generalisability of the included studies discussed?	Unclear	Yes	No
Did the review authors account for the quality of the primary studies when interpreting/discussing the results of the review? Was the scientific quality of the included studies used appropriately?	Unclear	Yes	No
Did the review authors provide a satisfactory explanation for, and discussion of, variation observed in the results of the review? Have the authors explicitly discussed the impact of different decision rules across jurisdictions when making comparisons on the basis of incremental costs and effects?	No	No	No
Did the review authors discuss the methods employed in the included studies for dealing with uncertainty? Did the authors report the key drivers of uncertainty from the included studies?	No	No	No
Does the review provide information of relevance to policymakers?	Yes	Yes	No
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	No	No

Key: HIQA – Health Information and Quality Authority; PICO – population, intervention, comparator, outcomes.

Table A8.2: Risk of bias of systematic reviews of cost-effectiveness of long acting bronchodilators and inhaled corticosteroids

Item	Einarson (2016)[28]	NCGC (2010)[121]	Van der Schans (2017)[32]	Mauskopf (2010)[29]	Rutten-van Molken (2012)[31]
Is a well-defined research question posed? Is the economic importance of the question clear?	Yes	Yes	Yes	Yes	Yes
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	No	No	No
Did the review contain an explicit statement that the review methods were established prior to the conduct of the review? Did the report justify any significant deviations from the protocol?	No	Yes	No	No	No
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	No	No	Yes
Did the review authors conduct a comprehensive literature search?	Yes	Yes	Yes	Yes	Yes
Did the review authors perform study selection in duplicate?	Yes	No	No	No	No
Did the review authors perform data extraction in duplicate?	Yes	No	No	No	No
Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No	No	No
Did the review authors describe the included studies in adequate detail? Were the characteristics of included studies presented sufficiently?	Yes	No	Yes	No	Yes*
Did the review authors use a satisfactory technique for assessing the quality individual studies that were included in the review? Where studies are considered low quality, were the reasons clear?	No	No	Yes	No	No
Did the review consider the transferability of the included studies? Is the generalisability of the included studies discussed?	No	Yes	Yes	No	No
Did the review authors account for the quality of the primary studies when interpreting/discussing the results of the review? Was the scientific quality of the included studies used appropriately?	Yes	Yes	Yes	No	No
Did the review authors provide a satisfactory explanation for, and discussion of, variation observed in the results of the review? Have the authors explicitly discussed the impact of different decision rules across jurisdictions when making comparisons on the basis of incremental costs and effects?	Yes	No	Yes	Yes	Yes
Did the review authors discuss the methods employed in the included studies for dealing with uncertainty? Did the authors report the key drivers of uncertainty from the included studies?	Yes	Yes	Yes	Yes	No
Does the review provide information of relevance to policymakers?	Yes	Yes	Yes	Yes	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No	Yes	Yes	Yes

Key: NCGC – National Clinical Guideline Centre; PICO – population, intervention, comparator, outcomes.

*Authors provided a link to a supplementary appendix which outlined the characteristics. However, the link no longer worked. This was outside the control of the authors and therefore it was assessed they fulfilled this criteria.

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