Evidence-based Commissioning Collaboration

Domiciliary non-invasive ventilation for patients with chronic obstructive pulmonary disease: policy options

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Date completed: 24 March 2006

Expiry date:

Discussed at Workshop of the Evidence-based Commissioning Collaboration on 3 April 2006

Publication information

Trent Research and Development Support Unit is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield. Members of staff in the Sheffield Unit, based in the School of Health and Related Research (ScHARR), have been engaged in reviewing the effectiveness and cost-effectiveness of health care interventions in support of the National Institute for Health and Clinical Excellence (NICE).

In order to share expertise on this work, we have set up a wider collaboration, InterTASC, with units in other regions. These are Southampton Health Technology Assessment Centre, University of Southampton; Aberdeen Health Technology Assessment Group, University of Aberdeen; Liverpool Reviews & Implementation Group, University of Liverpool; Peninsular Technology Assessment Group, University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration, University of Birmingham.

The Evidence-based Commissioning Collaboration (EBCC) is made up of four commissioning consortia - The North East Yorkshire & North Lincolnshire Primary Care Organisation (NEYNL), The North Derbyshire, South Yorkshire & Bassetlaw Commissioning Consortium (NORCOM), The Trent Commissioning Consortium (TrentCOM) and The West Yorkshire Primary Care Organisation (WYPCO) - which, on behalf of PCTs in their areas, are working with the School of Health and Related Research (ScHARR). ScHARR is based in the University of Sheffield and houses the northern arm of the Trent Research and Development Support Unit.

The objective of the Collaboration is to share research knowledge about the effectiveness and cost-effectiveness of service interventions to inform the commissioning process. These will usually be interventions which are not likely to be addressed by NICE in the near future. The main principle on which the arrangement is based acknowledges that PCTs have continually to review evidence on particular technologies in order to determine their commissioning priorities. Since different PCTs will be looking at the same issues, there are clear benefits and economies of scale through the avoidance of duplication of evidence reviews.

The choice of topics is determined collectively by the PCTs through their commissioning Consortia.

ScHARR will provide the capacity which the PCTs lack in evidence retrieval and assessment/review and in economic analysis.

As part of the process, a presentation of research evidence will usually be made to a workshop of the Collaboration on particular interventions. Clinicians and DPHs from the PCTs represented will be invited to take part in the discussions.

Contributions

David Black (Director of Public Health, Chesterfield PCT) conceived the review; Paul Sutcliffe (Research Fellow, ScHARR), Simon Dixon (Senior Lecturer, ScHARR), David Black, Stephen Crooks (Consultant in Respiratory Medicine, Chesterfield Royal Hospital) designed the review; Paul Sutcliffe coordinated the review.

Paul Sutcliffe and Simon Dixon developed the search strategy; Anna Wilkinson (Information Officer, ScHARR) and Paul Sutcliffe undertook searches, Paul Sutcliffe screened the search results; organised the retrieval of papers; screened retrieved papers against inclusion criteria; appraised the quality of papers; abstracted data from papers; and provided additional data about the papers.

Paul Sutcliffe and Simon Dixon wrote the executive summary. Paul Sutcliffe wrote the background section. Paul Sutcliffe wrote the clinical effectiveness section and performed the meta-analysis on the RCTs. Mike Holmes (Operational Research Analyst, ScHARR) and Simon Dixon wrote the cost effectiveness section.

Mark Elliott (Consultant in Respiratory Medicine, St James's University Hospital) and Stephen Crooks provided a methodological and clinical perspective on the evidence and data; David Black provided a policy and consumer perspective on the data.

All responsibility for the contents of the report remains with the authors.

The authors also wish to thank Andrea Shippam and Pat Holmes for their help in preparing and formatting the report.

Conflicts of Interest

Source of funding:
This report was commissioned by the Evidence-based Commissioning Collaboration.

Relationship of reviewer(s) with sponsor
None

Contents

	Executive Summary	7
	Abbreviations	11
	Definition of terms	12
1	Aims	13
2	Background	14
2.1	Types of COPD	14
2.2	Treating patients with COPD	15
2.3	Clinical need for guidelines	15
2.4	Clinical management	15
2.5	Ventilation	16
2.6	Further considerations	17
2.7	Equipment and Resources	19
2.8	Costs	21
3	Summary of literature concerning domiciliary non-invasive ventilation for patients with COPD	22
3.1	Reviews	22
3.2	Summary of key reviews	29
3.3	Conclusions	32
4	Review of published non-RCT studies	33
4.1	Non-RCT evidence	49
4.2	Conclusion	52
5	Review of RCT evidence	53
5.1	Search strategy	53
5.2	Description on RCTs	59
5.3	Results	64
5.4	Summary	68
5.5	Data extraction	68
5.6	Outcome measures	70
5.7	Hospitalisations	72
5.8	Meta-analyses	74
5.9	Summary of meta-analysis	77
5.10	Discussion	77
5.11	Limitations of RCT evidence	78
5.12	Further considerations	79
5.13	Which patients are likely to benefit?	79
5.14	Adequacy of ventilation	80
5.15	Number of hours on NPPV	81
5.16	Length of ventilation	81
5.17	Conclusions	81
6	Cost-effectiveness modelling	83
6.1	Introduction	83
6.2	Methods	83
6.3	Results	87
6.4	Discussion	89
7	References	105

Tables

Table 1	Systematic reviews, literature reviews and editorials which provide information about non-invasive ventilation in domiciliary setting for COPD patients	23
Table 2	Contraindications for non-invasive ventilation and indications for invasive ventilation	30

Table 3	Non-RCTs concerned with non-invasive ventilation in domiciliary setting for COPD patients	35
Table 4	Different patient groups	49
Table 5	Types of interventions	50
Table 6	Outcome measures	51
Table 7	Electronic bibliographic and review databases searched	54
Table 8	RCTs excluded from inclusion in the meta-analysis	56
Table 9	RCTs concerned with non-invasive ventilation in domiciliary setting for COPD patients	61
Table 10	Full range of outcome measures reported	65
Table 11	Randomised controlled trial quality assessment scale (Based on NHS CRD Report No. 4)	67
Table 12	Detailed extraction of RCTs outcomes	69
Table 13	Total non-completers	71
Table 14	Mortality	71
Table 15	Compliance rates	72
Table 16	Total hospital admissions	73
Table 17	Hospital admissions due to acute exacerbations	73
Table 18	Costs from Tuggey study	84
Table 19	Utilities	85
Table 20	Model validation	86
Table 21	Hospitalisation parameters	87
Table 22	SGRQ scores	87
Table 23	Cost-effectiveness results	87
Table 24	Length of ICU stay increased to two days	87

Figures

Figure 1	Classification of severity	15
Figure 2	Potential advantages of NPPV over endotracheal intubation	17
Figure 3	Guidelines provided by the American College of Chest Physicians (2005)	18
Figure 4	Equipment and supplies for Ventilator-Assisted Patients in home	20
Figure 5	Additional equipment and supplies for Ventilator-Assisted Patients in home	21
Figure 6	Hierarchy of study designs for questions about effectiveness of healthcare interventions	34
Figure 7	Relationship between SGRG and EQ-5D	85
Figure 8	Incremental cost-effectiveness plane	88
Figure 9	Cost-effectiveness acceptability curve	88

Appendices

Appendix 1	Additional background information concerning treatment	91
Appendix 2	Search strategies and databases	94
Appendix 3	Ongoing clinical trials concerning the evaluation of NIV in the domiciliary setting for patients with COPD	101
Appendix 4	Studies concerned with the economic analysis of non-invasive ventilation in domiciliary setting for COPD patients	103

Executive Summary

Aims:
The report aimed to summarise evidence concerned with domiciliary non-invasive ventilation (NIV) for chronic obstructive pulmonary disease (COPD) and evaluate which subtypes of patients would be most suitable for this form of treatment.

In order to meet this aim, the following objectives were set out:
- Undertake a systematic review of evidence concerned with clinical effectiveness and cost-effectiveness for the use of domiciliary NIV in patients with COPD in the stable/chronic state
- Summarise the effects of NIV in patients with COPD classified by the design, level of evidence and COPD subtype
- Discuss the outcomes of studies
- Summarise and update previous meta-analyses of randomised controlled trials (RCTs) which investigated the effects of non-invasive positive pressure ventilation (NPPV) in stable patients with COPD
- Estimate the cost-effectiveness of domiciliary NIV in patients with COPD in the stable/chronic state

Background:
Short-term non-invasive positive pressure ventilation (NPPV) is considered by many to be an accepted management approach for patients with acute hypercapnia. At present it remains unclear whether domiciliary NPPV for long term use can also be useful in patients with stable COPD. These patients often suffer from dyspnoea that can impair health-related quality of life (QOL). It is important to evaluate the optimal treatments for the various subgroups of patients with COPD.

The National Institute of Health and Clinical Excellence (NICE) have provided recommendations concerning the management of stable patients, management of acute exacerbations and prevention of progression of the disease. These state that COPD is the fifth commonest cause of death in England and Wales. It accounts for around 28,000 deaths each year. Britain has one of the highest death rates from COPD in Europe. An estimated 600,000 patients in the UK are diagnosed COPD and many remain undiagnosed. An estimated one in eight hospital admissions are due to COPD. There is an increase in consultation rate in general practice with age from 417 (aged 45-64) per 10,000 population per year to 1032 (aged 75-84) per year per 10,000 population.

Clinical effectiveness
We began by reporting the previous systematic reviews, literature reviews and editorials which provide information about non-invasive ventilation in domiciliary setting for patients with COPD. We then provide a thorough review of the published non-RCT evidence. We finally provided a summary and meta-analysis of RCT evidence.

a) Reviews
A total of nineteen relevant published articles were found: 11 literature review; five editorials; one systematic review and two meta-analyses. Each differed in the degree of relevance in terms of patient populations and types of intervention.

The key points reported were:

- Concerns about the high dropout and poor compliance rates in the RCTs
- Domiciliary NIV is unlikely to be effective in most stable COPD patients, particularly if they are normocapnic
- RCTs with larger sample sizes are needed to evaluate the impact on health economics, mortality, QOL and morbidity
- Subgroups of patients with poor tolerance of LTOT, marked nocturnal hypoventilation, severe hypercapnia and/or recurrent infective exacerbations could benefit from domiciliary NIV

b) Non-RCT evidence

This section provided a comprehensive and thorough coverage of the literature concerning domiciliary NIV for the treatment of patients with COPD. A total of 37 studies were identified.

The range of different patient groups included in the non-RCT studies varied considerably. Twenty different terms used to describe the patient groups were found within the 37 studies. The majority of studies used patients with various respiratory conditions, all of which did included COPD. Several studies referred to patients with hypercapnia, severe and stable COPD. Thirteen different terms were reported to describe the types of intervention involving NIV. Differences were noted in the length of time each intervention was given and the time of day (day or night). Several studies also reported the use of supplementary oxygen or LTOT.

Many of the studies did not use a comparison group. The majority of studies assessed patients at different time points or reported individual cases. Only one study compared the outcome of episodes of acute exacerbation of COPD treated with mask intermittent positive-pressure ventilation (MIPPV) in patients with home MIPPV and in patients without home ventilatory support. A total of 62 different outcome measures were reported. The most commonly used measures were the assessment of ABG, breathing patterns and lung function. A variety of different types of study design were reported in this section. The majority of studies reported in this section involved case series

In summary, the non-RCT studies have shown that in selective groups of patients (e.g., severe hypercapnia) NPPV can significantly improve gas-exchange. However, despite these positive findings, one must be careful in applying such findings to policy decision as these studies did not include an adequate control group who received the same medical management.

c) RCT evidence

The aim of the search was to provide a comprehensive retrieval of randomised controlled trials (RCTs) concerned with domiciliary non-invasive ventilation for COPD patients. Fourteen electronic bibliographic databases were searched, covering biomedical, health-related, science, social science and grey literature (including current research).

The main findings from the meta-analysis of the RCT evidence found only one overall effect for PIMax which was significantly in favour of NPPV ($Z = 2.05$ $p = .04$). Nocturnal NPPV completed in the domiciliary setting had no statistically

significant effect on gas exchange, lung function, and respiratory muscle strength or sleep efficiency. The small overall sample size restricts the overall conclusions that can be made concerning the effects of NPPV on subtypes of COPD.

Previous reviews reported that patients who are more hypercapnic appear to have more benefits from NPPV. Two RCTs showed significant benefits on several outcome parameters; however, neither of these RCTs included patients with a $PaCO_2$ under 6.6 kPa. Two other RCTs included normocapnic patients and one RCT included patients who were mildly hypercapnic. From the available evidence provided by RCTs there is some suggestion that patients who are more hypercapnic might benefit most from domiciliary NPPV.

The selection of patients, modalities of ventilation, types of ventilation and their setting might be considered when attempting to resolve the conflicting and discrepant results of NPPV studies. No study has shown that an increase in the hours on ventilatory support is better in reducing the work of breathing, resting the respiratory muscles or improving sleep quality.

We have highlighted the poor compliance and high drop-out rates in studies using NIV in stable patients with COPD. This should be carefully considered when developing policy options, since the current evidence available is based on a small number of RCTs with only a small number of patients in each. Since a large percent of participants drop-out or died during the trials, the findings may lack the statistical power to reliably make a judgement as to the effectiveness of such treatment.

Cost-effectiveness

Few economic evaluations have been undertaken of domiciliary NIV. One study examined the costs and consequences of domiciliary NIV for patients with recurrent acidotic exacerbations of COPD. This found NIV to be cost-saving; however, several aspects of the study mean that its findings needed to be treated with caution.

We constructed a Markov model based on the work of the previous study and developed it by using hospitalisation and QOL data from an RCT. A further analysis that looked at withdrawal from treatment can also be incorporated within the model, as too can a probabilistic sensitivity analysis.

The mean cost per patient for the two year period of the model was £5,412 and £5,391 for the NIV and usual care groups, respectively. The NIV group compared to the usual care group had a mean QALY gain of 0.008. The central estimate of the incremental cost per QALY is £2,597. The inclusion of withdrawal reduces benefits in the NIV arm but this has little effect on the incremental cost-effectiveness ratio.

The probabilistic sensitivity analysis produced a high degree of uncertainty around the central estimates. NIV has the potential to be more effective and less costly than usual care but the risk of NIV being more costly and less effective is also high.

The fundamental weaknesses in the economic analysis is the reliance on one small study for effectiveness data, and our reliance on the only useable RCT which was based in Italy. Consequently, we can not conclude that these results as reliable estimates of the cost-effectiveness of domiciliary NIV. The analysis does show that

domiciliary NIV has the potential to be extremely cost-effective if modest reductions in hospitalisation can be achieved. However, if more reliable results are to be produced, it is essential that UK based hospitalisation data are identified, and evidence of effectiveness obtained from good quality sources.

Discussion

The ability to evaluate the effectiveness of domiciliary NPPV is limited due to the lack of multi-centred, large-scale, RCTs that have specifically investigated the long-term use of domiciliary NPPV in patients with COPD. No RCT has provided sufficient evidence or rigorous experimental design to enable us to conclude whether the benefits found in gas-exchange were related to improvements in respiratory muscle function or in sleep efficiency. The current conflicting evidence, possibly due to the small samples and poor compliance, does not allow us to conclude accurately the magnitude of benefit and harm of domiciliary NPPV for a selective group of COPD patients. We can tentatively conclude that from the available evidence patients who are more hypercapnic might benefit most from domiciliary NPPV. It is hoped that current on-going trials and recently completed trials will enable a more complete decision to be made about the clinical effectiveness and how domiciliary NPPV might benefit patients with COPD. There is little doubt that NPPV has produced a significant advance in the treatment of patients with COPD, but greater consideration of its application to treatment in the domiciliary setting is needed.

The cost-effectiveness analysis produced a low cost per quality adjusted life year, indicating that NIV may be cost-effective. However, there is a lot of uncertainty around the central estimate. This could be reduced by collection of further data, and perhaps, through further refinement of the model. In the absence of these changes, commissioners will have to weigh-up the risks of purchasing a technology which produces uncertain benefits, against the potential health gains and reduced hospitalisations.

Abbreviations

6-MWD	6-minute walking distance
ABG	Arterial blood gases
BDI	baseline dyspnea index
BIPAP	Bilevel positive airway pressure
Bpm	Breaths per minute
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CVF	Chronic ventilatory failure
EPAP	Expiratory positive airway pressure
ESWT	endurance shuttle walking test
FEV_1	Forced expiratory volume in one second
GP	General Practitioner
HMV	Home mechanical ventilation
HRF	Hypercapnic respiratory failure
HRQL	Health-related quality of life
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
ISWT	incremental shuttle walking test
LT-NIMV	Long-term non-invasive mechanical ventilation
LTOT	Long-term oxygen therapy
MIPPV	Mask intermittent positive-pressure ventilation
MRC	Medical Research Council Scale
MRF-28	Maugeri Foundation Respiratory Failure Questionnaire
NAVG	Nottingham Assisted Ventilation Group
NPPV	Non-invasive positive pressure ventilation (be aware that some articles also refer to NPPV as NIPPV, see NIV and NNPPV)
NIV	Non-invasive ventilation
NNPPV	Nasal intermittent positive-pressure ventilation
NNV	Non-invasive negative ventilation
PFTs	Pulmonary function tests
PImax	Maximal inspiratory pressure
PSV	Pressure support ventilation
QOL	Quality of life
RCT	Randomised controlled trial
RM	Respiratory muscle strength
RR	Relative risk
RTD	Restrictive thoracic disorders
SGRQ	St. George's Respiratory Questionnaire
T-IPPV	Intermittent positive-pressure ventilation via tracheotomy
UMC	Usual medical care
WMD	Weighted mean difference

Definition of terms

Arterial blood gas test: blood test measuring oxygen and carbon dioxide in blood.
BIPAP (bi-level positive airway pressure) machine: machine that provides breathing assistance and uses two pressure levels (inspiratory and expiratory). Often used for patients with sleep apnea or respiratory failure.
Breathing rate: number of breaths per minute.
Cannula: small plastic tube used to supply additional oxygen through the nose.
CPAP (continuous positive airway pressure) machine: breathing machine that provides pressure to keep the upper airways open during breathing.
COPD (chronic obstructive pulmonary disease): general term for several lung diseases that includes chronic bronchitis, emphysema and chronic asthma.
Exacerbation: worsening.
Exhalation: breathing air out of lungs; expiration.
Inspiration: breathing air into lungs; inhalation.
Intubation: placing a tube in trachea to enable artificial breathing.
I/E ratio: inhalation/exhalation ratio, or relative length of inhalation compared to exhalation.
Maximal oxygen uptake: person's highest rate of oxygen consumption.
Nasal cannula: light-weight tube with two hollow prongs that fit inside nose. Nasal cannulas can deliver oxygen.
Peak expiratory flow rate: test used to measure how fast air is exhaled from lungs.
Positive expiratory therapy valve: see mucus clearing device.
Residual volume: volume of air remaining in lungs, measured after a maximum expiration.
Respiration: process of breathing which includes exchange of gases in blood (oxygen and carbon dioxide).
Respiratory failure: sudden inability of lungs to provide normal oxygen delivery or normal carbon dioxide removal.
Sleep apnea: sleep disorder in which a person's breathing stops in intervals that may last from 10 seconds to a minute or longer.
Tidal volume: quantity of air inhaled and exhaled in one respiratory cycle during regular breathing.
Total lung capacity test: test that measures amount of air in lungs after a person has breathed in as much as possible.
Tracheostomy: surgical opening made in trachea.
Ventilator: term for the breathing machine used to treat respiratory failure and help support breathing.
Vital capacity: maximal breathing capacity.
Wheezing: high-pitched whistling sound of air entering or leaving narrowed airways.

1. Aims

The aims of the project were discussed at an EBCC steering group on the 19th September 2005. A preliminary aim concerned the use of non-invasive ventilation for MND, other neuromuscular conditions, chronic obstructive pulmonary disease (COPD) and central respiratory failure. However, it was decided that the preliminary aim was too broad. Following a scoping search of the literature the aim was revised to focus on patients with COPD.

The aim of this report was to:

- Summarise evidence concerned with domiciliary non-invasive ventilation (NIV) for COPD and evaluate which subtypes of patients would be most suitable for this form of treatment
- Estimate the cost-effectiveness of domiciliary NIV in patients with COPD

In order to meet this aim, the following objectives were set out:

- Undertake a systematic review of evidence concerned with clinical effectiveness and cost-effectiveness for the use of domiciliary NIV in patients with COPD in the stable/chronic state
- Summarise the effects of NIV in patients with COPD classified by the design, level of evidence and COPD subtype
- Discuss the outcomes of studies
- Summarise and update previous meta-analyses of randomised controlled trials (RCTs) which investigated the effects of non-invasive positive pressure ventilation (NPPV) in stable patients with COPD

2. Background

Chronic obstructive pulmonary disease (COPD) is currently one of the leading causes of death in the world and further increases in the prevalence are predicted (Wijkstra 2003[1]). The use of short-term non-invasive positive pressure ventilation (NPPV) has received support as an accepted management approach for patients with acute hypercapnia, but it remains unclear whether it can also be useful in stable COPD patients within a domiciliary setting for long term use. Even with optimal medication, patients with COPD often suffer from dyspnoea that can impair health-related quality of life (QOL). There is an increased need to find the optimal treatment for the various subgroups of patients with COPD.

The use of NPPV delivered through a facial mask is now a well-established and is increasingly used for treating patients with chronic hypercapnic respiratory failure (HRF) due to various underlying diseases, such as chest wall deformities, neuromuscular diseases and COPD (Mehta & Hill, 2001[2]; Hill, 2004[3]). There is increasing use of NPPV at home predominantly during night while patients usually breathe spontaneously during daytime.

Numerous studies have explored whether intermittent ventilatory assistance using NPPV might be beneficial in patients with severe stable COPD. The results are inconsistent and no reliable positive outcome has been proven. It has been noted that some improvement in respiratory muscle function may occur after short-term rest and increasing of the overall length of sleep has been reported.

Hill (2000[4]) discussed two hypotheses for the effectiveness of NPPV in stable patients with COPD. The first hypothesis was that NPPV might be effective in resting the respiratory muscles. It has been further suggested that NPPV alleviates fatigue by improving inspiratory muscle capacity; although this has not been supported. The second hypothesis involves a theory related to sleep. Several researchers have claimed that sleep quality is often poor in patients with severe COPD. Furthermore, many patients frequently have desaturations and periods of hypoventilation. It has been hypothesised that NPPV may reduce the number of arousals and improve the quality of sleep. It is also possible that NPPV may prevent a deterioration of nocturnal hypoventilation, resetting the respiratory centre for CO_2, which ultimately might improve daytime ventilation.

2.1 Types of COPD

There are several synonymous terms which are used interchangeably to describe the condition of COPD. These included chronic obstructive airway disease and chronic obstructive lung disease. It should also be noted that in some countries like the United States of America (USA), COPD includes emphysema and chronic bronchitis.

A useful guideline to the various levels of severity of COPD is provided in Figure 1.

Figure 1. Classification of severity

Stage	Characteristics
0: At Risk	• normal spirometry • chronic symptoms (cough, sputum production)
I: Mild COPD	• $FEV_1/FVC < 70\%$ • $FEV_1 \geq 80\%$ predicted • with or without chronic symptoms (cough, sputum production)
II: Moderate COPD	• $FEV_1/FVC < 70\%$ • $50\% \leq FEV_1 < 80\%$ predicted • with or without chronic symptoms (cough, sputum production)
III: Severe COPD	• $FEV_1/FVC < 70\%$ • $30\% \leq FEV_1 < 50\%$ predicted • with or without chronic symptoms (cough, sputum production)
IV: Very Severe COPD	• $FEV_1/FVC < 70\%$ • $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

Classification based on postbronchodilator FEV_1
FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

The above figure was taken from Global Initiative for Chronic Obstructive Lung Disease Guidelines (GOLD): Global strategy for the diagnosis, management and prevention of COPD (2005[5]) (see http://www.goldcopd.org).

2.2 Treating patients with COPD

It is important to clearly differentiate the different types of ventilator assistance for patients. Guidelines concerning long-term mechanical ventilation (LTMV) have been provided by the American College of Chest Physicians (2005[6]). These will be referred to in this section of the report. Further information concerning the guidelines for the management of stable COPD can be found in the scope for the development of a clinical guideline on the management of COPD (see http://www.nice.org.uk/page.aspx?o=104441).[7]

2.3 Clinical need for guidelines

The NICE guidelines (2004[7]) provide some useful background to the clinical need for appropriate guidelines for COPD. The guidelines state that COPD is the fifth commonest cause of death in England and Wales. It accounts for around 28,000 deaths each year. Britain has one of the highest death rates from COPD in Europe. An estimated 600,000 patients in the UK are diagnosed COPD and many remain undiagnosed. An estimated one in eight hospital admissions are due to COPD. There is an increase in consultation rate in general practice with age from 417 (aged 45-64) per 10,000 population per year to 1032 (aged 75-84) per year per 10,000 population. COPD is estimated to result in approximately 27 million lost working days per year.

2.4 Clinical management

The NICE guidelines include recommendations concerning the management of stable patients, management of acute exacerbations and prevention of progression of the disease:

- Bronchodilator management including methods of delivery and methods of assessing efficacy
- Indications for surgery
- Inhaled and oral corticosteroid therapy
- Management of right heart failure as it pertains to COPD
- Non-invasive ventilation
- Non-pharmacological interventions, including pulmonary rehabilitation and respiratory physiotherapy, lifestyle advice including nutritional/metabolic assessment and management and self-management techniques
- Oxygen therapy including when it should be used and what type is appropriate in different circumstances
- Smoking cessation, including pharmacological and non-pharmacological approaches as they relate specifically to COPD

The GOLD (2005[5]) guidelines set out a number of important points:
- COPD is a disease state characterised by airflow limitation that is not fully reversible
- The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases
- A four-stage classification of COPD severity might provide an education tool and a general indication for the approach to management of COPD
- The report recognises that COPD is usually progressive if exposure to the noxious agent is continued
- Characteristic symptoms of COPD are cough, sputum production and dyspnea upon exertion
- Chronic cough and sputum production frequently precede the development of airflow limitation by many years. These symptoms can identify those individuals at risk of developing COPD
- COPD can coexist with asthma, which is the other major chronic obstructive airway disease characterised by an underlying airway inflammation, although this is distinctly different
- Pulmonary tuberculosis may affect lung function and symptomatology and it can lead to confusion in diagnosis of COPD

2.5 Ventilation

There are two main groups of ventilation: invasive methods and non-invasive. Invasive methods use a tracheostomy, a surgical hole in the windpipe through which a tube is channelled to assist breathing. Non-invasive methods use masks, nasal tubes and other techniques that do not require surgical entry into the respiratory tract. Some apply positive pressure to the mouth and/or nose. Other non-invasive methods apply negative pressure to the chest or body by lowering the pressure outside the body. It is important to recognise that negative pressure will not be considered further in this report.

Home mechanical ventilation (HMV) is increasingly being used to treat patients suffering from chronic respiratory failure. Diseases that have been treated by HMV include COPD, restrictive thoracic disorders (RTD), neuromuscular disorders and other causes of nocturnal hypoventilation syndrome (Chu et al., 2004[8]). The growth of HMV has been considered to be related to: 1) improved life expectancy in treated patient; 2) pressure to reduce hospital stay; 3) improved support by machine vendors;

and 4) increased awareness and experience with the indications and technologies (Leger, 2001[9]).

Non-invasive ventilation has been defined by Hill (1993[10]) as a technique that augments alveolar ventilation without using an endotracheal airway. NIV was first achieved with a variety of negative pressure ventilators, but this was limited by patient discomfort, lack of portability and the propensity of upper airway obstruction (Clark & Wilcox, 1997[11]; see Figure 2). This has since been replaced with positive pressure ventilation via more comfortable nasal and oronasal masks.

Figure 2. Potential advantages of NPPV over endotracheal intubation

Avoidance of sedatives and paralytic agents
Avoidance of tracheal injury
Facilitation of weaning from assisted ventilation
Improved patient comfort
Intervention earlier in the course of ventilatory failure
Preservation of airway defence mechanisms
Preservation of speech and swallowing

Adapted from information by Clark & Wilcox (1997[11])

2.6 Further considerations

In the guidelines provided by the American College of Chest Physicians (2005[6]) they evaluated the LTMV in terms of Who, When and Where. In this section we will provide a brief summary of the key points which might be useful for policy making (see Figure 3).

Figure 3. Guidelines provided by the American College of Chest Physicians (2005[6])

Who is most suitable to receive LTMV?
a) Patient's physician and respiratory care team decide (1) type of mechanical ventilation most appropriate for the patient after discharge from the ICU and (2) need for LTMV assistance b) Decisions are based on: (i) tests of daytime and sometimes of night time breathing efficiency, (ii) ability to breathe without help, (iii) complete medical assessment and (iv) patient's current illness and past medical history c) Patients who might benefit most from LTMV are patients with medical conditions that would become unstable if they were removed from mechanical ventilation. They might have recurrent or chronic conditions that make it more difficult for the patient to carry out activities of daily living
When is it best to provide Long-term Mechanical Ventilation?
a) Medical criteria can determine when a patient is discharged from ICU on LTMV to a site outside the ICU b) Successful discharge on LTMV is more likely when: • family is willing to participate in long-term care • financial resources are available for mechanical ventilation equipment and caregiver assistance such as nursing services • medical and respiratory care professionals are available to monitor and supervise long-term care • patient and his/her family understand all available options for long-term ventilation • patient is able to communicate with caregivers and give them direction • patient is highly motivated to accept the responsibility to make LTMV work • patient may independently do some activities of daily living
Where to provide Long-term Mechanical Ventilation?
a) The optimal location for long-term ventilator-assisted individuals may be with the family in the home b) In the home, the patient's QOL is likely to be better than at any other location c) Costs of care are usually lower when the patient is at home, but insurance coverage of home-care costs must be evaluated on an individual basis to determine if adequate reimbursement is available d) Usually, the cost of home care must be less than the cost of a long-term care facility in order for benefits to apply

Additional background information concerning treatment is provided in Appendix 1.

It is important to recognise that the domiciliary setting is not the only place patients can receive LTMV. One can consider the possibilities of other non-hospital sites which might be appropriate for a patient's needs and resources e.g. rehabilitation, medical care, respiratory care and psychological support. The choice of a site for LTMV is a joint responsibility of the patient, patient's family and patient's physician, with consultation from other members of the respiratory care team.

The guidelines presented in Figure 3 clearly state that all methods of ventilation require an initial assessment of comfort and efficacy and follow-up monitoring of daytime and night time breathing. The patient and caregivers should be educated in use and maintenance of the equipment needed to provide the support. Furthermore, it is recognised that patients have the right to choose whether to institute and continue, or withhold and withdraw, long term ventilatory assistance.

2.7 Equipment and Resources

A wide array of equipment and supplies is needed for long-term mechanical ventilation at home or other site (see Figure 4 & 5).

Figure 4. Equipment and supplies for Ventilator-Assisted Patients in home

Mechanical ventilator

- Primary
- Secondary or backup system (portability) 12-V battery and connecting cable for emergency (power source)
- Ventilator circuit
    - Exhalation valve
    - Tracheostomy tube adapter/connector
- Humidifier
    - Heat and moisture exchanger
    - Humidifier and heater
    - Humidifier bracket

Manual resuscitator oxygen

- Nasal cannulae
- Oxygen bleed-in adapter to ventilator
- Oxygen supply system (stationary and portable)
- Oxygen tubing
- Tracheostomy collar or t-tube adapter

Non-invasive patient interfaces

- Face mask
- Head gear, chin straps
- Mouthpiece: customized, standard, lipseal
- Nasal mask or nasal pillows

Suction machine (stationary and portable)

- Connecting tubing
- Gloves
- Other secretion clearance aids such as cough inex-sufflator
- Suction catheters
- Suction collection container

Disinfectant solution

- Quaternary ammonium compound
- Vinegar/water 1:3

Tracheostomy supplies

- 10-ml syringe used only to inflate or deflate cuff
- Antibiotic ointment
- Cotton-tipped applicators
- Hydrogen peroxide
- Spare tracheostomy tube (including next smaller size)
- Sterile saline solution
- Tracheostomy dressings or Velcro trach tube strap
- Tracheostomy tape

Figure was adapted from American College of Chest Physicians (2005[6]). Some of supplies may not be needed. For example, a patient on non-invasive ventilation would not need a tracheostomy tube adaptor or tracheostomy supplies unless the physician believes the supplies are medically necessary.

Figure 5. Additional equipment and supplies for Ventilator-Assisted Patients in home

Monitors and alarms for ventilator and patient
Patient communication system
Compressor for aerosolized medications
Wheelchair
Hospital bed and mattress
Commode, bedpan, urinal, or elevated toilet seat
Patient lifter
Safety bars in bathroom
Hand-held shower
Shower chair

Figure was adapted from American College of Chest Physicians (2005[6]). Some of supplies may not be needed.

2.8 Costs

In calculating the costs of domiciliary NIV one must consider the additional costs of training before a ventilator-assisted individual is discharged from the hospital to home or a long-term care institution. The patient and all caregivers must be trained in all aspects of ventilation and must show the physician and health-care team that they have learned to carry out all care techniques. One also must consider the severity of COPD patient and individual requirements based on their condition and personal situation in the home-place.

In the NICE guidelines (2004[7]) the total annual cost of COPD to the NHS is estimated to be £491,652,000 for direct costs only and £982,000,000 including indirect costs. This was further broken down by disease severity. The cost p.a. was: mild £149.68; moderate £307.74; and severe £1,307.10. The average cost per patient p.a. is £819.42, of this 54.3% appears to be due to inpatient hospitalisation, 18.6% for treatment, 16.4% for GP and specialist visits, 5.7% for accident and emergency visits and unscheduled contacts with the specialist or GP and finally 5% for laboratory tests (Britton, 2003[12]).

In addition to these costs, it has been estimated that around 21.9 million working days were lost in 1994-1995. In a survey of a random sample of patients with COPD, approximately 44% were below retirement age and 24% reported they were unable to work because of the disease. Further evidence was reported that 9% were limited in their ability to work and patients carers also lost time from work (Britton, 2003[12]).

3. Summary of literature concerning domiciliary non-invasive ventilation for patients with COPD

We will begin by reporting the previous systematic reviews, literature reviews and editorials which provide information about non-invasive ventilation in domiciliary setting for COPD patients. We will then provide a thorough review of the published literature. We will finally provide specific summary and meta-analysis of RCTs.

3.1 Reviews

A summary of the reviews relating to domiciliary non-invasive ventilation for patients with COPD is provided in Table 1. Several studies were considered to be of particular relevance, these have been highlighted.

Table 1: Systematic reviews, literature reviews and editorials which provide information about non-invasive ventilation in domiciliary setting for COPD patients

Author/country	Source	Type	Summary
Anton & Guell (2000)[13] Spain	Chest	Editorial	• Home mechanical ventilation in COPD • Evaluating if we know when/how to use it • Selected group of patients may benefit from domiciliary mechanical ventilation: Ø patients with significant hypercapnic respiratory failure Ø patients with poor response to long-term oxygen therapy Ø patients in whom nocturnal hypoventilation is corrected by NIV Ø patients who are motivated to comply with therapy and willing to be trained • Mixed results from the application of home mechanical ventilation of stable COPD patients • Solid clinical evidence of the usefulness of NIV in COPD patients is lacking • Need further RCTs to answer question of whether or not to administer NIV to patients with COPD in home setting
Chabot, Cornette, Robert, Vial, & Polu (2001)[14] French	Revue des maladies respiratoires	Literature review	• Abstract was extracted: article in French • Home ventilation after intensive care • Non-invasive ventilation with facial or nasal mask produced a less need for tracheostomy • Respiratory failure due to lung restriction is best indication of mechanical ventilation • The results in COPD are questionable
Consensus Conference Report (1999)[15] USA	Chest	Literature review	• Clinical indications for non-invasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation • Guidelines stated several recommendations concerning the indications for use of domiciliary NPPV in COPD include: • Symptoms (dyspnoea, morning headache, fatigue, etc.) • Physiologic criteria (one of from list): Ø $PaCO_2$ of 50 to 54 mm Hg (6.7-7.2 kPa) and hospitalization related to recurrent episodes (≥ 2 in a 12-month period) of hypercapnic respiratory failure Ø $PaCO_2$ of 50 to 54 mm Hg (6.7-7.2 kPa) and nocturnal desaturation (SpO_2 ≤ 88% for five continuous minutes while receiving FiO2 at 2 L/min) Ø $PaCO_2$ ≥ 55 mm Hg (7.33 kPa)
Cuvelier, Molano and Muir (2005)[16] French	Rev Mal Respir	Literature review	• Article written in French, only abstract was extracted • COPD has become one of the main indications for domiciliary NIV • Review provides evidence concerning the pathophysiology processes and clinical trials • Most published studies about domiciliary NIV in COPD have been short-term

			• Significant methodological problems with many of the trials • Two controlled studies of ≥ 12 months-duration found survival was not improved by long-term NIV • Provided descriptions of six RCTs • Domiciliary ventilation may be considered when LTOT is unsuccessful and in patients with recurrent episodes of acute hypercapnic respiratory failure • Diurnal $PaCO_2 \geq 55$ mmHg (7.3 kPa) is a necessary but not sufficient level for consideration of domiciliary ventilation • Domiciliary NIV is useful for a selected number of patients on the basis of clinical symptoms and exacerbation frequency
Elliott (2004)[17] United Kingdom	Thorax	Editorial	• Non-invasive ventilation in acute exacerbations of COPD • Evaluating what happens after hospital discharge • NIV at home might improve long-term outcome of patients at risk of later hospitalisation and death • Raised concerns about several studies that claim NIV reduced hospitalisation rates • Cannot discount possible placebo effect of NIV • Three potential roles for long-term domiciliary NIV in patients with severe COPD: Ø Patients intolerant of LTOT because of severe symptomatic hypercapnia may benefit from NIV if hypercapnia is controlled Ø NIV may improve the survival and QOL in patients who are established on LTOT but who are also hypercapnic Ø NIV may provide a role for patients who require it because of a severe exacerbation • Need an RCT comparing domiciliary NIV with conventional treatment in patients who have been ventilated non-invasively during an acute exacerbation
Elliott (2002)[18] United Kingdom	European Respiratory Journal	Editorial	• Non-invasive ventilation in chronic ventilatory failure due to COPD • Robust evidence base for the use of NIV for acute exacerbations of COPD • Evidence that NIV is effective in chronic COPD is less strong • Reports several studies have shown NPPV is feasible at home in patients with COPD • Need an economic evaluation • High technology interventions are being extended into home
Elliott & Ambrosino (2002)[19] United Kingdom	European Respiratory Journal	Editorial	• Discussion of advances in the use of NIV during last decade • NPPV first made mark in home environment • Since ventilation can be assisted without paralysis and sedating drugs, now feasible option outside ICU • Growing body of prospective RCT data to inform medical practice
Hill (2004[3])	32nd Respiratory	Literature	• Discusses several issues relevant to NIV for COPD:

USA	Care Journal Conference	review	Ø Rationale for NPPV in the long-term setting Ø Summary of potential benefits of NPPV in severe stable patients Ø Selection of patients with severe stable COPD to receive NPPV • Long-term NPPV adaptation is longer than in acute setting, as patients attempts to sleep whilst using ventilator • Adherence to this use is often relatively low • Criner et al. (1999[20]) found 50% of COPD patients still used NPPV after 6 months • Possible reasons for poor adherence probably include: Ø Advanced age of COPD patients Ø Frequent occurrence of comorbidities and cognitive defects • Lack of motivation
Kwok & Li (2005)[21] China	Respiratory Medicine	Literature review	• Long-term NIV • Use of NPPV in COPD has been controversial • Uncontrolled studies found favourable results with domiciliary NPPV for COPD • Improved hospitalisation rates, vital sign measurements, and blood gas parameters • Subsequent randomised controlled studies shown discrepant results
Miro, Fernandez-Montes, Ramos, Martinez, Anon, Jimenez, Pieras, & Quiroga (2001)[22] Spain	Archivos de bronconeumologia	Literature review	• Article writted in Spanish • Not extracted • Provides guidelines concerning domiciliary mechanical ventilation
Rossi & Polese (2000)[23] Italy	Eur Respir Rev	Literature review	• Provides an insight into major changes in approach to mechanical ventilation of patients with acute respiratory failure due to exacerbation of COPD • Claims that the benefits of LTOT for COPD patients with chronic hypercapnia are now established • LTOT is often supplemented by home ventilatory assistance with non-invasive positive pressure ventilation to prevent chronic retention of excess CO_2 • Details Meecham Jones et al study
Scala (2004)[24] Italy	Recenti Progressi	Literature review	• Article writted in Italian • Abstract was extracted • Not possible to draw guidelines about the domiciliary use of NIV in COPD • In order to avoid useless waste of resources, the application of NIV to stable COPD should be reserved to very selected cases (e.g., significant hypercapnia, frequent nocturnal desaturations and/or sleep disordered

			breathing and/or hospital admissions) if effectiveness and compliance are shown
Simonds (2003)[25] United Kingdom	European Respiratory Journal - Supplement	Literature review	• Home ventilation in COPD is controversial • Multicentric RCTs of LTOT versus NIV plus LTOT in COPD resulted in mixed findings • Several subgroups appear to benefit: Ø Recurrent infective exacerbations requiring short-term NIV Ø Patients aged > 65 years Ø Uncontrolled hypercapnia on LTOT Ø Symptomatic nocturnal hypoventilation • Domiciliary NIV is unlikely to be effective in most stable COPD patients, particularly if they are normocapnic • Lack of QOL measures
Singh (2003)[26] United Kingdom	British Journal of Intensive Care	Literature review	• Examines studies including those looking at domiciliary NPPV in COPD • Studies reported have been relatively small with recognised inadequacies compromising the potential of a true treatment effect • A subgroup of chronic hypercapnic patients with $PaCO_2$ likely to be above 7 kPa appear to be more likely to derive benefit • Nocturnal hypoventilation will need to be controlled to a certain arbitrarily defined degree (e.g., > 15% fall in $PaCO_2$) • Possible need for overnight CO_2/O_2 monitoring • Adequate pressure support needs to be administered to levels comparable to > 17 kPa (comparable to that reported by Meecham Jones et al., 1995[27]) until baseline ventilatory adequacy is established • Issues surrounding compliance • Setting up patients in hospitals may also increase usage rates • Need for studies with a sham ventilatory limb and a non-ventilatory group • Safety aspects of inappropriate ventilation need addressing
Wedzicha & Meecham-Jones (1996)[28] United Kingdom	Thorax	Editorial	• Provided a useful review of earlier studies concerning non-invasive nasal positive pressure ventilation (NPPV) • Makes recommendations for home NPPV in COPD – patients must be motivated and prepared to accept ventilator in home • Suggests that there is sufficient clinical evidence to justify the use of NPPV with a selected group of patients with hypercapnic COPD who are complicated with nocturnal hypoventilation
Wedzicha (2002)[29] United Kingdom	Respiratory Care Clinics of North America	Literature review	• Introduction of NPPV has been an important advance in management of patients at home with chronic respiratory failure • Ventilatory support in addition to LTOT may provide advantages

			• Control of nocturnal hyperventilation might be an important factor in use of NPPV in hypercapnic COPD • Benefit obtained from therapy depends on underlying cause • Data on long-term use of NPPV in COPD is mainly from uncontrolled studies • Worse compliance in patients with COPD for NPPV compared with other causes of chronic respiratory failure e.g. chest wall disease • Evaluated studies in terms of survival, changes in arterial blood gases (ABG), sleep quality, effect on exacerbation and hospital admission, respiratory muscle function, exercise tolerance and QOL • Significant improvements in exercise tolerance and QOL after training in conjunction with NPPV in comparison to training alone • Longer-term effects of NPPV in hypercapnic COPD are not clear and further large, well-designed controlled studies are required to evaluate the effects of NPPV on survival, QOL and disease exacerbation
Wijkstra, Lacasse, Guyatt, & Goldstein (2002)[30] The Netherlands	Cochrane Collaboration	Systematic review	• Evaluated benefits of nocturnal NPPV in COPD • Assessed RCTs in stable hypercapnic patients with COPD that compared nocturnal non-invasive positive pressure ventilation plus standard therapy with standard therapy alone • Examined blood gases, dyspnoea (during daily activities), health status (QOL), lung function, respiratory muscle function, six minute walking distance (6-MWD) and sleep efficiency • Examined nocturnal NPPV via nasal mask or face mask • Found only outcome for which the 95% confidence interval (CI) excluded zero was maximal inspiratory pressure (PI max) • Mean effect on 6-MWD was modest at 27.5 metres, some had big improvement • Due to small sample sizes was difficult to make definite conclusion regarding effects of NPPV in COPD • Nocturnal NPPV for three months in hypercapnic patients with COPD had no clinically or statistically significant effect on lung function, gas exchange, respiratory muscle strength or sleep efficiency • High upper limit of CIs for 6-MWD suggested some patients might improve walking distance, but not possible to identify such patients a priori • Further research is needed with larger sample sizes that investigate length of ventilation, patient selection, rehabilitation, role of treatment, training, and ventilator settings • Future studies might consider patients to monitor ventilation, to observe the precisely changes that occur from NIV • Long-term NIV for COPD should only be started in context of a clinical trial
Wijkstra, Lacasse, Guyatt, Casanova, Gay, Jones, & Goldstein (2003)[31]	Chest	Meta-analysis	• Evaluated the use of nocturnal NPPV in patients with stable COPD • Analysis of the four RCTs reported in the Cochrane review by Wijkstra et al. (2002[30]) • Meta-analysis showed that nocturnal NPPV for 3 months in hypercapnic patients with COPD did not have a clinically or statistically significant effect on lung function, gas exchange, respiratory muscle strength or

The Netherlands			sleep efficiency • Design of this meta-analysis only included studies in which nocturnal NPPV was applied for 5 hours per night
Wijkstra (2003)[1] The Netherlands	Respiratory Medicine	Meta-analysis	• Evaluated the use NPPV in patients with stable COPD • The meta-analysis update the earlier reviews[31,30] • Examines short-term NPPV (≤ 3 months) and long-term nocturnal NPPV (≥ 12 months) • It should be noted that some of these short-term trials were not domiciliary (e.g., Lin et al., 1995[32]; Renston et al., 1994[33]) • Concludes that there is no conclusive evidence that NPPV should be provided routinely with stable patients with COPD • However, a selected group of patients who are clearly hypercapnic, who tolerate an effective level of ventilatory support and who can adjust to the ventilator might show clinical benefits after three months

Note: those articles highlighted in grey were considered by the authors of this report to be of most relevance to the topic of domiciliary NIV for treatment of patients with COPD

3.2 Summary of key reviews

The large number of reviews and editorials in this area illustrates the considerable interest and importance of this topic. A total of nineteen relevant published articles were found: 11 literature review; five editorials; one systematic review and two meta-analyses. Each differed in the degree of relevance in terms of patient populations and types of intervention.

To summarise some of the key findings from this literature we will focus on those considered to be of most important in terms of appropriate patient group (e.g., COPD) and intervention (NIV), these were highlighted in grey.

a) Cuvelier et al. (2005[16])

The article was written in French. Only a limited amount of information was extracted. The review was concerned with the pathophysiology processes and clinical trials in the area of domiciliary NIV in COPD. It recognises that the majority of early studies have been short-term and there are significant methodological problems with some of the trials. The review provided a description of six RCTs. Two controlled studies involved study periods of more than 12 months and found survival was not improved by long-term NIV. The authors proposed that domiciliary ventilation may be considered when LTOT is unsuccessful and for a sub-group of patients with recurrent episodes of acute hypercapnic respiratory failure. It was further reported that diurnal $PaCO_2 \geq 55$ mmHg (7.3 kPa) was a necessary but not sufficient level for consideration of domiciliary ventilation. Overall it was concluded that domiciliary NIV is useful for a selected number of patients on the basis of clinical symptoms and exacerbation frequency.

b) Elliott (2004[17])

In this comprehensive editorial, it was reported that patients who receive NIV for an acute exacerbation of COPD tend to be those patients who are at high risk of later hospitalisation and death. It was further considered that NIV at home in these patients might improve their long-term outcome. Elliott provided coverage of two important clinical trials in this area (Casanova, Celli, Tost, Soriano, Abreu, Velasco & Santolaria, 2000[34]; Clini, Sturani, Rossi, Viaggi, Corrado, Donner, Ambrosino, Rehabilitation and Chronic Care Study Group, 2002[35]). It was highlighted that although both of these studies claimed that NIV reduced hospitalisation rates, Elliott points out that neither study was powered to address this end point. The level of ventilatory support in both was modest. Furthermore, Elliott claims that it is possible that NIV reduced the impact of exacerbations upon the patient and this in fact may have influenced the trend in reduced hospitalisation. This is supported by similar findings found in a small group of highly selected patients admitted to hospital recurrently with exacerbations of COPD requiring NIV. Tuggey, Plant, and Elliott (2003[36]) showed a decrease in ICU and hospital admission in the year after the introduction of home NIV compared with the year before. This was associated with a reduction in costs. However, it is important to recognise that this study was uncontrolled and measures of QOL were not assessed. As Elliott recognises in his editorial, one cannot discount a possible placebo effect of NIV. Furthermore, the placebo effect of a ventilator for a patient who is experiencing difficulties with breath should not be underestimated.

Elliott further emphasises three potential roles for long term domiciliary NIV in patients with severe COPD:

- Patients who are genuinely intolerant of LTOT because of severe symptomatic hypercapnia may benefit from NIV if hypercapnia is controlled.
- NIV may improve the survival and QOL in patients who are established on LTOT but who are also hypercapnic. Although the current published evidence does not support this claim, a multi-centre study by Köhnlein et al. (2004[37]) may help to answer this question.
- NIV may provide a role for patients who required it because of a severe exacerbation.

As well as survival data, QOL and a detailed health economic analysis are needed. It was suggested that patients should be encouraged to use the ventilator each night during sleep but, if they are unable to do this, daytime use may still be beneficial. Elliott concluded that what is now required is a RCT comparing domiciliary NIV with conventional treatment in patients who have been ventilated non-invasively during an acute exacerbation.

c) Kwok and Li (2005[21])

This review concerned the long-term management of chronic respiratory failure of various aetiologies (e.g., COPD) with NPPV and invasive ventilation. The authors provided a summary of the contraindications for non-invasive ventilation and indications for invasive ventilation (see Table 2). The use of NPPV with COPD patients has been controversial. Earlier uncontrolled studies were reported to provide positive results for domiciliary NPPV in COPD patients, with improvements in blood gas parameters, hospitalization rates and vital sign measurements. Kwok and Li documented several mechanisms that have been proposed to explain the observed improvements:

- Improvement in sleep quality
- Resetting of the central chemoreceptor
- Improvement in respiratory muscle functions

Table 2: Contraindications for non-invasive ventilation and indications for invasive ventilation

Contraindications to non-invasive ventilation
• Vocal cord paralysis • Inability to cooperate • Significant swallowing disorders • Inability to clear secretions • Severe cough impairment with chronic aspiration
Indications for invasive ventilation
• Failure to adequately ventilate with non-invasive ventilation • Failure to tolerate non-invasive ventilation • High level of dependence on assisted ventilation (> 20 hours/day) • Uncontrollable oral air leaks during non-invasive ventilation

Table was adapted from Kwok and Li (2005[21])

Although Kwok and Li (2005[21]) recognised that several RCTs have found conflicting results; these will be discussed later in this report. In recognition of these

discrepancies concerning NPPV in COPD, the 1999 Consensus Conference issued guidelines on clinical indications for NPPV (1999[15]). The guidelines stated several recommendations that, following a clear diagnosis, the indications for use of domiciliary NPPV in COPD include:

- Symptoms (dyspnoea, morning headache, fatigue, etc.)
- Physiologic criteria (one of from list):
  - $PaCO_2$ of 50 to 54 mm Hg (6.7-7.2 kPa) and hospitalization related to recurrent episodes (≥ 2 in a 12-month period) of hypercapnic respiratory failure
  - $PaCO_2$ of 50 to 54 mm Hg (6.7-7.2 kPa) and nocturnal desaturation ($SpO_2 \leq$ 88% for five continuous minutes while receiving FiO_2 at 2 L/min)
  - $PaCO_2 \geq 55$ mm Hg (7.33 kPa)

Kwok and Li (2005[21]) concluded that it is increasingly likely that more patients with COPD will be prescribed long-term NIV. The efficacy of NPPV use in restrictive diseases is far more compelling than for COPD. Like Elliott (2004[17]), it was suggested that there is a need for several large RCTs of LTOT with or without NPPV in COPD patients to evaluate its impact on health economics, mortality, QOL and morbidity.

d) Simonds (2003[25])

It was claimed that there was a significant mortality and morbidity associated with the tracheostomy; therefore, non-invasive methods of treatment could be more suitable. Simonds stated that there have been few large-scale RCTs of domiciliary NIV versus LTOT in stable COPD patients with chronic respiratory failure. Several case series reports suggested home NIV may be feasible (e.g., Marino, 1991[38]; Elliott, Simonds, Carroll, Wedzicha, & Brathwaite, 1992[39]). Furthermore, several large cohort studies have been reported (e.g., Simonds & Elliott, 1995[40]). It is clear that additional RCTs are needed with exacerbation frequency, hospitalisation and QOL as outcome measures, as well as survival. In this review by Simonds, it was concluded that from existing evidence domiciliary NIV is unlikely to be effective in most stable COPD patients, particularly if they are normocapnic. However, subgroups of patients with poor tolerance of LTOT, marked nocturnal hypoventilation, severe hypercapnia and/or recurrent infective exacerbations could find such treatment beneficial.

e) Wijkstra et al. (2002[30]), Wijkstra et al. (2003[31]) and Wijkstra (2003[1])

Short-term crossover studies comparing NIV to NIV plus LTOT have produced inconsistent results, which is most likely due to differences in patient selection. Therefore, one might not be surprised to see that in a recent meta-analysis of crossover studies lasting three months or more the mean effect of NIV was small and there was no significant effect when sleep efficiency, pulmonary function, gas exchange, exercise tolerance and respiratory muscle strength were accounted for. There was a high upper limit of the confidence interval for the 6-MWD which might suggest that some people did improve their walking distance, while some might have deteriorated. Due to a limited number of included patients in the meta-analysis, the authors were unable to report a clear clinical direction regarding the effects of NPPV in COPD. It is important to recognise that the design of this meta-analysis only included studies in which nocturnal NPPV was applied for five hours per night. Wijkstra (2003[1]) concluded that there is no conclusive evidence that NPPV should be provided routinely with stable patients with COPD.

3.3 Conclusions

It is important to note that although many of the reviews documented in this section report the findings from trials concerning nocturnal NPPV in patients with stable COPD, these trials are predominantly undertaken with patients in the domiciliary setting. The key points reported were:

- Domiciliary NIV is unlikely to be effective in most stable COPD patients, particularly if they are normocapnic
- Subgroups of patients with poor tolerance of LTOT, marked nocturnal hypoventilation, severe hypercapnia and/or recurrent infective exacerbations could benefit from domiciliary NIV
- Concerns about the high dropout and poor compliance rates in the RCTs
- RCTs with larger sample sizes are needed to evaluate the impact on health economics, mortality, QOL and morbidity

4. Review of published non-RCT studies

In the next section we will provide a thorough review of individual studies concerned with domiciliary NIV for patients with COPD. Each study has been summarised to provide the reader with key elements to the study which should be considered when attempting to evaluate its importance. For example, caution when interpreting is needed in terms of what type of NIV and patient group is being investigated. Furthermore, please pay careful attention to the level of evidence reported.

We aim, were possible, to quantify the level of evidence using the NHS Centre for Reviews and Dissemination (2001[41]; see Figure 6).

The included studies in this section were concerned with nocturnal NIV or daytime NIV and all were patients treated in the domiciliary setting.

The summary of evidence has relied extensively on the original articles. It should be noted that a number of reviews and editorials were consulted to strengthen the reporting of the original articles.

Table 3 provides a comprehensive summary of the non-RCTs concerned with domiciliary NIV for patients with COPD.

Figure 6: Hierarchy of study designs for questions about effectiveness of healthcare interventions

Description of the design	Levels assigned to evidence based on soundness of design
Experimental study A comparative study* in which the use of different interventions among participants is allocated by the researcher. • **Randomized controlled trial (with concealed allocation)** Random allocation of participants to an intervention and a control (e.g. placebo or usual care) group, with follow-up to examine differences in outcomes between the two groups. Randomization (with concealment of allocation sequence from caregivers) avoids bias because both known and unknown determinants of outcome, apart from the intervention, are usually equally distributed between, the two groups of participants.	**I**
• **Experimental study without randomization** (sometimes erroneously called quasi-experimental or quasi-randomized or pseudo randomized studies) A study in which the allocation of participants to different interventions is managed by the researcher but the method of allocation falls short of genuine randomization, e.g. alternate or even-odd allocation. Such methods fail to conceal the allocation sequence from caregivers. **Observational study with control group** A comparative study* in which the use of different interventions among participants is not allocated by the researcher (it is merely observed). • **Cohort study** Follow-up of participants who receive an intervention (that is not allocated by the researcher) to examine the difference in outcomes compared to a control group, e.g. participants receiving no care. • **Case-control studies** Comparison of intervention rates between participants with the outcome (cases) and those without the outcome (controls).	**II$**
Observational study without control groups • **Cross-sectional study** Examination of the relationship between outcomes and other variables of interest (including interventions) as they exist in a relevant population at one particular time. • **Before-and-after study** Comparison of outcomes in study participants before and after an intervention. • **Case series** Description of a number of cases of an intervention and their outcomes.	**III**
Case reports **Pathophysiological studies or bench research**	**IV**
Expert opinion or consensus	**V**
* A comparative study assesses the effect of an intervention using comparison groups. $ In Level II evidence, experimental studies without randomization (and allocation concealment) are considered better than cohort studies, which in turn are considered better-than case-control studies	

Above Figure was adapted from NHS Centre for Reviews and Dissemination (2001[41]).

Table 3: Non-RCTs concerned with non-invasive ventilation in domiciliary setting for COPD patients

Author/country	Source	Study type/Level /Patients/Sample size	Summary
Alfaro, Torras, Palacios, & Ibanez (1997)[42] Spain	Respiration	**Study type:** Case study **Level:** IV **Patients:** Severe stable COPD with severe hypoxemia (pO_2 = 32.0 mmHg) and hypercapnia (pCO_2 = 90.0 mmHg) **Sample size:** N = 1	**Aim:** To report experience of a patient receiving a long-term domiciliary combination of nasal intermittent positive-pressure ventilation (NNPPV) plus supplemented oxygen therapy **Design:** Eight months domiciliary treatment with NNPPV and O_2 **Outcomes:** Spirometric basal test, physiological measures during sleep, blood gases, incremental exercise test output **Results:** Hypercapnia significantly decreased during first four months of treatment. pCO_2 was stabilised are 30% less that initial value. Degree of airway obstruction was less severe after eight months of therapy, although a restrictive pattern was observed in this period. A positive change in QOL was found. There was an increase in physical activity **Conclusion:** Reduction of hypoxemia parallel to the alleviation of hypercapnia may reverse the patient's continuously declining condition of advanced COPD
Benhamou, Muir, Raspaud, Cuvelier, Girault, Portier, & Menard (1997)[43] France	Chest	**Study type:** Comparative case-controlled study **Level:** II **Patients:** Diffuse bronchiectasis and severe chronic respiratory failure **Sample size:** N = 28	**Aim:** Evaluate long-term efficacy and tolerance of nasal mask ventilation (NMV) **Design:** Two groups of 14 patients with diffuse bronchiectasis and severe chronic respiratory failure (CRF) given either Long-term Oxygen (LTO) plus NMV or LTO only **Outcomes:** hospitalizations, blood gases, vital capacity, FEV_1 and survival **Results:** Days of hospitalization were significantly reduced after institution of NMV in the patient group. No significant difference between groups on PaO_2 evolution and overall survival. Long-term tolerance and compliance remained satisfactory for 11 patients **Conclusion:** NMV is feasible long-term home treatment in patients with diffuse bronchiectasis
Budweiser, Heinemann, Fischer, Dobroschke, & Pfeifer (2005)[44] Germany	Respiratory Medicine	**Study type:** Uncontrolled retrospective explorative study **Level:** III **Patients:** Stable COPD **Sample size:** N = 46	**Aim:** Investigate long-term reduction of hyperinflation in stable COPD by non-invasive nocturnal home ventilation **Design:** Review of patients after 6 and 12 months. Oxygen was supplemented as required to achieve oxygen saturation of more than 90% **Outcomes:** Blood gas, inspiratory muscle function and survival **Results:** One-year survival was 89.1%. Ventilation was significantly associated with reduction in nocturnal and daytime partial pressure of arterial carbon dioxide ($PaCO_2$). Decreases in the ratio of residual volume to total lung capacity (RV/TLC) of 5.2% at 6 months and 3.9% at 12 months, with consequent improvements in inspiratory capacity, vital capacity and FEV_1. For

			patients with the most severe hyperinflation, inspiratory positive airway pressure correlated with reductions in $PaCO_2$ and RV/TLC **Conclusion:** In stable COPD, long-term application of nocturnal NPPV decreased hyperinflation in terms of reduction in RV/TLC, thus improving inspiratory capacity
Cano, Roth, Court-Fortune-, Cynober, & Gerard (2002)[45] France	European Respiratory Journal	**Study type:** Cross-sectional survey **Level:** III **Patients:** COPD, restrictive disorders, mixed respiratory failure, neuromuscular diseases, bronchiectasis **Sample size:** N = 744	**Aim:** identify clinically-relevant tools for routine nutritional assessment; estimate the prevalence of malnutrition; and determine the relationships between nutritional status and respiratory impairment/disability and smoking. Important to note study does not define whether HMV refers to invasive or NIV **Design:** 744 patients with COPD (40%), restrictive disorders (27%), mixed respiratory failure (15%), neuromuscular diseases (13%) and bronchiectasis (5%). Twenty-two outpatient clinics participated in assessment of nutritional status of patients on home LTOT and/or HMV within Association Nationale pour Le Traitment à domicile de l'Insuffisance Respiratoire chronique network **Outcomes:** underlying respiratory disease, length and type of home treatment, blood gases in room air and with LTOT/HMV, forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and six-minute walking distance test in room air **Results:** FFM was the most sensitive parameter for detecting malnutrition, being abnormal in 53.6% of patients, while BMI was < 20 in 23.2%, serum albumin < 35 g·L–1 in 20.7 %, and serum transthyretin < 200 mg·L–1 in 20% **Conclusion:** Malnutrition is highly prevalent in home-assisted respiratory patients and is related to causal disease, forced expiratory volume in one second, smoking and disability
Carroll & Branthwaite (1988)[46] United Kingdom	Thorax	**Study type:** Case series **Level:** III **Patients:** Respiratory failure and hypoventilation **Sample size:** N = 10 (4 with COPD)	**Aim:** Examined nocturnal hypoventilation by nasal intermittent positive pressure ventilation **Design:** Patients were reassessed from three to nine months when all had stated that they had complied with request to use ventilator at home while sleeping at night **Note:** Insufficient detail to ascertain outcomes for COPD patients alone; no further additional data extraction made
Chailleux, Fauroux, Binet, & Dautzenberg (1996)[47] France	Chest	**Study type:** Analysis of national French database **Level:** NA	**Aim:** Study performed 10-year analysis of survival predictors in patients receiving domiciliary oxygen therapy or mechanical ventilation **Design:** Patients receiving LTOT or Prolonged mechanical ventilation (non-invasive or via tracheostomy) **Note:** Specific effects of non-invasive ventilation were not examined – no further data

		Patients: Variety of obstructive, restrictive and mixed lung diseases **Sample size:** N = 26,140	extraction was made due to lack of detail concerning NIV
Chevrolet, Rossi, Chatelain, Pahud, Rochat, & Junod (1989)[48] Germany	Therapeutische Umschau	**Study type:** Case reports **Level:** IV **Patients:** COPD and restrictive disorders **Sample size:** N = 11	**Aim:** Described 11 patients receiving nocturnal mechanical ventilation **Design:** Investigated intermittent mechanical ventilation as home care **Outcomes:** No known **Results:** Unclear **Conclusion:** Careful patient selection is needed. Nocturnal mechanical ventilation seems rarely useful in patients with COPD **Note:** Article was written in German, only the abstract was extracted
Chu, Yu, & Tam (2004)[8] Hong Kong	European Respiratory Journal	**Study type:** Survey **Level:** NA **Patients:** Various respiratory conditions **Sample size:** N = 249 (121 with COPD)	**Aim:** Survey several disease categories treated and outcomes of home mechanical ventilation (HMV) use in Hong Kong. Explore differences in pattern of use with other parts of the world **Design:** Survey **Outcomes:** Failure to be completed weaned, repeated respirator failure, symptomatic hypercapnia, sleep disturbance, failure to respond to CPAP **Results:** Bilevel pressure-support ventilators were used in all NIV cases. COPD accounted for 48.6% of all cases; most patients were started on HMV. Predominant mode of HMV was NIV; with only a few tracheostomised patients Most patients tolerated HMV reasonably well. The 3-year HMV continuation rate was 57.5% in the COPD group **Conclusion:** Increase in the number of HMV in Hong Kong
Clini, Sturani, Vitacca, Scarduelli, Porta & Ambrosino (1997)[49] Italy	European Respiratory Journal Supplement	**Study type:** Matched controlled trial **Level:** II **Patients:** Stable COPD patients with chronic hypercapnia **Sample size:** N = 57	**Aim:** Evaluate clinical effectiveness of NIV in domiciliary setting **Design:** Two groups: NIV plus LTOT vs. LTOT alone **Outcomes:** Hospital stay and ICU admissions after 3 and 6 months **Results:** No change in respiratory function and respiratory muscle strength in either group. No significant differences between groups in mortality rate after 1, 2 and 3 years **Conclusion:** Overall, addition of domiciliary NIV to LTOT significantly reduced the high risk of an ICU management and slightly improved the exercise capacity of patients **Note:** Only available in abstract format

Clini, Vitacca, Foglio, Simoni, & Ambrosino (1996)[50] Italy	European Respiratory Journal	**Study type:** Non-randomised, controlled trial **Level:** II **Patients:** Severe COPD **Sample size:** N = 34 (COPD) N = 29 (Controls)	**Aim:** Evaluated effectiveness of home care programmes **Design:** Three groups: HMV plus LTOT (Group A), or LTOT in home (Group B) and historical group receiving LTOT (Group C) **Outcomes:** Spirometry, maximal inspiratory pressure, arterial blood gas values, mortality rate, hospital and ICU admissions, days of hospitalization **Results:** Four out of 17 (23%) patients in Group A, 3 out of 17 (18%) in Group B, and 5 out of 29 (17%) in Group C died within 18 months. Significant increase in maximal inspiratory pressure following 18 months only in Group A. Compared to 18 months prior to study, hospital admissions and days of hospitalisation significantly decreased two groups submitted to home care **Conclusion:** Home care programmes may be effective in long-term treatment of chronically hypercapnic COPD patients and might reduce hospital admissions. Overall, patients with COPD undergoing long-term home supervision programmes with either NMV plus LTOT or LTOT alone had similar successes in maintaining stability of lung function and ABG values and in reducing number of respiratory and ICU admissions
Criner, Brennan, Travaline, & Kreimer (1999)[20] USA	Chest	**Study type:** Descriptive analysis of prospectively collected data **Level:** III **Patients:** Restrictive ventilatory disorders or COPD **Sample size:** N = 40 (20 with severe COPD)	**Aim:** Examine acute and chronic effects of NPPV on gas exchange, functional status, and respiratory mechanics in patients with chronic respiratory **Design:** Initiated NPPV in a non-invasive respiratory care unit then followed patients after discharge in a comprehensive outpatient program **Outcomes:** Gas exchange and functional status **Results:** NPPV improved gas exchange and functional status for chronic respiratory failure. In moderately ill patients with chronic respiratory failure, NPPV was associated with acute and chronic improvements in gas exchange and functional status. In chronic NPPV was not associated with an improvement in spirometry or respiratory muscle strength. 65% of patients continued to use NPPV on a chronic basis. Only half of patients with severe COPD and hypercapnic respiratory failure continued to use NPPV therapy **Conclusion:** Minor complications and changes in gas exchange required frequent adjustments in face mask or ventilator settings to maintain effectiveness of outpatient therapy. Many patients did not tolerate NPPV on a chronic basis. Follow-up is needed to correct problems with NPPV and ensure patient compliance
Dobrynski, Janssens, De Muralt Breitenstein, & Pavlovic (1997)[51]	European Respiratory Journal Supplement: abstract	**Study type:** Cohort Study **Level:** II **Patients:**	**Aim:** Evaluate all patients enrolled at their clinic following home non-invasive NPPV **Design:** Single arm study with patients receiving NPPV. Follow-up under NPPV was 17±2 months **Outcomes:** ABG, breathing pattern, airway occlusion pressure, hospital stays **Results:** Indications for home NPPV were: a) repeated episodes of acute respiratory failure (n =

Switzerland		Severe COPD **Sample size:** N = 87 (nine with COPD)	4); progressive hypercapnia (n = 4) and sever cor pulmonale (n = 1). Eight patients received bi-level pressure devices and one a volume ventilator. No patient abandoned treatment. Shortly after beginning NPPV there was a significant improvement of $PaCO_2$. After several months treatment this was maintained. In-house hospital days were significantly reduced **Conclusion:** In selected hypercapnic COPD patients NPPV at home is well accepted, can have longstanding benefits on $PaCO_2$ and may decrease frequency and length of hospital admission for acute respiratory failure **Note:** Information was extracted from a conference abstract
El-Husseini, Roche, Dusser, Viaux, Fuhrman, Similowski, Herer, & Huchon (2002)[52] France	Meeting of the American Thoracic Society	**Study type:** Longitudinal study: Case series **Level:** III **Patients:** COPD **Sample size:** N = 876 (316, 36.1% with COPD	**Aim:** Describe characteristics/outcomes of COPD patients treated with LT-NIMV. Examine initial and follow-up records of 1,025 patients in whom domiciliary NIMV was provided for respiratory assistance (CARDIF) between 1988 and 2001 **Design:** LT-NIMV in home **Outcomes:** Duration of treatment and survival **Results:** Initial characteristics of COPD patients were (mean ± SD): age 65±9 years, male gender 71.2%, FEV_1 33±16% of predicted, FEV_1/FVC ratio 45±17%. 244 (77%) patients had long-term oxygen therapy before initiation of NIMV. NIMV was stopped after a mean duration of 52±31 months in 206 patients including 161 deaths. Survival of COPD patients in whom LT-NIMV was initiated during 1993 was significantly lower than all patients (9-year survival rate 25.8% vs 50.5%; p = 0.03) **Conclusion:** Severe hypercapnic COPD is the main motive of LT-NIMV. COPD patients receiving NIMV had poorer prognosis than the whole group **Note:** abstract to ATS meeting 2002
Elliott, Mulvey, Moxham, Green, & Branthwaite (1991)[53] United Kingdom	European Respiratory Journal	**Study type:** Case series **Level:** III **Patients:** Severe COPD **Sample size:** N = 8	**Aim:** Examine domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD in relation to mechanisms underlying changes in arterial blood gas tensions. Investigate contribution of changes in respiratory muscle strength, the ventilatory response to CO_2 and ventilatory function to changes in arterial blood gas tensions **Design:** six months of domiciliary nasal intermittent positive pressure ventilation **Outcomes:** Arterial blood gas tensions, breathing pattern during resting ventilation, airway occlusion pressure, respiratory muscle strength, load and drive. Each measured at start and after six months home use **Results:** Six patients had reduction and two had increase in arterial carbon dioxide tension ($PaCO_2$). Seven had improvements in arterial oxygen tension (PaO_2), during daytime spontaneous breathing. Reduction in $PaCO_2$ was not related to increased inspiratory muscle strength but was correlated with a decrease in gas trapping and in the residual volume. Change in $PaCO_2$ correlated with increase in ventilation at an end-tidal CO_2 of 8 kPa during re-breathing

			Conclusion: Data do not support the hypothesis that improvements were due to the relief of muscle fatigue since the changes in arterial blood gas tensions were small. Raises questions about benefits of NPPV for routine use for COPD
Elliott, Simonds, Carroll, Wedzicha, & Branthwaite (1992)[39] United Kingdom	Thorax	**Study type:** Case series **Level:** III **Patients:** Hypercapnic respiratory failure due to chronic obstructive lung disease **Sample size:** N = 12 (eight pts with six months)	**Aim:** Investigate nocturnal nasal intermittent positive pressure ventilation (NNPPV) in home setting for hypercapnic respiratory failure due to chronic obstructive lung disease. Evaluate effects on sleep and QOL **Design:** NNPPV in home at night **Outcomes:** Arterial blood gas tensions and QOL were measured at start and after 6 months of home use **Results:** Improvements found at 6 and 12-month follow-up in terms of PaO_2 and bicarbonate ion concentration during the day. No changes in QOL **Conclusion:** Nasal intermittent positive pressure ventilation can be used effectively at home during sleep in selected patients with chronic obstructive lung disease. Need a comparison with long-term oxygen therapy
Farre, Lloyd-Owen, Ambrosino, Donaldson, Escarrabill, Fauroux, Robert, Schoenhofer, Simonds, & Wedzicha (2005)[54] European	European Respiratory Journal	**Study type:** Large-scale survey **Level:** NA **Patients:** Chronic respiratory failure **Sample size:** > 20,000	**Aim:** Examine quality control of equipment in home mechanical ventilation (HMV) **Design:** Survey of HMV **Outcomes:** Servicing of ventilators, information the prescriber receives about ventilator servicing, role played by patient regarding servicing, part played by prescriber in ventilator quality control, whether prescriber was aware of adverse incident centres **Results:** Quality-control procedures of HMV showed considerable variability between and across European countries. Lack of standardised protocols. Poor exchange of information and feedback between the prescribing centres and the external companies performing the ventilator servicing **Conclusion:** Minority of centres participate in aspects related to equipment quality control. Few centres are aware of the procedures of vigilance of medical devices and few knew about the existence of associations of HMV patients. Larger prescribe centres appear to have improved HMV quality-control procedures **Note:** Difficult to formally evaluate benefits of NIV in this study since HMV encompassed both NIV or ventilation via tracheotomy
Foglio, Clini, Simoni, Quadri, Vitacca (1994)[55] Italy	European Respiratory Journal	**Study type:** Case series **Level:** III **Patients:** COPD who presented with	**Aim:** Report preliminary results in the follow up of 12 COPD patients **Design:** Two groups – Home care ventilation for 18 months or periodic domiciliary controls. Patients were trained in hospital. Pressure support ventilation was delivered by nasal mask for at least 8 hours during the night, oxygen was added if $SaCO_2$ did not reach 90% **Outcomes:** Number of hospitalisations and total days in hospital **Results:** Before home NIV the following values were obtained: pH 7.37±0.02, $PaCO_2$ 51±6 and

		chronic respiratory failure **Sample size:** N = 12	PaO_2 65±5 mm Hg. After 18 months the mean lung function data changed as follows: FEV_1 984±385 ml/sec, FVC 2170±1094 ml, MVV 30±10 l/m, pH 7.37±0.03, $PaCO_2$ 54±10 and PaO_2 66±9 mm Hg. Number of hospitalisations and total days of hospital stay significantly decreased comparing the follow-up with similar period before home NIV **Conclusion:** Results encourage the use of home NIV in COPD **Note:** Abstract from a conference
Goldstein, Psek, & Gort (1995)[56] Canada	Chest	**Study type:** Small-scale survey **Level:** NA **Patients:** Various respiratory conditions **Sample size:** 98 (9% with COPD)	**Aim:** Examine the perception of impact of home mechanical ventilation on the lives, ability to cope and level of satisfaction with their decision to cope with ingoing ventilatory support **Design:** HMV group **Outcomes:** Impact of HMV **Results:** Three patients with COPD used HMV at night and occasionally during the day and six used it at night. Seven patients with COPD thought HMV improved their symptoms. Six patients with COPD thought HMV limited their mobility and freedom **Conclusion:** Ventilator users adapted well to ongoing ventilator support at home, which shows the positive aspects of HMV
Hilbert, Vargas, Valentino, Gruson, Gbikpi-Benissan, Cardinaud, & Guenard (2002) [57] France	Critical care medicine	**Study type:** Prospective non-randomised controlled clinical study **Level:** II **Patients:** Episodes of acute exacerbation of COPD **Sample size:** N = 109	**Aim:** Compare outcomes of episodes of acute exacerbation of COPD with mask intermittent positive-pressure ventilation (MIPPV) in patients with home MIPPV and in patients without home ventilatory support **Design:** Two groups - with home MIPPV (n = 31) and without home MIPPV (n = 78) all with acute exacerbations of COPD. Compared patients successfully ventilated with MIPPV with those failing MIPPV. MIPPV was performed in a sequential mode and delivered through a full-face mask with a bilevel positive airway pressure system **Outcomes:** Need for endotracheal intubation and mechanical ventilation at any time in study, septic complications, pneumonia, length of stay in ICU, mortality **Results:** No significant differences between groups with and without home ventilation, in success rates and ICU deaths. Significant difference between groups in length of ICU stay. In survivors and in groups with and without home ventilation, respectively, the total time of ventilatory assistance in intensive care unit was significant **Conclusion:** MIPPV may be favourable during episodes of acute exacerbations in COPD. MIPPV could benefit selected patients in management of acute respiratory failure
Janssens, Derivaz, Breitenstein, De Muralt, Fitting, Chevrolet, & Rochat (2003)[58]	Chest	**Study type:** Prospective descriptive study **Level:** III	**Aim:** Examine changing patterns in long-term NIV **Design:** Home nasal positive-pressure ventilation (NPPV) using annual, elective and standardised medical evaluations **Outcomes:** Pulmonary function tests, arterial blood gas levels, health status, compliance, survival, probability of pursuing NPPV and hospitalization rates

Switzerland		**Patients:** Various respiratory conditions **Sample size:** N = 211 (58 with COPD)	**Results:** Home NPPV therapy was associated with a significant reduction in hospitalizations in all groups, although limited to the first two years of treatment in COPD patients. Compliance with treatment was satisfactory. Home NPPV therapy was associated with acceptable health-related QOL, with low dyspnea scores and anxiety or depressive disorders similar to general population. NPPV appears cost-effective, mainly due to reduction in number of hospitalizations for cardiac or respiratory illness **Conclusion:** Cost-effectiveness has improved over 10 years because of wider use of pressure-cycled ventilators, which appear as effective as volume-cycled ventilators for home care and are less expensive
Janssens, Penalosa, Degive, Rebeus, & Rochat (1996[59]) Switzerland	Monaldi Arch Chest Dis	**Study type:** Prospective non-randomised controlled clinical study **Level:** II **Patients:** Various respiratory conditions **Sample size:** N = 31	**Aim:** Compare the QOL of patients under home mechanical ventilation (HMV) for restrictive lung disease, with QOL of patients with COPD, having similar decrease in forced expiratory volume in one second (FEV_1), but not receiving HMV **Note:** Not directly relevant to present report, but this paper provides a useful discussion of the impact of HMV in various respiratory conditions in comparison to patients with COPD who receive just LTOT
Jones, Packham, Hebden, & Smith (1998)[60] United Kingdom comments: Cooper (1999)[61]	Thorax	**Study type:** Case series **Level:** III **Patients:** Severe stable chronic type II respiratory failure due to COPD **Sample size:** N = 11	**Aim:** Examine long-term benefits of home treatment in COPD and application of nocturnal intermittent positive pressure ventilation (NNPPV) **Design:** NNPPV plus LTOT **Outcomes:** Hospital admissions, spirometric parameters, body mass index, arterial blood gas tensions, survival, use of general practitioner resources and patient satisfaction **Results:** Eleven patients in severe stable chronic type II respiratory failure due to COPD who were unresponsive to conventional treatments experienced symptomatic hypercapnia when receiving sufficient supplementary oxygen to result in an arterial oxygen saturation (SaO_2) of > 90% were included in the study. Hospital admissions and GP consultations were reduced by 50% after one-year compared with the year before NNPPV. Sustained improvement in arterial blood gas tensions at 12 and 24 months. Median survival was 920 days, no patient died in first 500 days **Conclusion:** Domiciliary NNPPV resulted in improved arterial blood gas tensions, reduced both hospital admissions and GP visits in patients with severe COPD in hypercapnoeic respiratory failure

Laub, Berg, & Midgren (2004)[62] Sweden	Respiratory Medicine	**Study type:** Prospective descriptive study **Level:** III **Patients:** Unclear **Sample size:** N = >1000	**Aim:** Examine local differences in prescription pattern of home mechanical ventilation (HMV) for a Swedish population **Note:** Unclear whether this involved COPD patients no differentiation. No further data extraction was made
Leger, Bedicam, Cornette, Reybet-Degat, Langevin, Polu, Jeannin, & Robert (1994)[63] France	Chest	**Study type:** Case series: Retrospective analysis **Level:** III **Patients:** Various respiratory conditions **Sample size:** N = 276 (50 were COPD)	**Aim:** Long-term follow up in patients with severe chronic respiratory insufficiency **Design:** Nasal intermittent positive pressure ventilation (NNPPV) followed up for ≥ three years **Outcomes:** Lung function, ABG, complications, hospital admissions, management of NNPPV **Results:** Of the COPD patients 24 patients were given NIV following an acute-on-chronic exacerbation, 26 were receiving NIV due to chronic ventilatory failure. Mean age was 63 years, and forced expiratory volume per second of 39% pred. 88% received LTOT plus NIV. 16% of patients died and a large number discontinued NIV. Total of 53% continued with NIV at 3 years. Non-significant arterial oxygen tension (PaO_2) rise and significant $PaCO_2$ decline **Conclusion:** More positive results might have been found had NIV been commenced sooner in natural history of disease
Lloyd-Owen, Donaldson, Ambrosino, Escarabill, Farre, Fauroux, Robert, Schoenhofer, Simonds, & Wedzicha (2005)[64] European	European Respiratory Journal	**Study type:** Multi-centred survey **Level:** NA **Patients:** Various respiratory conditions **Sample size:** N = 21,526	**Aim:** Perform a detailed survey of HMV use in 16 European countries **Note:** HMV was defined as non-invasive ventilation or ventilation via a tracheostomy for a period of ≥ 3 months on a daily basis carried out mostly in the user's home or other long-term care facility. This study did not differentiate different forms of HMV. Different patterns of HMV use were found, especially for application in older patients with COPD Also see Lloyd-Owen & Wedzicha (2002[65]) in Meeting of the American Thoracic Society
Marino (1991)[38] USA	Chest	**Study type:** Case series **Level:** III **Patients:** COPD, obesity	**Aim:** Evaluate intermittent mechanical ventilation via nasal CPAP mask **Design:** Ventilation support provided 6 to 10 hours daily in home and reassessed six to ten months on daily volume cycled ventilation **Outcomes:** ABG, spirometric and clinical status classification **Results:** Six patients with COPD and the patient with hypothyroidism responded well with improvements in blood gas values and clinical status. Two remaining patients with COPD and

		hypoventilation syndrome, severe hypothyroidism **Sample size:** N = 13 (10 with COPD)	two with OHS were unable to use system. Four patients with COPD and chronic respiratory failure were maintained on daily volume ventilation via nasal mask for 20 months with improvements **Conclusion:** Volume ventilation through nasal CPAP mask is feasible strategy for long-term mechanical ventilation to selected patients with COPD and respiratory failure
Mikelsons, Muncey, & Wedzicha (2006) United Kingdom	Masters degree thesis, Cambridge University	**Study type:** Mixed methods multiple embedded case study design **Level:** III **Patients:** COPD **Sample size:** 26	**Aim:** Explore COPD patients' experience of using NIV at home, compliance rates, recommendations for improving machine use, and rating of QOL and anxiety/depression **Design:** Data was collected from participants with COPD using NIV at home. Interviews at home, demographic data and questionnaires **Outcomes:** St. George's Respiratory Questionnaire (SGRQ) and the Hospital Anxiety & Depression Scale (HADS) **Results:** Domains of 'activity' (mean: 90.42, SD 9.12) and 'anxiety' (mean: 8.73, SD 5.14) were rated highest in SGRQ and HADS, respectively. All participants described symptomatic relief from using NIV. Seven participants reported feeling less anxious about breathlessness since beginning NIV because of relief they gained. Three participants did not suffer with depression either before or since beginning NIV **Conclusion:** By using data sources the study provided a useful insight into the variability between participants in terms of presentation of disease, scores for QOL and anxiety and depression and in self-reported experience. The findings suggest that patients using NIV at home appear to benefit from identifying and self-selecting care and services appropriate to their own individual needs
Oscroft, Pilsworth, Quinnell, Shneerson, & Smith (2005)[66] United Kingdom	Thorax	**Study type:** Retrospective case note analysis **Level:** III **Patients:** Severe hypercapnic COPD **Sample size:** N = 28	**Aim:** Examine commencing domiciliary long-term NIV in patients with poor prognostic markers and in whom consideration of long-term NIV is recommended by NICE **Design:** Long-term NIV at home **Outcomes:** ABG and survival **Results:** Blood gases at discharge following initiation of long-term NIV were significantly improved. Good survival and sustained improvements in arterial blood gas measurements. **Conclusion:** RCTs of long-term NIV have so far provided little evidence of survival benefit. It should be recognised that previous trials have had poor compliance, patient selection, a lack of monitoring to confirm correction of nocturnal hypoventilation and the use of low ventilatory pressures. The present study found that long-term domiciliary NIV can improve survival in severe hypercapnic COPD
Perrin, El Far,	European	**Study type:**	**Aim:** Examined domiciliary nasal intermittent positive pressure ventilation (NNPPV) plus long-

Vandenbos, Tamisier, Dumon, Lemoigne, Mouroux, & Blaive (1997)[67] France	Respiratory Journal	Prospective case series **Level:** III **Patients:** Hypercapnic patients with stable COPD **Sample size:** N = 14	term oxygen therapy on QOL and lung function **Design:** Baseline data at four weeks were compared to 6-month retesting **Outcomes:** Arterial blood gas tensions, spirometric parameters and QOL **Results:** Gastro-intestinal inflation was found in eight patients. Arterial carbon dioxide tension and daytime arterial oxygen tension improved. Significant improvements for: the total SGRQ score, total FVNHP score, physical mobility, energy component and emotional reactions scores **Conclusion:** Domiciliary NNPPV plus long-term oxygen therapy improved blood gases in spontaneous ventilation and QOL of patients with COPD
Quinnell, Pilsworth, Shneerson, & Smith (2006)[68] United Kingdom	American Journal of respiratory Critical Care Medicine	**Study type:** Retrospective analysis **Level:** III **Patients:** All had a discharge diagnosis of COPD **Sample size:** N = 67	**Aim:** Present outcomes for COPD patients from 1992 to 2003. Attempt to identify factors associated with weaning outcome and survival **Design:** Weaning from invasive mechanical ventilation. NIV and no NIV, LTOT **Outcomes:** Weaning success, hospital and long-term survival **Results:** NIV was used in weaning 40 of 67 patients, including 2 of the 3 patients who failed to wean. Twenty-five patients continued with long-term NIV. Mean inspiratory pressure (n = 21) was 28 cm H2O (SD, 4.7 cm H2O). Five long-term NIV patients were discharged with LTOT, and 11 patients were discharged on LTOT alone. Median survival was 2.5 years. One-year, 2-year, and 5-year survival rates were 68%, 54%, and 25%, respectively. Long-term survival was inversely associated with age and LOS in the ICU and the RSSC. Provision of maintenance NIV after weaning was associated with better long-term survival, independent of age and LOS ($p = 0.03$) **Conclusion:** Results showed use of NIV can be successful in weaning most COPD patients from prolonged invasive ventilation. Long-term NIV may improve survival in selected patients.
Schucher, Hein, & Magnussen (1999)[69] Germany	Medizinische Klinik	**Study type:** Retrospective analysis **Level:** III **Patients:** Various respiratory conditions **Sample size:** N = 144 (54 with COPD)	**Aim:** Retrospectively analyzed long-term results of non-invasive home mechanical ventilation **Design:** NIV HMV **Outcomes:** Acceptance rates **Results:** Twenty-eight patients did not accept HMV (19%), 17 of which had COPD (32%). Thirty-nine of 113 patients completed nasal ventilation for at least one-year. Significant improvement in hypercapnia in COPD group. HMV improves hypercapnic ventilatory failure independent of disease **Conclusion:** Acceptance rate is lower in patients with COPD in comparison to CWD and NMD **Note:** Article was written in German, only abstract was extracted
Schucher, Hein, &	Pneumologie	**Study type:**	**Aim:** Analyse results of blood gases and lung function in stable COPD patients who underwent

Magnussen (1999)[70] Germany		Retrospective analysis **Level:** III **Patients:** Stable hypercapnic COPD **Sample size:** Unclear	a trial of NPPV **Design:** NPPV was performed over through nasal mask. Patients applied ventilator during night for at least 6 hours **Outcomes:** ABG, compliance, respiratory muscle strength **Results:** At baseline $PaCO_2$ during NPPV was 43 +/- 6 mmHg. Five patients discontinued NPPV for long-term treatment, 20 patients (80%) continued NPPV for 13 +/- 8 months, two patients died during NPPV. NPPV had no significant influence on lung function or respiratory muscle strength. Significant improvement in $PaCO_2$ during spontaneous breathing **Conclusion:** NPPV improves hypercapnic ventilatory failure in subgroup of severe stable COPD, if patients are motivated and home ventilation is adequately performed **Note:** Article in German, only abstract was extracted
Simonds & Elliott (1995)[40] United Kingdom	Thorax	**Study type:** Retrospective analysis **Level:** III **Patients:** Hypercapnic respiratory failure - chest wall restriction, neuromuscular disorders, or COPD **Sample size:** N = 180 (33 with COPD)	**Aim:** Evaluate outcomes of domiciliary nasal intermittent positive pressure ventilation (NNPPV) **Design:** Domiciliary NNPPV **Outcomes:** health status, survival and pulmonary function **Results:** Five-year probability of continuing NNPPV for COPD (n = 33) was 43% (95% CI 6 to 80). One-year after beginning NPPV electively mean (SD) PaO_2 compared with pre-treatment value was PaO_2 +0.8 (1.0) kPa, $PaCO_2$ - 0.9 (0.8) kPa in patients with obstructive lung disease. Withdrawal from NNPPV due to intolerance was higher in patients with COPD than other groups with a probability of continuing NNPPV at 5 years being 43% **Conclusion:** Outcome in patients with end stage hypercapnic COPD who fail to tolerate LTOT is positive. Long-term outcome of domiciliary NNPPV in patients with COPD and progressive neuromuscular disorders show benefit in some subgroups
Sivasothy, Smith, & Shneerson (1998)[71] United Kingdom	European Respiratory Journal	**Study type:** Retrospective analysis **Level:** III **Patients:** Hypercapnic ventilatory failure due to COPD **Sample size:** N = 26	**Aim:** Retrospectively study of hypercapnic ventilatory failure due to COPD in whom oxygen therapy caused worsening hypercapnia **Design:** Retrospective examination. All patients received mask ventilation (15 nasal; 11 face masks) at night or daytime sleep. Additional oxygen therapy was required in 15 patients. Patients were reviewed at 1 month, 6 months, 12 months and 2 years **Outcomes:** Survival, QOL, ABG measurements **Results:** Mean annual death rate was 10.8%, survival was 92% (1 year) and 68% (3-year). At 1-year median daytime $PaCO_2$ declined by 1.35 kPa and arterial oxygen tension increased by 2.4 kPa. QOL improved significantly at 6 months **Conclusion:** No difference in survival between mask intermittent positive pressure ventilation alone or mask intermittent positive pressure plus supplementary oxygen therapy
Windisch, Kostic,	Chest	**Study type:**	**Aim:** The objective of the present study was to assess changes in blood gas levels and long-term

Dreher, Virchow, & Sorichter (2005)[72] Germany		Retrospective study **Level:** III **Patients:** COPD due to chronic hypercapnia **Sample size:** N = 34	outcomes of patients were treated by controlled NPPV aimed at achieving maximal improvement of $PaCO_2$ **Design:** Retrospectively examined patients who had titrated controlled pressure-limited NPPV to achieve a maximal improvement in $PaCO_2$ **Outcomes:** ABG, lung function parameters, inspiratory mouth occlusion pressures, duration in hospital, time of death **Results:** Daytime $PaCO_2$ during spontaneous breathing decreased by 6.9 ± 8.0 ($p < 0.001$); while daytime PaO_2 increased by 5.8 ± 9.4 ($p = 0.002$); and FEV_1 increased by 0.14 ± 0.16 ($p < 0.001$) after 2 months of NPPV. Achieved with mean inspiratory pressures of 27.7 ± 5.9 cm H2O at a mean respiratory rate of 20.8 ± 2.5 breaths/min. Two-year survival rate was 86% **Conclusion:** NPPV using relatively high inspiratory pressures with a mean of 28 cm H_2O been significantly improve lung function and blood gas levels during spontaneous breathing in patients with stable hypercapnic COPD. FEV_1 increased by a mean of 0.14 L, $PaCO_2$ could be decreased by a mean of nearly 7 mm Hg, and PaO_2 could be increased by nearly 6 mm Hg following two months of predominantly nocturnally applied NPPV. Previous studies that concluded that NPPV has no effect on lung function and blood gas levels in patients with stable COPD are premature and most likely related to insufficient inspiratory pressures
Windisch, Vogel, Sorichter, Hennings, Bremer, Hamm, Matthys, & Virchow (2002)[73] Germany	Respiratory Medicine	**Study type:** Retrospective study **Level:** III **Patients:** Chronic hypercapnic respiratory failure (HRF) due to COPD **Sample size:** N = 14	**Aim:** Investigated whether nasal intermittent positive pressure ventilation (NNPPV) aimed at normalising $PaCO_2$, will reduce $PaCO_2$ during subsequent spontaneous breathing **Design:** Patients were established on passive pressure-controlled NNPPV in a stepwise approach. Assisted ventilation with supplemental oxygen to reach normoxemia was started followed by passive ventilation with a stepwise increment in inspiratory pressure and finally by a stepwise increase in respiratory rate to establish normocapnia **Outcomes:** ABG, lung function parameters **Results:** Baseline pulmonary function parameters were: $PaCO_2$ 59.5 ± 8.4, FEV_1 0.97 ± 0.43 l, mmHg, pH 7.39 ± 0.04, PaO_2 49.9 ± 7.8 mmHg, HCO_3 35.6 ± 5.2 mmol/l. Normoxemia and normocapnia was established by decreasing $PaCO_2$ by 19.5 ± 7.0 mmHg during NNPPV within 8.8 ± 3.8 days ($p < .001$). Spontaneous $PaCO_2$ measured four hours after cessation of NNPPV decreased to 46.0 ± 5.5 mmHg ($p < .001$), and HCO_3 decreased to 27.2 ± 3.0 mmol/l ($p < .001$). At 6 months of follow-up, 11 patients continued NNPPV with stable blood gases and with a significant decrease of P0.1/PImax ($p < .005$) **Conclusion:** Normalisation of $PaCO_2$ by passive NNPPV in patients with HRF due to COPD seems achievable and produces a significant reduction of $PaCO_2$ during subsequent spontaneous breathing. This was associated with improved parameters of respiratory muscle function
Windisch, Dreher,	Respiratory	**Study type:**	**Aim:** Investigated short-term and long-term effects of NPPV on the course of $PaCO_2$ and tidal

Storre, & Sorichter (2006)[74] Germany	Physiology and Neurobiology	Retrospective study **Level:** III **Patients:** Chronic hypercapnic respiratory failure (HRF) due to COPD **Sample size:** N = 24 (12 COPD and 12 restrictive)	volume (TV) during daytime spontaneous breathing **Design:** Two groups of twelve patients (six COPD/six restrictive) who were established on NPPV and 12 controls (six COPD/six restrictive) **Outcomes:** Blood gases, breathing patterns, lung function, inspiratory muscle strength, HR-QOL. Measurements were taken between 0 and 15 hours after cessation of nocturnal controlled NPPV **Results:** $PaCO_2$ decreased step by step during first three hours of spontaneous breathing after switching from NPPV to spontaneous breathing ($p < .05$), but was unchanged in controls. $PaCO_2$ decrease was due to a stepwise increase in TV ($p < .05$). Minute ventilation also stepwise increased ($p < .03$). No significant changes in controls. Maximal inspiratory mouth pressures increased in COPD patients ($p < .05$). Inspiratory impedance and lung function parameters were unchanged. Improvements in HR-QOL were found and correlated with decline of elevated bicarbonate levels ($p < .01$) **Conclusion:** There was a stepwise adaptation process lasting three hours when switching from nocturnal controlled NPPV to daytime spontaneous breathing in which TV increases. Furthermore $PaCO_2$ appears to drop following an initial $PaCO_2$ decrease while on NPPV

4.1 Non-RCT evidence

This section aimed to provide a comprehensive and thorough coverage of the literature concerning domiciliary NIV for the treatment of patients with COPD. A total of 37 studies were identified. Table 3 clearly describes each individual study known to be relevant. We have given specific attention to describing the type of NIV used and the type of COPD being investigated. We have provided information about the level of evidence based on literature provided by the NHS Centre for Reviews and Dissemination (2001[41]). This should be considered carefully when evaluating each individual study.

Due to the wealth of non-RCT evidence reported in Table 3, we have chosen to briefly summarise specific elements of the papers into: patients; interventions; comparators; outcomes; levels of evidence; and place of publication.

a) Patient included in non-RCT studies

The range of different patient groups included in the non-RCT studies varied considerably. Table 4 summarises the 20 different terms used to describe the patient groups found within the 37 studies. The majority of studies used patients with various respiratory conditions, all of which did included COPD. Several studies referred to patients with hypercapnia, severe and stable COPD. On personal communication with Mark Elliott (Consultant in Respiratory Medicine, St James's University Hospital) it was pointed out the terms used to describe patients with COPD are synonymous. Careful consideration of each definition of these patient groups could not be undertaken within the time scale of this report.

Table 4: Different patient groups

Chronic hypercapnic respiratory failure due to COPD **(2 studies)**
COPD **(3 studies)**
COPD due to chronic hypercapnia
COPD who presented with chronic respiratory failure **(2 studies)**
COPD, obesity hypoventilation syndrome, severe hypothyroidism
Diffuse bronchiectasis and severe chronic respiratory failure
Episodes of acute exacerbation of COPD
Hypercapnic patients with stable COPD
Hypercapnic respiratory failure - chest wall restriction, neuromuscular disorders, or COPD
Hypercapnic respiratory failure due to chronic obstructive lung disease
Hypercapnic ventilatory failure due to COPD
Respiratory failure and hypoventilation
Severe COPD **(3 studies)**
Severe hypercapnic COPD
Severe stable chronic type II respiratory failure due to COPD
Severe stable COPD with severe hypoxemia and hypercapnia
Stable COPD
Stable COPD patients with chronic hypercapnia
Stable hypercapnic COPD
Various respiratory conditions **(12 studies)**

The number of participants included in each study also varied. Three studies were surveys involving more than 20,000 participants.[47,54,64]

b) Interventions

Thirteen different terms were reported to describe the types of intervention involving NIV (see Table 5). It is again important to recognise that these differences seem to be

related more to differences in terminology rather than treatment methods. However, differences were noted in the length of time each intervention was given and the time of day (day or night). Several studies also reported the use of supplementary oxygen or LTOT. It was also noted that home mechanical ventilation (HMV) did sometimes refer to patients who were receiving invasive or non-invasive ventilation.[45,54]

Table 5: Types of interventions

Domiciliary NPPV
HMV plus LTOT
Home care ventilation
Long-term NIV
LTOT and/or HMV
LTOT or Prolonged mechanical ventilation (non-invasive or via tracheostomy)
Mask ventilation
NPPV plus LTOT
NPPV was performed through nasal mask
NIV plus LTOT
Passive pressure-controlled NPPV
Titrated controlled pressure-limited NPPV
Weaning from invasive mechanical ventilation

HMV = Home mechanical ventilation; LTOT = Long-term oxygen therapy; NPPV = Non-invasive positive pressure ventilation; NIV = Non-invasive ventilation

c) Comparators

Many of the studies did not use a comparison group. Several studies compared a type of NIV plus LTOT with LTOT alone.[45,47,49,50,68] The majority of studies assessed patients at different time points or reported individual cases. Only one study compared the outcome of episodes of acute exacerbation of COPD treated with mask intermittent positive-pressure ventilation (MIPPV) in patients with home MIPPV and in patients without home ventilatory support. The authors concluded that MIPPV may also be favourable during episodes of acute exacerbations in patients with COPD. Concerning the surviving patients, the total time of ventilatory assistance in ICU and the length of ICU stay were significantly shortened for those with home MIPPV in comparison with patients without home MIPPV.

d) Outcome measures

A total of 62 different outcome measures were reported in the non-RCTs (see Table 6). The most commonly used measures were the assessment of ABG, breathing patterns and lung function. Several studies provided information concerning length of hospital stay (including ICU admission and duration), but less information was reported about the compliance rates of home ventilation.

More recently there appears to be an increasing interest in the assessment of QOL in patients receiving domiciliary NIV[39,67,40,75] In the thesis by Mikelsons et al. (2006[75]) a mixed methods multiple embedded case study design was used to explore COPD patients' experience of using NIV at home, compliance with using their machine, recommendations for improving NIV usage and rating of QOL and anxiety/depression. This is an important study as it provides information from a variety of data sources and demonstrates the variability between participants in terms of presentation of the disease, scores for quality of life and anxiety and depression. Several studies have shown that domiciliary NPPV can produce significant and sustained improvements in arterial blood gas tensions in patients with severe COPD

and hypercapnic respiratory failure who are unresponsive to other treatments. Although the number of patients reported in many of these studies is small, the results appear to be positively in favour of treatment.

Table 6: Outcome measures

Airway occlusion pressure	Acceptance rates
Body mass index	ABG
Breathing patterns	Breathing pattern during resting ventilation
Compliance	Clinical Status Classification
Complications	Complications
Duration of treatment	Duration in hospital
Failure to respond to CPAP	Failure to be completed weaned
Forced expiratory volume in one second	Forced vital capacity
Functional status	Gas exchange
Gases in room air and with LTOT/HMV	Health status
Health status	Hospital admissions
Hospital anxiety & depression scale	Hospital stays
HR-QOL	ICU admissions
Impact of HMV	Incremental exercise test output
Information prescriber gets on ventilator servicing	Inspiratory mouth occlusion pressures
Inspiratory muscle function	Weaning success
Prescriber awareness of adverse incident centres	Inspiratory muscle strength
Load and drive	Lung function
Lung function parameters	Management of NPPV
Maximal inspiratory pressure	Mortality
Need for endotracheal intubation	Involvement of prescriber in quality control
Patient satisfaction	Physiological Measures During Sleep
Pneumonia	Probability of pursuing NPPV
Pulmonary function	QOL
Repeated respirator failure	Respiratory muscle strength
Role played by patient regarding servicing	Servicing of ventilators
Six-minute walking distance test in room air	Sleep disturbance
Spirometric basal test	Spirometric parameters
St. George's respiratory questionnaire	Survival
Symptomatic hypercapnia	Time of death
Use of general practitioner resources	Vital capacity

HMV = Home mechanical ventilation; LTOT = Long-term oxygen therapy; NPPV = Non-invasive positive pressure ventilation; HR-QOL = Health-related quality of life; CPAP = Continuous positive airway pressure

e) Levels of evidence

A variety of different types of study design were reported in this section. The levels of evidence ranged from II to IV. Six studies were rated level II, 24 were level III and two were level IV. The remaining five papers reported were not rated as these each involved surveys. The majority of studies reported in this section involved case series. Therefore, a major limitation of the majority of studies reported was that it they mainly involved retrospective analyses and uncontrolled groups, with only a few providing group comparisons. Few of the studies provided a comprehensive follow-up, assessment of complications and compliance with NPPV.

f) Place of publication

Papers have been reported from United Kingdom (n = 9), France (n = 7), Germany (n = 7), Italy (n = 3), Switzerland (n = 3), European studies (n = 2), United States of America (n = 2), Canada (n = 1), Hong Kong (n = 1), Spain (n =1) and Sweden (n =1).

4.2 Conclusion

In summary, these non-RCT studies have shown that in selective groups of patients (e.g., severe hypercapnia) NPPV can significantly improve gas-exchange. However, despite these positive findings, one must be careful in applying such findings to policy decision as these studies did not include an adequate control group who received the same medical management. What is needed are studies that investigate in a crossover study patients who receive home and hospital-based treatment of NPPV. This will be considered in the next section.

5. Review of RCT evidence

This section of the review will update the previous meta-analysis conducted by Wejkstra et al. (2003[31]).

The search strategy used to identify studies for the review of clinical effectiveness is reported in this section, according to the explicit Quality Standards agreed by InterTASC.

5.1 Search strategy

The aim of the search was to provide a comprehensive retrieval of as many randomised controlled trials (RCTs) concerned with domiciliary non-invasive ventilation for COPD patients

The central issue evaluated in this section of the review relates to what types of patients benefit most from the use of domiciliary non-invasive ventilation for COPD patients

a) Sources searched

Fourteen electronic bibliographic databases were searched, covering biomedical, health-related, science, social science and grey literature (including current research). A list of databases searched is provided in Table 7.

b) Keyword strategies

A combination of free-text and thesaurus terms was used. Filters to retrieve systematic reviews, guidelines, randomised controlled trials and economic evaluations were used with the searches. The search strategies for the major databases are provided in Appendix 2.

c) Search restrictions

Date limits were not used on any other database. Language restrictions were not used on any database, although due to time limitations only relevant studies published in English were reported. All searches were undertaken in January 2006. The review was started in January 2006 and completed in March 2006.

Table 7: Electronic bibliographic and review databases searched

Electronic Bibliographic Databases Searched
BIOSIS previews CINAHL Embase Medline
Review Databases searched
American Thoracic Society British Thoracic Society Clinical trials databases (for example ClinTrials.gov Cochrane Airways Group COPD trial register (contains Medline, Embase, CINAHL trials) Cochrane Controlled Trials Register (CCTR) Cochrane Database of Systematic Reviews (CDSR) Cochrane Library Current Controlled Trials register Current research was identified through searching the National Research Register (NRR) European Respiratory Society Evidence-based medicine reviews Health Technology Assessment Database MRC Clinical Trials Register NHS Economic Evaluation Database OHE HEED Pre-Medline will also be searched to identify any studies not yet indexed on Medline. Science Citation Index and the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA)

Further keyword searching of the WWW was undertaken using the Google search engine. In addition, reference lists were searched for cross-references and abstracts from conference proceedings and meetings were checked.

Inclusion criteria

One reviewer independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by the reviewer were obtained where possible. The relevance of each study was assessed according to the criteria set out below. Any uncertainty was discussed with a second reviewer and resolved by discussion.

Excluded RCTs

The preliminary results of a long-term European multi-centre RCT investigating NIV versus LTOT plus NIV in stable COPD has been reported by Muir et al. (1999[76]). Details of this trial are presented in Table 8. These results found no overall advantage of NIV, rather they suggested that subgroups (e.g., aged > 65 years) might benefit and hospital admissions decline. It should be recognised, however, that the frequency of infective exacerbations was not a primary end point when the study was constructed. These long-term trial of Muir and colleagues were not included in the meta-analysis of RCTs as no full paper has been published. The authors were contacted, but no further information was provided.

Studies which involved the use of exercise as a comparison were excluded from the report (e.g., Garrod, 2000[77]). One study was excluded because it was unclear whether it had been conducted in a domiciliary setting.[78] Finally, one study was excluded because it was principally concerned with ventilator settings and physiological outcomes.[79] A summary of these studies are provided in Table 8.

Table 8: RCTs excluded from inclusion in the meta-analysis

Author/country	Source	Study type/Level /Patients/Sample size	Summary
Diaz, Gallardo, Ramos, Torrealba, & Lisboa (1999)[80] Chile See also: Diaz et al. (2005[78])	American Journal of Respiratory and Critical Care Medicine	**Study type:** Prospective randomised controlled trial **Level:** I **Patients:** Severe stable hypercapnic COPD **Sample size:** N = 18	**Aim:** Evaluate the effects of non-invasive mechanical ventilation (NIMV) on gas exchange and exercise capacity in severe hypercapnic COPD patients **Design:** Two groups – NIMV using BiPAP 3 hours daily, 5 days a week, during 3 weeks (n = 9) and sham ventilation (s-NIMV) using Siemmens Servo 900C ventilator on CPAP = 0cm H_20 **Outcomes:** Spirometry, lung volumes, ABG, breathing pattern, airway occlusion pressure, PIMax and six-minute walking distance (6-MWD) measured at baseline and at end of each week **Results:** Significant increases in NIMV group for PaO_2, V_T, PIMax, 6-MWD and significant decreases in NIMV group for $PaCO_2$, $P_{0.1}$and $P_{0.1}/V_T/T_I$ and FRC decreased and inspiratory capacity increased **Conclusion:** NIMV improves gas exchange and exercise capacity in sever hypercapnic COPD patients. The study does not provide information about mechanisms involved in the decrease of pulmonary hyperflation nor in increase of inspiratory muscle strength **Note:** Abstract from a conference. Unclear whether this was conducted on in domiciliary setting. Based on a recent study by Diaz et al. (2005[78]) (excluded from this review) it appears that ventilation may have been applied under direct supervision by an experienced, registered nurse at the pulmonary function laboratory, on an outpatient basis. If this is the case then this trial should be disregarded. Author was contacted but no response
Garrod, Mikelsons, Paul, & Wedzicha (2000)[77] United Kingdom	American Journal of respiratory Critical Care Medicine	**Study type:** Randomised controlled trial **Level:** I **Patients:** Severe COPD **Sample size:** N = 45	**Aim:** Tested hypothesis that nocturnal domiciliary NPPV with pulmonary rehabilitation will provide greater improvements in exercise capacity, health status, and respiratory muscle performance compared with training alone in patients with severe COPD **Design:** Either exercise training with domiciliary NPPV or exercise training alone **Outcomes:** Lung function, exercise tolerance, exercise capacity (shuttle walk test), mood state, activity of daily living, QOL and sleep monitoring **Results:** Significant improvements in QOL and exercise tolerance after training plus NPPV, compared with exercise training alone. NPPV group showed a significant improvement in inspiratory muscle strength. Found that after 4 weeks of training, improvements in exercise tolerance were similar across groups, but then the NPPV-treated group continued to improve while the exercise-only group showed no additional change **Conclusion**: Study supports use of NPPV as an adjunct to a pulmonary rehabilitation program, but not routine use of domiciliary NPPV in normocapnic COPD patients

Muir, De La Salmoniere, Cuvelier, Chevret, Tengang, Chastang (1999)[76] France	American Journal of Respiratory and Critical Care Medicine	**Study type:** Multi-centre trial **Level:** I **Patients:** Severe hypercapnic COPD **Sample size:** N = 123	**Aim:** Evaluate the survival of severe hypercapnic COPD with long-term home mechanical ventilation **Design:** Two groups - oxygenotherapy alone or nocturnal NPPV with diurnal oxygenotherapy **Outcomes:** Primary endpoint was overall survival. Secondary endpoints were hospitalisation rate and QOL **Results:** Mean ventilation per day was 8.2 hours in NPPV group and oxygenotherapy was taken for 16.5 hours per day. Estimated hazard ratio of death of NPPV treated patients was 0.91 (95%CI: 0.52-1.58) as compared with the oxygen group **Conclusion:** Long-term home mechanical ventilation with NPPV in severe hypercapnic COPD was not associated with improvements in survival **Note:** Abstract from a conference: authors were contacted but no reply
Vitacca (2000)[79]	Chest	**Study type:** Randomised controlled physiological study **Level:** I **Patients:** Stable COPD with chronic hypercapnia **Sample size:** N = 23	**Aim:** Evaluate short-term physiological effects of two settings of nasal pressure-support ventilation (NPSV) in stable COPD patients with chronic hypercapnia **Design:** NPSV in two settings: (a) a usual setting (U) at patient's comfort, actually used in a population who are prescribed home NPSV; and (b) a physiologic setting (PHY) **Outcomes:** ABG, breathing pattern, respiratory muscle function and patient–ventilator interaction **Results:** Twenty-three patients were on domiciliary nocturnal NPSV for mean duration of 31 ± 20 months. All patients tolerated NPSV well throughout the procedure. NPSV significantly improved ABG independent of setting. Both settings induced significant increase in minute ventilation. Both settings reduced diaphragmatic pressure-time product, but reduction was significantly greater with PHY than with U. Eleven of 23 patients with U and seven of 23 patients (30%) with PHY showed ineffective efforts **Conclusion:** NPSV appears effective in unloading inspiratory muscles independent of setting and improving ABG **Note:** This trial was excluded from meta-analysis as it was principally concerned with the ventilator settings and physiological outcomes

Included RCTs

a) Population

Studies that included persons aged over 18 years old. All publications related to children and non-humans were excluded.

b) Intervention

The review included studies investigating nocturnal NPPV via a nasal or facemask for at least five hours each day for at least three weeks. Only studies that were completed in the domiciliary setting were included. Patients in the actively treated group continued to receive their usual management for COPD next to NPPV. The control group received the same management as the study group with the exception that they did not receive NPPV.

c) Comparators

Patients in the treated group with NIV continued to receive their usual management for COPD. The control group received the same management as the study group with the exception of that they did not receive NIV.

d) Types of outcome measures

Blood gases (BG), 6-minute walk (6-MWD), dyspnoea, health status (health-related QOL measurements), and respiratory muscle function (muscle endurance or muscle strength, including PI max (maximal inspiratory pressure). Lung function (FEV_1 & Vital Capacity) and sleep efficiency.

e) Study design

RCTs of patients with COPD comparing NPPV ventilation plus standard therapy with standard therapy alone. Any exceptions are discussed. Only studies that were completed in the domiciliary setting were included.

Data extraction strategy

Data relating to both study design and quality were extracted by one reviewer into a standardised data extraction form and independently checked for accuracy by a second. Any discrepancies were resolved through consensus. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Quality assessment strategy

The quality of the individual studies was assessed by one reviewer and independently checked for agreement by a second. Disagreements were resolved through consensus. The quality of the clinical effectiveness studies was assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination (2001[41]). Included studies were assessed for quality and methodological details without any bias towards the results of the study, and there was no blinding of authorship. For all the included studies, quality scores for concealment of allocation, completeness of follow up and blinding of assessment of outcome measures were given to each study.

Methods of data synthesis

Details of the extracted data and quality assessment for each individual study of clinical effectiveness are presented in structured tables and as a narrative description.

The possible effects of study quality on the effectiveness data and review findings are discussed. Data are reported separately for each outcome measure.

In addition, results of eligible studies were statistically synthesised (meta-analysed) if appropriate (there was more than one trial with similar populations, interventions and outcomes) and possible (there were adequate data). All analyses were by intention-to-treat. Combined hazard ratios and 95% confidence intervals (CI) were calculated using the Cochrane Collaboration Review Manager 4.2.3 software. This uses the log hazard ratio and its variance from the relevant outcome of each trial. These, in turn, were calculated using a Microsoft Excel spreadsheet.

A fixed effects model was used for the analyses. Heterogeneity between studies was tested where appropriate using the chi^2 test and I^2 measure. The chi^2 test measures the amount of variation in a set of trials. Small p-values suggest that there is more heterogeneity present than would be expected by chance. Chi^2 is not a particularly sensitive test: a cut-off of $p < 0.10$ is often used to indicate significance, but lack of statistical significance does not mean there is no heterogeneity. The I^2 measure is the proportion of variation that is due to heterogeneity rather than chance. Large values of I^2 suggest heterogeneity. I^2 values of 25%, 50%, and 75% could be interpreted as representing low, moderate and high heterogeneity.

5.2 Description on RCTs

A summary of the RCT evidence are provided in Table 9.

Casanova et al. (2000[34]) found that in patients randomised to receive NPPV they had a reduction in admissions at three and six months, but this was not maintained at long-term follow-up. The number of hospital admissions decreased significantly in the NPPV group compared with the control group at three months, but this was not maintained. There was an improvement in the Borg dyspnea scale and in the psychomotor coordination neuropsychological measure at six months, but the clinical importance of these changes appeared minimal. There was no significant difference in the number of COPD exacerbations or survival at six months. Overall, the authors concluded that this study did not demonstrate a benefit of NPPV when added to standard treatment. These results support the findings from several other studies (e.g., Strumpf et al., 1991[81]; Gay et al., 1996[82]; Clini et al., 1998[83]) that demonstrated little benefit of NPPV in patients with stable severe COPD, and conflict studies which show favourable results (e.g., Meecham Jones et al., 1995[27])

Clini et al. (2002[35]) conducted an Italian multi-centre study. Patients were randomized to receive NPPV plus long-term oxygen therapy or long-term oxygen therapy alone. At the end of the two-year follow-up period they found improved QOL, lower $PaCO_2$ and reduced dyspnoea scores in COPD patients who were using NIV compared to LTOT. However, there was no difference found in other parameters, including exercise tolerance, hospital admission rate, lung function, survival and sleep quality. Although hospital admissions were not found to differ between the groups, the ICU admissions did decline among NIV patients. In terms of the cumulative days spent in hospital due to respiratory exacerbations there was a trend in favour of those receiving NPPV (12.6±7.9 vs. 16.9±10.3), respectively. It is important to note that this study was only powered to investigate a reduction in $PaCO_2$ of 5 mm Hg (0.67 kPa) but not in other parameters, this is an important consideration

when interpreting the findings. Wijkstra (2003[1]) claimed this study suggests that NPPV could provide beneficial effects to some patients with COPD, but these improvements were not sufficiently large enough to advocate the widespread use of NPPV.

Gay et al. (1996[82]) performed a study in which patients were randomized to receive NPPV with 10cm H_2O positive inspiratory pressure or sham NPPV with no delivered pressure for three months. There were found to be no significant difference between the two groups in terms of lung function modification, $PaCO_2$ reduction, sleep efficiency and nocturnal O_2 saturation.

Following the earlier findings by Elliott et al. (1992[39]) which found an improvement in diurnal PaO_2 and $PaCO_2$ in COPD patients using NIV compared to LTOT, Meecham-Jones et al. (1995[27]) reported a randomized crossover study comparing oxygen therapy alone with NPPV plus long-term oxygen therapy. After 6-months the addition of NPPV was associated with an improvement in PaO_2 from 44.3 mm Hg (5.9 kPa) to 50.3 mm Hg (6.7 kPa), and a reduction in $PaCO_2$ from 57 mm Hg (7.6 kPa) to 52.5 mm Hg (7.0 kPa). Furthermore, improvements were also found in the NPPV group in terms of total sleep time, sleep efficiency and QOL scores (impact, symptoms, & total QOL scores) as measured by the St George's Respiratory Questionnaire. One possibility for the positive findings in this study compared to other studies in this area may relate to the benefit of NPPV for subgroups of COPD patients who have a greater degree of hypercapnia. Alternatively, it may also relate to these studies aiming to control nocturnal hypercapnia, rather than rest the respiratory muscles.

Strumpf et al. (1991[81]) performed a randomized crossover study of nasal ventilation using a bilevel ventilator in patients with severe COPD. The authors reported that with the exception of neuro-psychological function there was no significant changes (i.e., pulmonary function, exercise endurance, gas exchange sleep efficiency, quality, oxygenation, dyspnoea ratings, & respiratory muscle strength) between patients treated with nocturnal positive-pressure ventilation via nasal mask and those with conventional treatment for severe COPD. However, only seven out of the 19 patients completed the study, thus it was under-powered. In addition, it was noted in the meta-analysis by Wijkstra (2003[1]) that many of the patients were not especially hypercapnic; in fact some patients were even normocapnic.

Table 9: RCTs concerned with non-invasive ventilation in domiciliary setting for COPD patients

Author/country	Source	Study type/Level /Patients/Sample size	Summary
Casanova, Celli, Tost, Soriano, Abreu, Velasco, & Santolaria (2000)[34] Spain	Chest	**Study type:** Prospective randomised study **Level:** II **Patients:** Stable severe COPD (FEV_1 < 45%) **Sample size:** N = 52	**Aim:** Determine one-year efficacy of NPPV plus LTOT in patients with stable severe COPD **Design:** Two groups – NPPV plus LTOT (n = 26) vs. LTOT alone (n = 26) **Outcomes:** Arterial Blood Gas, respiratory muscles (RM), dyspnea, pulmonary function tests (PFTs), hospital admissions, intubations, rate of acute COPD exacerbations, mortality at 3 months, 6 months and 12 months **Results:** One-year survival was similar in both groups (78%). No significant differences between groups in number of acute exacerbations. Significant decrease in hospital admissions at 3 months in the NPPV group (5% vs. 15% of patients, $p < .05$), but not at 6 months (18% vs. 19%, respectively). Significant improvement in NPPV group on Borg dyspnoea rating, which dropped from 6 to 5 ($p < .039$), and in psychomotor coordination at 6 months. No difference in survival at 1-year which was around 78% **Conclusions:** NPPV did not affect natural course of COPD and provided marginal benefit. Multi-centre trial of hypercapnia and without sleep apnea is needed. NPPV with bilevel-type ventilation in the spontaneous mode when used in addition to LTOT has limited efficacy in patients with stable severe COPD. Possible NPPV may have little impact on a system that, in patients in chronic stable condition, is functioning at its optimal level
Clini, Sturani, Rossi, Viaggi, Corrado, Donner, & Ambrosino (2002)[49] See also abstract by Clini & Sturani (1999[84]) Italy	European Respiratory Journal	**Study type:** Multi-centre, prospective, randomised, controlled trial **Level:** I **Patients:** Stable hypercapnic COPD patients **Sample size:** N = 90	**Aim:** Effect of NPPV plus LTOT on: severity of hypercapnia, use of healthcare resources and HRQOL **Design:** Two groups – NPPV plus LTOT (n = 43), LTOT alone (n = 47). Only patients with a $PaCO_2$ > 6.6kPa were included **Outcomes:** *Primary outcomes* - ABG, hospital and intensive care unit (ICU) admissions, total hospital and ICU length of stay, HRQOL; *Secondary outcomes* – survival, drop-out rates, dyspnoea and sleep quality symptoms, exercise tolerance, RM **Results:** Follow-up was performed at three-month intervals up to two years. Lung function, inspiratory muscle function, exercise tolerance and sleep quality score did not change over time in either group. However, carbon dioxide tension in arterial blood on usual oxygen, resting dyspnoea and HRQOL changed over time in two groups in favour of NPPV plus LTOT. No significant difference in hospital admissions between groups during the follow-up. Overall hospital admissions decreased by 45% in NPPV plus LTOT compared with the LTOT group who increased by 27% when comparing the follow-up with the follow-back periods. ICU stay decreased over time by 75% and 20% in the NPPV plus LTOT and LTOT groups, respectively **Conclusion:** NPPV plus LTOT slightly decreased the trend to carbon dioxide retention in

			patients receiving oxygen at home and improved dyspnoea and HRQOL
Gay, Hubmayr, & Stroetz (1996)[82] USA	Mayo Clin Proc	**Study type:** Randomised controlled trial **Level:** I **Patients:** Severe hypercapnic COPD **Sample size:** N = 35	**Aim:** Examine efficacy of nocturnal nasal ventilation in stable, severe COPD during a 3-month controlled trial **Design:** Two groups - Randomized to receive NPPV with 10cm H_2O positive inspiratory pressure or sham NPPV with no delivered pressure for 3 months. Both groups received treatment at home. All participants still received usual COPD therapy e.g. supplemental oxygen, bronchodilators, theophylline and steroids. Nocturnal oxygen supplementation was bled in bilevel PAP circuit in both groups if it had already been prescribed **Outcomes:** ABG, PFTs, 6-MWD, dyspnea, gas exchange assessment, sleep patterns **Results:** 43% percent of patients in the NPPV group dropped out. No significant difference observed between the two groups in terms of $PaCO_2$ reduction, lung function modification, nocturnal O_2 saturation and sleep efficiency **Conclusion:** Overall, disabled but clinically stable patients with COPD and hypercapnia do not readily accept and are unlikely to benefit from NNPV. However, it was recognised that the results were only based on a small sample
Meecham Jones, Paul, Jones, & Wedzicha (1995)[27] United Kingdom	American Journal of Respiratory & Critical Care Medicine	**Study type:** Randomised, crossover, controlled trial **Level:** I **Patients:** Stable COPD **Sample size:** N = 18 (only 14 completed all stages)	**Aim:** Compared oxygen therapy alone with nocturnal nasal positive pressure ventilation (NPPV) plus long-term oxygen therapy (LTOT). Investigated effect of addition of NPPV on patients already established on LTOT **Design:** Two stages - NPPV plus LTOT and LTOT alone **Outcomes:** ABG, exercise capacity, dyspnea, HRQOL lung function, PFTs, sleep monitoring, 6-MWD **Results:** Patients showed good compliance: 14 patients completed both arms of study. At 6-month NPPV plus long-term oxygen therapy was associated with: improved PaO_2; reduced $PaCO_2$; and improvements in total sleep time, sleep efficiency and HRQOL scores. Improvement in daytime blood gas values correlated with change in overnight $PaCO_2$. Patients who showed greatest improvement in $PaCO_2$ with nocturnal nasal ventilation seem to most likely gain most benefit from treatment **Conclusion:** NPPV may be a useful addition to LTOT in stable hypercapnic COPD. Longer-term studies are needed to define the exact role of this treatment. Nasal ventilation in COPD is unlikely to produce improvements unless used in combination with LTOT
Strumpf, Millman, Carlisle, Grattan, Ryan, Erickson, & Hill (1991)[81]	American Review of Respiratory Dis	**Study type:** Randomised, crossover, controlled trial **Level:** I	**Aim:** Investigated whether intermittent positive pressure ventilation administered nocturnally via a nasal mask would improve patients with severe COPD **Design:** NNV plus oxygen supplementation (if it had already been prescribed) or standard care for sequential 3-month periods **Outcomes:** ABG, PFTs, RM, 6-MWD, dyspnea, treadmill walking time, neuropsychological

		Patients: Severe COPD **Sample size:** N= 7	functioning and sleep patterns **Results:** The seven patients used ventilator for an average of 6.7 hours/night. No changes in exercise endurance, gas exchange, pulmonary function, sleep efficiency, sleep quality, oxygenation, or dyspnea rating between two arms of trial. Improvements were only found in neuropsychological function. Although these patients had severe airflow obstruction, they did have severe derangement of blood gases and lesser degrees of hypercapnia, than some patients in normocapnia range **Conclusion:** NNV was not well tolerated and produced minimal improvements in this small sample of stable outpatients with severe COPD. Compliance was a major problem in this study

5.3 Results

a) Number of studies:
Five RCTs were considered for inclusion in the final analysis.

b) Interventions:
Three RCTs examined LTOT plus NPPV compared with LTOT alone.[34,49,27] One RCT examined LTOT plus NPPV with IPAP (10 cm H_2O) and EPAP (2 cm H_2O) compared to LTOT plus NPPV with IPAP (2 cm H_2O) and EPAP (2 cm H_2O).[82] One RCT examined NPPV plus oxygen supplement if prescribed compared with standard care alone.[81]

c) Multicentre trials
There was one multi-centre trial.[49]

d) Design
Three studies included in the review and the final analysis were randomised, parallel, controlled trials[34,49,82] and two were randomised, cross-over controlled studies.[27,81]

Outcomes studied
A detailed list of all primary and secondary outcome measures are reported in Table 10.

Table 10: Full range of outcome measures reported

ABG
6-MWD
6-MWT, m
Airway occlusion pressure
Breathing pattern
Drop-out rates
Dyspnoea
Exercise tolerance
FEV_1 % pred.
FEV_1, L
FVC, L
Hospital
HRQL
ICU admissions
ICU length of stay
$PaCO_2$, mm Hg
PaO_2, mm H_20
PEMax, cm H_20
PIMax, cm H_20
Respiratory muscle strength (RM)
Residual volume % pred.
Sleep efficiency, %
Sleep quality symptoms
Survival
Total hospital
Total lung capacity % pred.
Vital capacity % pred.

Quality of research available
The quality of the RCT evidence was assessed using a checklist based on NHS CRD Report No. 4. A summary of the quality assessment is provided in Table 11. In the previous review by Wijkstra et al (2003[31]) two potential sources of bias were assessed: unconcealed randomisation and unblended personnel. We have attempted to provide a more comprehensive quality assessment. No attempt was made to provide a global score of scientific quality to each trial.

a) Randomisation:
Gay et al. (1996[82]) did not provide an adequate description of the method used to randomise within the published results. Wijkstra et al (2003[30]) stated that the method of randomisation was well-described and appropriate. This discrepancy might be due to additional information being provided by the authors. The use of number tables as stated by Casanova et al. (2000[34]) was considered appropriate. The central block randomisation method used by Clini et al. (2002[49]) was also considered appropriate. Meecham-Jones et al. (1995[27]) and Strumpf et al. (1991[81]) provide limited information concerning their methods of randomisation.

b) Concealment of allocation:
Casanova et al. (2000[34]), Gay et al. (1996[82]) and Strumpf et al. (1991[81]) had adequate concealment. Meecham-Jones et al. (1995[27]) had inadequate concealment. There was insufficient information provided to decide if the concealment of allocation was adequate in the trial by Clini et al. (2002[49]).

c) Blinding:
There was insufficient information provided to decide if the blinding procedure was adequate in the trial by Clini et al. (2002[49]). The blinding procedure was recognised as appropriate in the trial by Gay et al. (1996[82]), but in the trials by Meecham-Jones et al. (1995[27]) or Strumpf et al. (1991[81]).

d) Withdrawals and intention to treat analysis:
An intention to treat analysis was performed in the Clini et al. (2002[49]) trial. No other trial reported the use of intention to treat.

e) Power calculations:
All of the trials were significantly underpowered. Even the two trials by Clini et al. (2002[49]) and Casanova et al. (2000[34]) which provided details of a power calculation were still lacking in power considering the number of outcome measures they were evaluating.

f) Statistical analysis:
Clini et al. (2002[49]) and recognised that they did not correct for multiple comparisons. None of the other trials considered the use of tests for multiple comparisons.

Table 11: Randomised controlled trial quality assessment scale (Based on NHS CRD Report No. 4)

	Casanova et al. (2000[34])	**Clini et al. (2002[49])**	**Gay et al. (1996[82])**	**Meecham-Jones et al. (1995[27])**	**Strumpf et al. (1991[81])**
Was the method used to assign participants to the treatment groups really random?	**P**	**P**	?	**O**	?
What method of assignment was used?	Table of random numbers	Block randomisation	Not stated	Not concealed randomisation	Not stated
Was the allocation of treatment concealed?	**P**	?	**P**	**O**	?
What method was used to conceal treatment allocation?	?	?	Patients remained naïve to result	?	?
Was the number of participants who were randomised stated?	**P**	**P**	**P**	**P**	**P**
Were details of baseline comparability presented?	**P**	**P**	**P**	**O**	**P**
Was baseline comparability achieved?	**P**	**P**	**P**	?	**P**
Were the eligibility criteria for study entry specified?	**P**	**P**	**P**	**P**	**P**
Were any co-interventions identified that may influence the outcomes for each group?	?	?	?	?	**P**
Were the outcome assessors blinded to the treatment allocations?	Psychiatrist & cardiologist blinded	?	**P**	**O**	**O**
Were the individuals who administered the intervention blinded to the treatment allocation?	Partially blinded for gas exchange & lung function	?	**P**	**O**	**O**
Were the participants who received the intervention blinded to the treatment allocation?	NA	NA	NA	NA	NA
Was the success of the blinding procedure assessed?	**O**	**O**	**O**	**O**	?
Were at least 80% of the participants originally included in randomised process followed up?	**O**	**O**	**O**	**O**	**O**
Were the reasons for withdrawal stated?	**P**	**P**	**P**	**P**	**P**
Was an intention-to-treat analysis included?	?	**P**	**O**	**O**	**O**
Was an a power calculation included?	**P**	**P**	**O**	**O**	**O**

ü – item addressed; **O** – no; ? – not enough information or not clear; NA – not applicable

5.4 Summary

A total of 805 titles were screened for inclusion in the review of clinical effectiveness. Eighty-nine papers were considered useful of which 57 publications were obtained by inter-library loan. Publications were subdivided into RCTs, reviews and general information. Five randomised controlled trials which had been published in full were identified and a meta-analysis was performed on the outcome measures. The majority of the excluded articles were non-systematic reviews, cohort studies, commentaries and letters to the editor. Several trials were excluded because they had not been conducted in the domiciliary setting. Furthermore, there were several RCTs that examined outcomes following < 2 weeks of treatment, these were also excluded.

5.5 Data extraction

A full data extraction for each of the five RCTs is provided in Table 12.

Table 12: Detailed extraction of RCTs outcomes

Author	Type of Trial	Intervention	Study population (T1/T2)	Mean FEV_1, L (range)	Mean PaCO2, mm Hg (range)	Length in Months	IPAP/ EPAP	Outcome measures
Casanova et al. (2000)[34]	Randomised parallel, controlled study	T1 = LTOT plus NPPV T2 = LTOT alone	Randomised (26/26) Completed (17/19)	0.85 (0.44-1.28)	51 (37-66)	12	12-14/4	ABG, RM, Dyspnoea, lung function
Clini et al. (2002)[49]	Randomised parallel, controlled study	T1 = LTOT plus NPPV T2 = LTOT alone	Randomised (43/47) Completed (23/24)	0.70 (0.30-1.35)	55 (50-75)	24	14/2	***Primary outcomes:*** ABG, hospital and intensive care unit (ICU) admissions, total hospital and ICU length of stay, HRQL ***Secondary outcomes:*** survival, drop-out rates, dyspnoea and sleep quality symptoms, exercise tolerance
Gay et al. (1996)[82]	Randomised parallel, controlled study	T1 = LTOT plus NPPV with IPAP (10 cm H_2O) and EPAP (2 cm H_2O) T2 = LTOT plus NPPV with IPAP (2 cm H_2O) and EPAP (2 cm H_2O)	Randomised (7/6) Completed (4/6)	0.68 (0.5-1.1)	55 (45-89)	3	10/2	ABG, 6-MWD, dyspnoea, lung function, sleep study
Meecham-Jones et al. (1995)[27]	Randomised, cross over controlled study	T1 = LTOT plus Nasal pressure support ventilation T2 = LTOT alone	Enrolled (n = 18) Completed (n = 14)	0.86 (0.33-1.7)	56 (52-65)	3	18/2	ABG, 6-MWD, HRQL, lung function, sleep study
Strumpf et al. (1991)[81]	Randomised, cross-over, controlled study	T1 = NPPV with O_2 supplement if prescribed T2 = standard care	Enrolled (n = 19) Completed (n = 7)	0.54 (0.46-0.88)	49 (35-67)	3	15/2	ABG, RM, walking test, dyspnoea, lung function, sleep study

5.6 Outcome measures

A summary of the main outcome measures examined in the meta-analysis are provided in Table 10. In the following section we will discuss several additional outcome measures that were not evaluated in any previous systematic review.

a) Health-related quality of life (HRQOL)

Clini et al. (2002[49]) reported that after two years the SGRQ total score improved in both groups (4 & 5%); this appeared to be mainly due to an improvement in symptoms. Unlike the SGRQ, the MRF-28 total score showed an improvement only in NPPV group. The authors claimed that this provides evidence for the long-term benefit of NPPV plus LTOT over LTOT alone in terms of HRQOL. However, since these results were inconsistent across the two measures this should be treated with caution, or might suggest the need for careful consideration of appropriate measures.

Meecham Jones et al. (1995[27]) used the St George's Respiratory Questionnaire to examine some factors of QOL. During the three-month study conducted by Meecham-Jones et al. (1995[27]) the NPPV group had an improvement in SGRQ scores. They found an improvement in disease impact score and total symptoms with NIV compared to oxygen therapy.

b) Drop-out

In this section we aim to provide coverage of drop-out and poor compliance rates in the studies. Previous reviews have indicated that many of the reported RCTs had problems with withdrawal and compliance. We have attempted to differentiate patients who have failed to complete the study protocol. Several possible reasons for non-completion were:

a) Difficulties with equipment
b) Death
c) Non-compliance with protocol

A summary of the findings from the RCTs related to non-completers, deaths and compliance are presented in Tables 13, 14 and 15, respectively.

Clini et al. (2002[35]) reported the drop-out rate during follow-up was eight and 15 patients in the NPPV and LTOT groups, respectively. The causes were related to non-compliance to oxygen (one in LTOT) or to ventilator use (three in NPPV), voluntary withdrawal from the study (four and two in LTOT & NPPV, respectively), new diagnosed neoplasm (two and one in LTOT & NPPV, respectively), lost to follow-up (seven and one in LTOT & NPPV, respectively), tracheostomy (one in both LTOT & NPPV). The mortality rate was similar in two groups (18 and 17% in NPPV and LTOT, respectively). Deaths were due to acute respiratory failure (three and five in LTOT & NPPV, respectively), cardiac failure (one in both LTOT & NPPV) and other acute diseases (four and two in LTOT & NPPV, respectively).

In the study by Strumpf et al. (1991[81]) there were considerable difficulties encountered in terms of patient withdrawal. Of the 23 patients who were entered into the study, a total of 16 patients did not complete the protocol. Four patients were shown to have obstructive sleep apnea during the initial adaptation polysomnogram; these patients were withdrawn prior to randomisation. Seven patients withdrew from the study because they could not tolerate the mask. It should be noted that the authors

maintain that every effort had been made to alleviate the discomfort and encourage patients to continue in the protocol. These patients complained of intolerable nasal mucosal irritation which appeared to be unresponsive to nasal corticosteroids or humidification in four patients and there was an inability to sleep using the ventilator in two patients, and an excessive anxiety associated with the ventilator in just one patient. A further five patients withdrew from the study because of co-occurring illnesses that were considered to be disruptive to the protocol (three during NNV arm and two during control arm phase).

Gay et al. (1996[82]) found that forty-three percent of patients in the NPPV group dropped out of the study.

In the study by Meecham Jones et al. (1995[27]) at total of 14 of the 18 completed all stages of the study. One patient was withdrawn for lung transplantation; one was withdrawn because they developed a bronchial carcinoma, another patient died at home during an acute exacerbation. Only one patient was withdrawn because they were intolerant to the equipment.

Table 13: Total non-completers

Author	Non-completers
Casanova et al. (2000)[34]	NPPV = 9/26 (34.6%) LTOT = 7/26 (26.9%)
Clini et al. (2002)[49]	NPPV = 20/43 (46.5%) LTOT = 23/47 (48.9%)
Gay et al. (1996)*[82]	NPPV = 3/7 (42.9%) LTOT = 0/6 (0%)
Meecham Jones et al. (1995)[27]	Cross-over study: Overall = 4/18 (22.2%)
Strumpf et al. (1991)[81]	Cross-over study: Overall = 12/19 (63.2%)

* Difference between groups was statistically significant $p < .05$

Table 14: Mortality

Author	Death
Casanova et al. (2000)*[34]	NPPV = 4/26 (15.4%) LTOT = 4/26 (15.4%)
Clini et al. (2002)[49]	NPPV = 8/43 (18.6%) LTOT = 8/47 (17.0%)
Gay et al. (1996)**[82]	3/13 (23.1%)
Meecham-Jones et al. (1995)[27]	1/18 (5.6%)
Strumpf et al. (1991)[81]	No patients

* On patient died who had not tolerated the NPPV treatment.

** These patients died during a long-term follow-up at 8, 15 and 25 months. No patient died during three-month trial period.

Table 15: Compliance rates

Author	Non-compliance
Casanova et al. (2000)[34]	11% of patients had a compliance rate < 3 hours per day Majority of patients reached an IPAP of at least 12 cm H2O and EPAP of 4 cm H2O, but two reached IPAP of 10 cm H2O and could not tolerate higher pressure
Clini et al. (2002)[49]	Compliance to NPPV was defined as the use of ventilator for > 5 hours per night compliance to LTOT was defined by ≥ 15 hours per day use. Patients not compliant to NPPV or refusing their consent within 10 days after randomisation (before discharge from the hospital) were defined as "early drop-outs" and replaced. A "drop-out" was defined as a patient who refused to continue the protocol, showed any exclusion criteria, or was not compliant to therapy after 10 days from randomisation (after discharge)
Gay et al. (1996)[82]	Only four of seven patients tolerated bilevel NIV
Meecham-Jones et al. (1995)[27]	Median daily use of oxygen was 16 hours per day (range 12 to 24 hours). Median reported nightly usage was 7.1 hours (4.2 to 11 hours). Median measured nightly usage was 6.9 (4.2 to 10.8 hours)
Strumpf et al. (1991)[81]	Compliance has been a major problem in this study, as only seven patients completed both arms of the protocol

5.7 Hospitalisations

In the study by Clini et al. (2002[49]) at follow-up, there was no significant differences between the two groups in terms of hospital admissions (0.9±1.2 and 1.4±2.3 per patient per year in NPPV plus LTOT and LTOT alone, respectively) and ICU admissions (0.2±0.4 and 0.4±0.8 per patient per year in NPPV plus LTOT and LTOT alone, respectively). In comparing follow-up results with the three years preceding the study, there was no significant reduction in terms of the days spent in hospital (from 19.9±20.2 to 13.6±18.3 per patient per year) for the NPPV plus LTOT group and a slight increase in the LTOT alone group (from 18.5±18.3 to 19.3±32.9 per patient per year). The authors reported that compared to before the start of the study, total hospital admissions increased by 27% in the LTOT alone group and decreased by 45% in the NPPV plus LTOT group. It was also found that the ICU admissions decreased more in the NPPV plus LTOT than the LTOT alone group (by 20% and 75% in LTOT alone and NPPV plus LTOT groups, respectively) but this difference was not found to be significant.

Casanova et al. (2000[34]) reported that during their 12-month study of NPPV plus standard care versus standard care alone (of which 93% with LTOT) the number of hospital admissions decreased significantly during the third month in the NPPV group (5 vs. 15%), but there was no significant differences between the groups after the third month of the study.

In the study by Strumpf et al. (1991[81]) four patients had repeated hospitalisations. However, only one of these patients was admitted to hospital for repeated

exacerbations, the other patients had hospital admissions not connected with their respiratory conditions.

A summary of the findings from the RCTs related to the total number of admissions before and after the study period are presented in Table 16 and 17.

Table 16: Total hospital admissions

Author	Total hospital admissions	
	Before	**After**
Casanova et al. (2000)*[34]	?	3 months: NPPV = 4% LTOT = 17% 12 months NPPV = 19% LTOT = 18%
Clini et al. (2002)[49]	NPPV = 19±20 LTOT = 18±18	NPPV = 0.9±1.2 LTOT = 1.4±2.3
Gay et al. (1996)**[82]	?	2/13 (15.4%)
Meecham-Jones et al. (1995)[27]	?	3/18 (16.7%)
Strumpf et al. (1991)[81]	?	5/19 (26.3%)

* Extracted from graph in paper

** During long-term follow-up at 8, 15 and 25 months these two patients required hospitalisation for respiratory failure on two occasions each. No patients required hospitalisation during three-month trial period.

Table 17: Hospital admissions due to acute exacerbations

Author	Hospital admissions due to acute exacerbations	
	Before	**After**
Casanova et al. (2000)*[34]	?	3 months: NPPV = 53% LTOT = 57% 12 months NPPV = 65% LTOT = 68%
Clini et al. (2002)[49]	?	?
Gay et al. (1996)**[82]	?	2/13 (15.4%)
Meecham-Jones et al. (1995)***[27]	?	1/18 (5.6%)
Strumpf et al. (1991)[81]	?	1/19 (5.3%)

* Extracted from graph in paper. It is not clear how many of the patients were admitted to hospital due to the acute exacerbations. The differences between both groups at each time period were not statistically significant.

** During long-term follow-up at 8, 15 and 25 months these two patients required hospitalisation for respiratory failure on two occasions each. No patients required hospitalisation during three-month trial period.

*** This patient died of acute exacerbation at home.

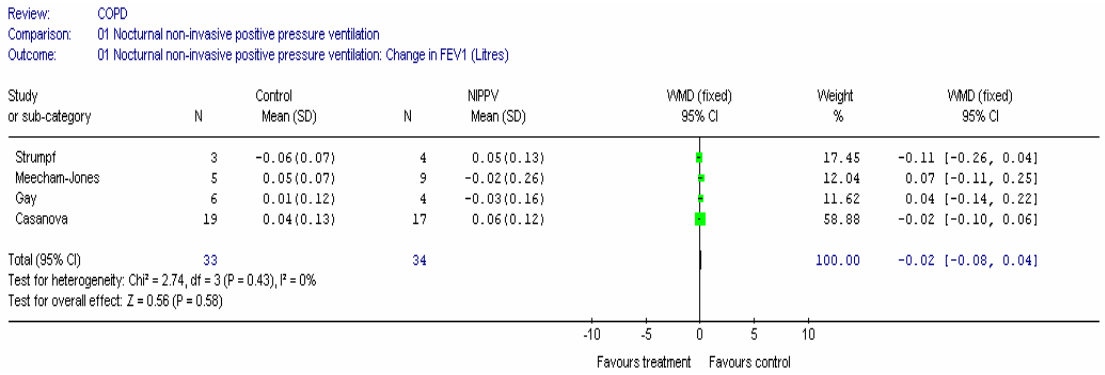
5.8 Meta-analyses:

In updating the previous meta-analysis (see Wijkstra et al. 2003[31]) with the additional Clini et al. (2002[35]) trial, the weighted means and 95% CIs were calculated by meta-analysis software (Review Manager 4.2.7, Update Software Ltd., Oxford, United Kingdom). This used the inverse of the variance to assign a weight to the mean of the within-study treatment effect. Only two outcomes measures could be analysed using the Clini et al. (2002[35]) trial data (6-MWD and PIMax) as the published data was not compatible with the outcomes of previous trials. Therefore, all the other outcomes remained unchanged from the previous meta-analysis. The meta-analysis by Wijkstra et al. 2003[31]) should be consulted for more detailed descriptions and discussion of the results.

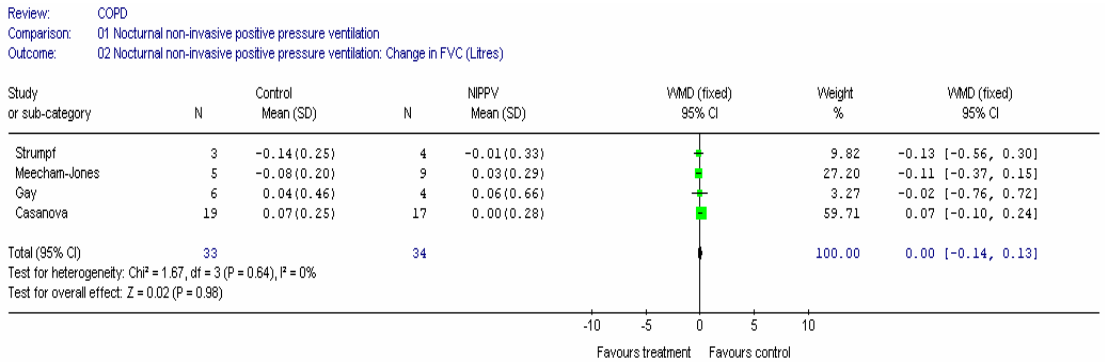
For two outcome measures extracted from the Clini et al. (2002[35]) trial the mean change for treatment or control group was obtained by subtracting the mean estimate at post treatment from the mean estimate at pre-treatment. In order to calculate the associate change in standard deviation (SD), firstly, the variance of the change was calculated [variance pre-treatment + variance post-treatment - 2 x (SD pre-treatment x SD post-treatment x correlation between pre-treatment value and post-treatment value)]. Secondly, we took the square root of the variance of change to calculate the standard deviation for the treatment group and the control group. It was assumed that the correlation value was 0.4 between pre-treatment and post-treatment, as suggested in the Cochrane Handbook (Mulrow et al., 1997[85]).

The following section will provide a diagrammatic and written summary of the meta-analysis for each of the outcome measures.

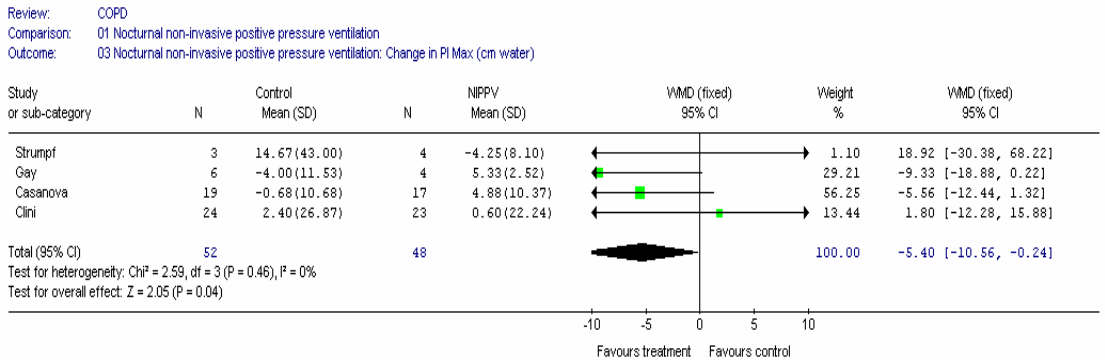
a) Change in FEV_1



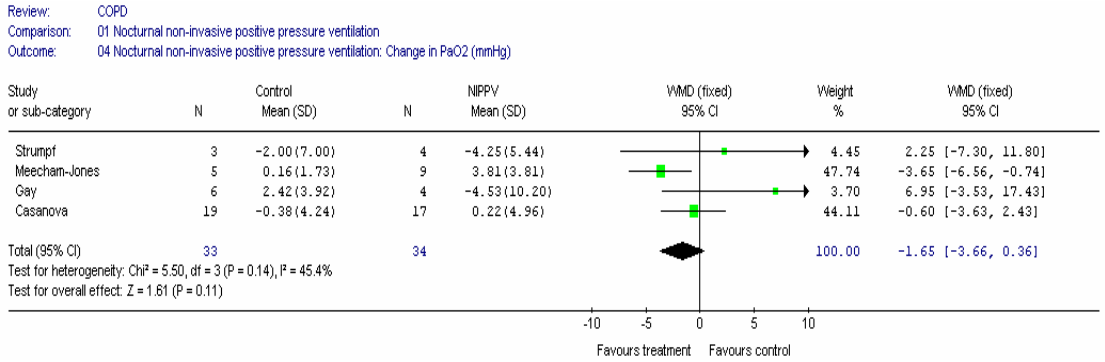
b) Change in FVC



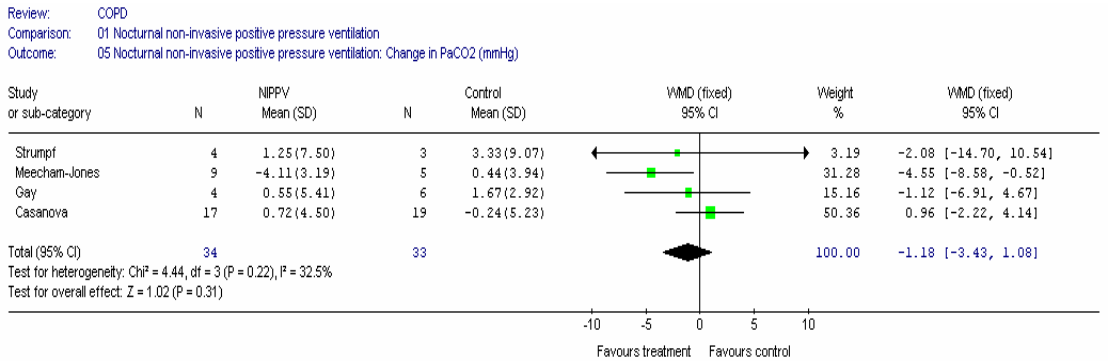
c) Change in PI Max



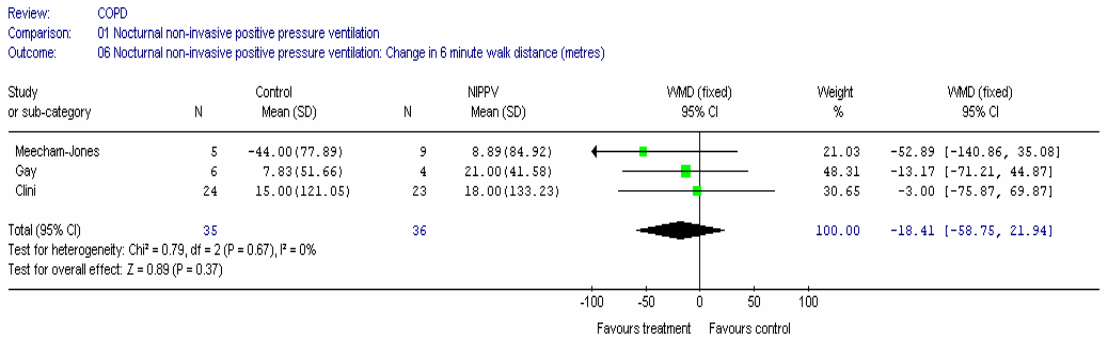
d) Change in PaO_2



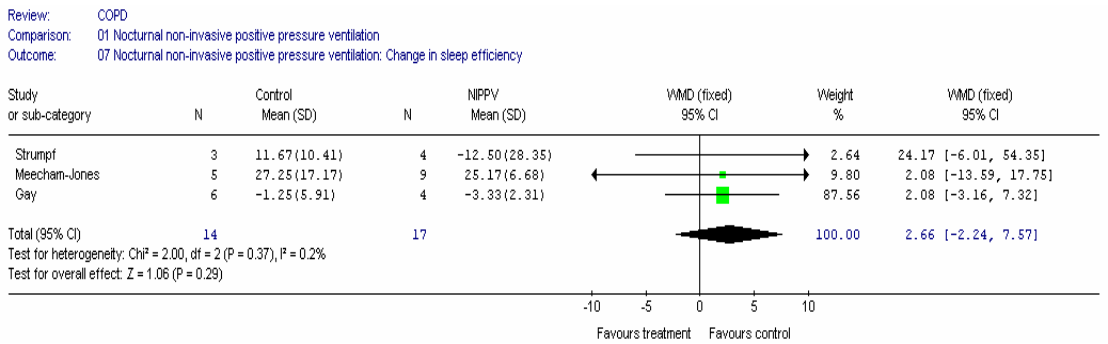
e) Change in $PaCO_2$



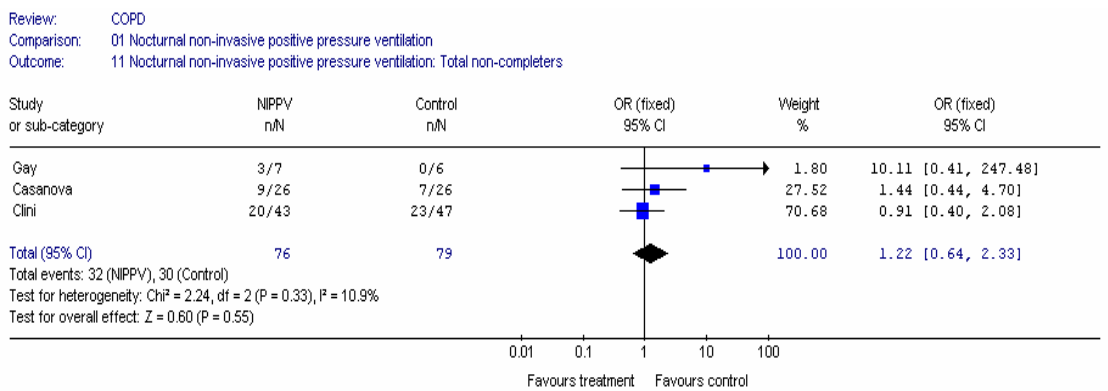
f) Change in 6-MWD



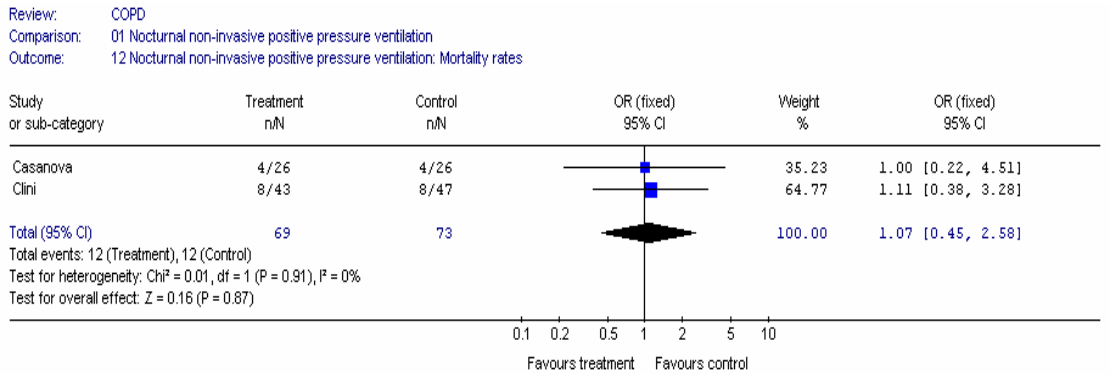
g) Change in sleep efficiency



h) Overall total non-completers



g) Mortality



5.9 Summary of meta-analysis

There was no evidence of heterogeneity in any outcome ($p > 0.05$). The only overall effect was found for PIMax which was significantly in favour of NPPV ($Z = 2.05$ $p = .04$). Nocturnal NPPV completed in the domiciliary setting had no statistically significant effect on gas exchange, lung function, and respiratory muscle strength or sleep efficiency. The small overall sample size restricts the overall conclusions that can be made concerning the effects of NPPV on subtypes of COPD.

5.10 Discussion

We will begin this section of the report by detailing the main findings. We will then discuss future studies which might advance our understanding of this area. Finally, we will comment on the implications of the current work for policy decision.

Clinical effectiveness

Many of the reviews reported the findings from trials concerning nocturnal NPPV in patients with stable COPD; these trials were predominantly undertaken with patients in the domiciliary setting. The key points reported were:

- Domiciliary NIV is unlikely to be effective in most stable COPD patients, particularly if they are normocapnic
- Subgroups of patients with poor tolerance of LTOT, marked nocturnal hypoventilation, severe hypercapnia and/or recurrent infective exacerbations could benefit from domiciliary NIV
- Concerns about the high dropout and poor compliance rates in the RCTs
- RCTs with larger sample sizes are needed to evaluate the impact on health economics, mortality, QOL and morbidity

In the section concerning non-RCT evidence we provided a comprehensive and thorough coverage of the literature. A total of 37 studies were identified. We gave particular attention to describing the type of NIV used and the type of COPD being investigated. These non-RCT studies appeared to show that in selective groups of patients (e.g., severe hypercapnia); NPPV can significantly improve gas-exchange. However, despite these positive findings, one must be careful in applying such findings to policy decision as many of these studies did not include adequate control groups with patients who received the same medical management. It was concluded that what is needed are studies that investigate in a crossover study design those patients who receive home and hospital-based treatment of NPPV.

The main findings from the meta-analysis of the RCT evidence found only one overall effect for PIMax which was significantly in favour of NPPV (Z = 2.05 p = .04). Nocturnal NPPV completed in the domiciliary setting had no statistically significant effect on gas exchange, lung function, and respiratory muscle strength or sleep efficiency. The small overall sample size restricts the overall conclusions that can be made concerning the effects of NPPV on subtypes of COPD.

5.11 Limitations of RCT evidence

Several difficulties were encountered during the review of RCT evidence. Firstly, in attempting to evaluate the effects of domiciliary NIV we relied on studies which examined the effects of BiPAP compared with normal medical treatment. This resulted in several difficulties. One might question whether the use of BiPAP with IPAP pressures below 14 cm H_2O was appropriate to show an improvement in COPD patients. Both Gay et al. (1996[82]) and Casanova et al., 2000[34]) used pressures of 10 to 14 cm H_2O. Similarly, Clini et al. (2002[35]) used a mean IPAP setting of 14±3 and EPAP of 2±1 cm H_2O. Whereas, Meecham Jones et al. (1995[27]) used mean IPAP pressures of 18 cm H_2O (range 16 to 22 cm H_2O). Wijkstra (2002[30]) claimed that this suggests that these higher ventilating pressures might be more beneficial.

A second limitation relates to possible inconsistencies in findings across the entire study duration. For example, despite reporting significant changes, on careful examination of some of the Figures reported by Clini et al. (2002[35]) there appear to be inconsistent patterns of benefit shown in carbon dioxide tension in arterial blood on usual oxygen/ambient air. Therefore, whether benefits are seen across these long-term studies at intermittent time points needs to be considered. Although the benefits might be seen at the end of a study, one might consider at what point in time this benefit is recognised.

A third limitation relates to the lack of statistical power of some clinical trials. Clini et al. (2002[35]) recognised that there study was only powered to investigate a reduction in $PaCO_2$ of 5 mm Hg (0.67 kPa) and not in other parameters. The majority of the other studies did not report a power analysis or sample size calculations.

A fourth limitation relates to the comparative group. In many trials it is not clear what the comparative treatment is. Since, many trials report that this is the usual or normal treatment being prescribed to a patient. Although this is difficult to control, the heterogeneity of these samples and ranges of treatments being given to patients needs to be recognised. Furthermore, although not evaluated in the present review, one must consider the different types of study designs being used. The differences relate to cross-over and parallel controlled trials. Wijkstra (2002[30]) did not find differences between these two types of study design. It is also important to recognise that the inclusion of one of the RCTs may have been inappropriate (Gay, Hubmayr, & Stroetz, 1996[82]). The control group in this trial received a different treatment compared to the other RCTs included in this meta-analysis.

A fifth limitation is the use of the term “non-invasive ventilation”. As Casanova and colleagues stated in their conclusion, this term should not be used as a blanket treatment for all patients with COPD. Furthermore, the variations in delivering NIV, timing, and supplementary treatments need to be considered carefully.

Finally, there has been a mixed number of results concerning the application of home NIV in stable COPD patients. One possible reason for these differences might relate to the variable enrolment criteria which have been used in studies. Thus, as Anton and Guell (2000[13]) pointed out the Meecham Jones et al. (1995[27]) study used patients with high initial PaO_2, while patients with nearly normocapnia at the beginning of the Strumpf et al. (1991[81]) study had little benefit.

It is important to recognise that many of these limitations are currently being addressed in several clinical trials that are in progress or have recently been completed. These should be given consideration and exemplify the continued interest in this area (see Appendix 3).

5.12 Further considerations

Gay et al. (1996[82]) raised an important consideration in future studies of NIV with stable COPD patients. It was claimed that studies have not yet determined whether lower inspiratory PAP levels are better tolerated, improve compliance, or remain sufficient to elicit the desired effect on daytime ABG s in patients with stable COPD and hypercapnia. This might be worth further consideration for these patients if NIV was being applied to the domiciliary setting.

We have highlighted the poor compliance and high drop-out rates in studies using NIV in stable patients with COPD. This should be carefully considered when developing policy options, since the current evidence available is based on a small number of RCTs with only a small number of patients in each. Since a large percent of participants drop-out or died during the trials, the findings may lack the statistical power to reliably make a judgement as to the effectiveness of such treatment.

From the evidence reviewed it remains unclear whether NPPV in stable COPD is beneficial or not. We will refer to the review by Wijkstra (2003[1]) which attempts to provide the rationale for NPPV and the various issues that might explain the differences in outcomes.

5.13 Which patients are likely to benefit?

Wijkstra (2003[1]) reported that patients who are more hypercapnic seemed to have more benefits from NPPV. Meecham Jones et al. (1995[27]) and Clini et al. (2002[35]) both showed significant benefits on several outcome parameters. However it was noted by Wijkstra (2003[1]) that in contrast to other RCTs, they did not include patients with a $PaCO_2$ under 6.6 kPa. Furthermore, Meecham Jones et al. (1995[27]) found that those patients who had an increase of $PaCO_2$ at night prior to being on NPPV showed the largest benefit in decreasing daytime $PaCO_2$ after beginning NPPV. Two RCTs included normocapnic patients (Strumpf et al., 1991[81]; Casanova et al., 2000[34]) and one RCT included patients who were mildly hypercapnic (Meecham Jones et al., 1995[27]). Nevertheless, from the available evidence provided by RCTs there is some suggestion that patients who are more hypercapnic might benefit most from domiciliary NPPV. Wijkstra (2003[1]) pointed out that it might also be important to identify unstable patients ($\geq$ 2 hospitalisations due to respiratory failure in a 12-month period) who could possibly benefit from chronic ventilatory support.

In the current report, in addition to the focus on RCT evidence, we aimed to evaluate the non-RCT evidence concerning those patients who might benefit from NIV

treatment. This has been extremely difficult due to a number of reasons. Firstly, the majority of studies reported various respiratory conditions other than just COPD. Several studies referred to patients with hypercapnia, severe and stable COPD, but many of the terms used to describe patients appeared to be synonymous.

Secondly, like some of the RCTs many of the studies used different terms to describe the same types of intervention involving NIV. Only one study compared the outcome of episodes of acute exacerbation of COPD treated with mask intermittent positive-pressure ventilation (MIPPV) in patients with home MIPPV and in patients without home ventilatory support. It was suggested that MIPPV might be more favourable during episodes of acute exacerbations in patients with COPD.

Thirdly, 62 outcome measures were identified from the non-RCT literature. The most commonly used measures were the assessment of ABG, breathing patterns and lung function. Several studies have shown that domiciliary NPPV can produce significant and sustained improvements in arterial blood gas tensions in patients with severe COPD and hypercapnic respiratory failure who are unresponsive to other treatments. Several studies provided information concerning length of hospital stay (including ICU admission and duration), but less information was reported about the compliance rates of home ventilation. There is a growing interest in the assessment of QOL in patients receiving domiciliary NIV, but recent work has identified considerable variability between participants in terms of presentation of the disease, scores for QOL and anxiety and depression. Despite the number of patients reported in many of these studies being small, the results appear to be positively in favour of treatment.

Overall, the non-RCT studies discussed in this report have shown that in selective groups of patients (e.g., severe hypercapnia) NPPV can significantly improve gas-exchange. However, despite these positive findings, one must be careful in applying such findings to policy decision as many of the studies reported did not include an adequate control group who received the same medical management. There is a clear need for more studies investigating patients who receive home and hospital-based treatment of NPPV.

5.14 Adequacy of ventilation

Wijkstra (2003[1]) made further considerations in terms of the type of ventilation that would be most suitable for NPPV. They claim that there is no evidence that pressure-cycled ventilation is better or worse than volume cycled. The recognise that all RCTs using BiPAP found both positive and negative results, while the majority of uncontrolled studies used mainly volume-cycled ventilation and showed many positive effects.

Meecham Jones et al. (1995[27]) assessed the adequacy of ventilation by transcutaneous $PaCO_2$, while Strumpf et al. (1991[81]) assessed it intermittently using end tidal CO_2. In all the remaining RCTs reported in this review the effectiveness of ventilation was not assessed, which prevents us making a conclusive evaluation of the efficacy. Like the claims made by Wijkstra (2003[1]) this means that we do not know whether the inspiratory pressure used were high enough. Meecham Jones et al. (1995[27]) used a mean inspiratory pressures of 18 cmH_2O. Wijkstra (2003[1]) claimed that these investigators probably needed these higher levels to achieve effective ventilation.

Therefore this is a possible explanation as to why the other RCTs did not assess their ventilatory effectiveness and did not find beneficial effects of NPPV.

It was reported in one study (Clini et al., 2002[35]) that selection of patients, modalities of ventilation, types of ventilation and their setting might be considered when attempting to resolve the conflicting and discrepant results of NPPV studies. Clini et al. (2002[35]) used pressure support ventilation (PSV) with the addition of an EPAP, which was set at a patients comfort level. This was reported to lead to an improvement in ABG.

Leger, Bedicam, Cornette, Reybet-Degat, Langevin, Polu, Jeannin, and Robert (1994[63]) claimed that more aggressive ventilation aimed at maximally decreasing $PaCO_2$ might provide beneficial effects for patients with stable hypercapnic COPD. Nevertheless, there are no RCTs that have examined this.

5.15 Number of hours on NPPV

Some consideration must be made to the different durations of NPPV being given to patients. At present it is not clear what the optimal duration of ventilatory support is. Individual patients will require settings and levels to accommodate. Two RCTs have been reported that treated patients with COPD for a short period with ventilatory support during the day although these trials were not completed in the domiciliary setting (Renston et al., 1994[33]; Diaz, 2002[86]). In one trial patients received BiPAP for two hours daily for five days a week, while in the other BiPAP was given for three hours daily, five days a week for three consecutive weeks. These trials reported that despite their short durations they produced significant benefits in clinical outcomes. In contrast, the long-term trial of Clini et al. (2002[35]) reported a mean number of hours on BiPAP of 9±2 hours. Meecham Jones et al. (1995[27]) reported the median number of hours was 6.9 hours (range 4.2–10.8). Wijkstra (2003[1]) concluded no study has shown that an increase in the hours on ventilatory support is better in reducing the work of breathing, resting the respiratory muscles or improving sleep quality.

5.16 Length of ventilation

The length of ventilatory support can also influence the outcomes (Wijkstra, 2003[1]). The majority of studies reported in this area have been of short duration (three months). However, Meecham Jones et al. (1995[27]) found significant clinical benefits after only a short duration. Two European studies investigated patients for the longest period (Clini et al., 2002[35]; Muir et al., 1999[76]).

5.17 Conclusions

The ability to evaluate the effectiveness of domiciliary NPPV is limited due to the lack of multi-centred, large-scale, RCTs that have specifically investigated the long-term use of domiciliary NPPV in patients with COPD. No RCT has provided sufficient evidence or rigorous experimental design to enable us to conclude whether the benefits found in gas-exchange were related to improvements in respiratory muscle function or in sleep efficiency. The current conflicting evidence, possibly due to the small samples and poor compliance, does not allow us to conclude accurately the magnitude of benefit and harm of domiciliary NPPV for a selective group of COPD patients. We are unable to conclude what is the most effective length of time that treatment should be given in order to gain most benefit. However, we can

tentatively conclude that from the available evidence patients who are more hypercapnic might benefit most from domiciliary NPPV. It is hoped that current on-going trials and recently completed trials will enable a more complete decision to be made about the clinical effectiveness and how domiciliary NPPV might benefit patients with COPD. There is little doubt that NPPV has produced a significant advance in the treatment of patients with COPD, but greater consideration of its application to treatment in the domiciliary setting is needed.

6. Cost-effectiveness modelling

6.1 Introduction

Three economic studies were identified (see Appendix 4). However, only one study assessed costs in sufficient detail to be included in our economic analysis. Tuggey and colleagues (2003[36]) examined the costs and consequences of domiciliary NIV for patients with recurrent acidotic exacerbations of COPD. This found NIV to be cost-saving; however, several aspects of the study mean that its findings needed to be treated with caution. Firstly, and most importantly, the study was based on a small (n = 13) non-randomised study. Secondly, the patient group appeared to be untypical of the majority of patients who are eligible for domiciliary NIV. Thirdly, as recognised the authors, the analysis was limited by the lack of information on patient outcomes, mortality and associated NHS costs (e.g. outpatient and GP attendances).

We have constructed a Markov model based on the work of Tuggey et al. (2003[36]), and developed it by using hospitalisation and QOL data from a randomised controlled trial (Clini et al., 2002[35]). A further analysis that looked at withdrawal from treatment can also be incorporated within the model, as too can a probabilistic sensitivity analysis. Although there are problems with the Clini study as discussed in Section 5, it is considered the best source of data for the cost-effectiveness model.

Consequently, the model represents patients with COPD being treated either with usual care or with usual care plus domiciliary NIV. Usual care includes LTOT.

6.2 Methods

Of the five RCTs included in the effectiveness section of this report only the study by Clini et al reported sufficient information on hospitalisation and HRQL to populate the model. This study contains data on the length of stay in hospital, the number of hospital admissions and the number of ICU admissions. Two assumptions have to be made in order to use this data. The first relates to the length of stay for an ICU admission. No data is available from the Clini study to differentiate between the two groups for ICU length of stay. We are therefore assuming an equal length of stay for each group and this is set at one day per ICU admission for the baseline. However, as the number of ICU admissions varies by group and because ICU is expensive, the impact of ICU length of stay will be investigated in the sensitivity analysis. The second assumption relates to outpatient visits. The cost of outpatient visits are small in comparison to hospitalisation costs and are expected to have a small impact on overall costs. We have therefore assumed that the number of outpatient visits is the same for both groups.

Model structure

There are three possible health states in the model: domiciliary treatment, hospital treatment and death. The cycle time of the model is one week and the time horizon is two years. Results are expressed in terms of cost per quality adjusted life years gained (QALY). Differences in costs and QALYs between the two treatments are determined by the different transition probabilities between the different health states (i.e. hospitalisation rates) and their treatment type (i.e. NIV or usual care).

The cost-effectiveness results are driven by three main factors: the cost of providing the NIV treatment at home, the difference between the groups in terms of

hospitalisation and the health related quality of life (HRQL) associated with each health state.

Costs
The cost of hospitalisation and the capital and ongoing costs associated with NIV are taken from the Tuggey study, Table 18. Costs are based on 1999/2000 prices. The cost of the ventilators was discounted at 6% by the authors to allow for a five year lifespan.

Table 18: Costs from Tuggey study

Ward costs (daily)	
Capital costs	78
Nursing	37
Pharmacy	3
Intensive care	
Per day	1277
Additional ward NIV costs	
Per admissions:	
Nursing time	5
Recurring equipment cost	12
Annual fixed costs:	
Ventilator (each)	570
Annual servicing	28
Equipment	551
Training	140
Home NIV costs	
Per patient:	
Ventilator	570
Humidifier	179
Annual servicing	28
Consumables	149
Annual fixed costs:	
Respiritory nurse specialist	760
Outpatient attendance	67

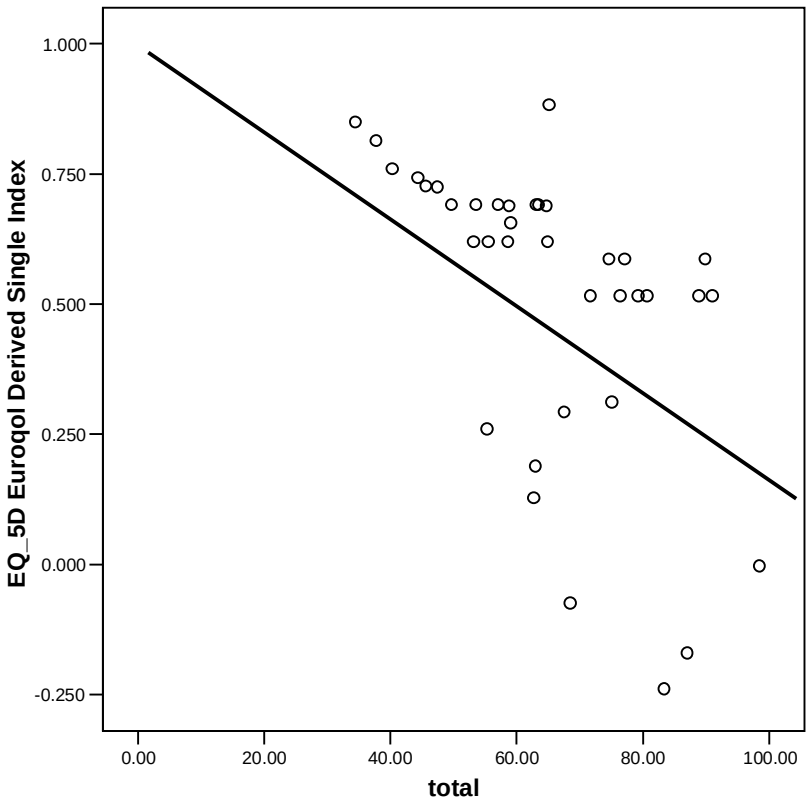
Hospitalisation
Hospitalisation data is based on the Clini RCT and can be seen in Table 21.

HRQL utilities
HRQL was assessed in the Clini et al. (2002[35]) study by the St George's Respiratory Questionnaire (SGRQ). The Clini study reports baseline SGRQ scores for both the NIV and the LTOT group. At baseline there is no difference between these groups in terms of treatment received. The SGRQ score for usual treatment has therefore been assumed to be the mean of the baseline scores of both groups. The Clini study found a 1% difference at two years between the two groups in the trend to improve. This difference in improvement has been applied in the model to the baseline SGRQ score to represent the SGRQ score for domiciliary NIV treatment.

The SGRQ scores were converted to EQ5D utility values by estimating a statistical relationship between SGRQ total score and EQ5D score from a previous study in

Sheffield that compared the two instruments in an outpatient COPD population. This analysis (shown in Figure 7), where EQ5D= 1- 0.008 * SGRQ total ($p < .001$). The relationship is defined so that the regression line passes through unity (i.e. when there are zero symptoms, patients are in full health). Applying this relationship to the Clini data produces the utilities in Table 19.

Figure 7: Relationship between SGRG and EQ-5D



The utility for HRQL during hospitalisation for COPD exacerbation is based on a study by Andersson (2002[87]). This study used the SGRQ to measure the HRQL of elderly COPD patients during hospital stay and at follow-up. A limitation of using this study is the mean age (77 years) of the patients. The SGRQ used in the model for hospital stay was estimated by adding the point difference (14 points) between hospital stay and follow-up found in the Andersson study to the SGRQ score for usual care in the Clini study. This method assumes that the difference between HRQL in hospital and HRQL at home will remain constant regardless of the severity of COPD.

Table 19: Utilities

	SGRQ	EQ5D from mapping	Source
Home NIV	63	0.496	Clini
No home NIV	64	0.488	Clini
Hospital Stay	78	0.376	Andersson

Mortality

The review of effectiveness found no evidence to suggest a difference in survival between treatments. It was therefore decided that a complicated representation of mortality based on survival curves was not warranted. However, mortality will affect the results of the analysis even if the rates are the same for both groups. Mortality

was therefore represented in the model by a simple method of assuming a median survival of three years.

Transition rates
The transition rates between the home and hospital states are based on the hospitalisation data in the Clini study. Rates were estimated based on the proportion of time spent in hospital and at home.

Mortality rates were estimated based on a median survival time of three years.

Continuance
Continuance is potentially an important issue as drop-out form treatment appears to quite high, and consequently, the costs and outcomes of those dropping out are not included in the analyses. If drop-out is due to lack of effectiveness, inclusion of these patients would reduce our estimates of the effectiveness of treatment, and be associated with the costs of providing domiciliary NIV equipment.

In order to assess the possible impact of continuance it was included in the model as part of the sensitivity analysis. Continuance was included in the model by assuming that a proportion of patients would have the ventilation machines in the home for a given length of time but not use them. There is therefore a cost implication and a reduction of benefit. Withdrawal rates were taken from a study by Janssens et al. (2003[58]). The rate of withdrawal in the model is 30% in the first year and 40% in the second year. The machines are assumed to be kept for three months per year by those people who withdraw.

Validation
In order to validate the model against the Tuggey study, mortality was set at 0%. Hospitalisation data and mean cost per patient were compared and found to be reasonably close, Table 20. There is a small imbalance between the groups in that the model underestimates the cost of usual care and overestimates the cost of domiciliary NIV. The results would therefore tend to be conservative.

Table 20: Model validation

Mean Values	Usual care		Domiciliary NIV	
	Tuggey	Model	Tuggey	Model
Admissions	5	4.57	2	3.15
Total days in hospital	78	77.8	25	25.2
Annual mean cost per patient	£13,163	£12,990	£4,909	£4,988

Probabilistic sensitivity analysis
A probabilistic sensitivity analysis (PSA) of the cost-effectiveness of NIV was undertaken in order to characterise parameter uncertainty within the model. Cost and utility parameters were ascribed distributions based on the standard deviations given in the literature, and the model was repeatedly analysed by drawing at random from these distributions to generate a distribution around the cost-effectiveness results. The parameters used in the PSA are listed in Tables 21 and 22, below.

Table 21: Hospitalisation parameters

Hospitalisation	Usual care		NIV	
	mean	sd	mean	sd
LOS per admission (days)	13.79	14.30	15.11	15.25
Total days in hospital	19.3	32.9	13.6	18.3
Days in ICU	0.4	0.8	0.2	0.4
Outpatient visits	5	1	5	1

Table 22: SGRQ scores

SGRQ scores	Mean	sd
Difference	1	0.521
Baseline	64	17.5

6.3 Results

The mean cost per patient for the two year period of the model was £5,412 and £5,391 for the NIV and usual care groups respectively (Table 23). The NIV group compared to the usual care group had a mean QALY gain of 0.008. The central estimate of the incremental cost per QALY is £2,597.

Table 23: Cost-effectiveness results

Group	Costs	QALYs	Cost per QALY
NIV	£5,412	0.404	
Usual care	£5,391	0.396	
Incremental	£20	0.008	**£2,597**

The inclusion of withdrawal reduces benefits in the NIV arm but this has little effect on the incremental cost-effectiveness ratio (results not shown).

The results are very sensitive to the length of stay in ICU. Increasing the ICU length of stay to two days increases costs in the usual care group and results in NIV dominating treatment, Table 24.

Table 24: Length of ICU stay increased to two days

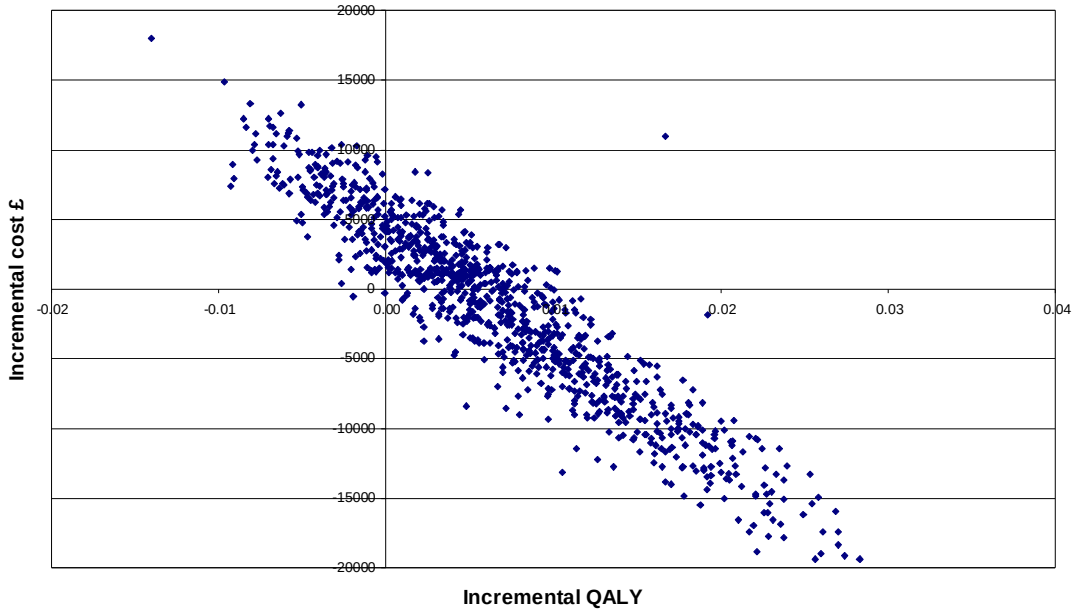
Group	Costs	QALYs	Cost per QALY
NIV	£5,763	0.404	
Usual care	£6,111	0.396	
Incremental	-£348	0.008	**Dominated**

Probabilistic sensitivity analysis

In the PSA, the process of re-sampling from each of the distributions and re-calculating the cost-effectiveness was repeated 1,000 times. The results of the simulation are presented by means of incremental cost-effectiveness planes (Figure 8) and cost-effectiveness acceptability curves (Figure 9).

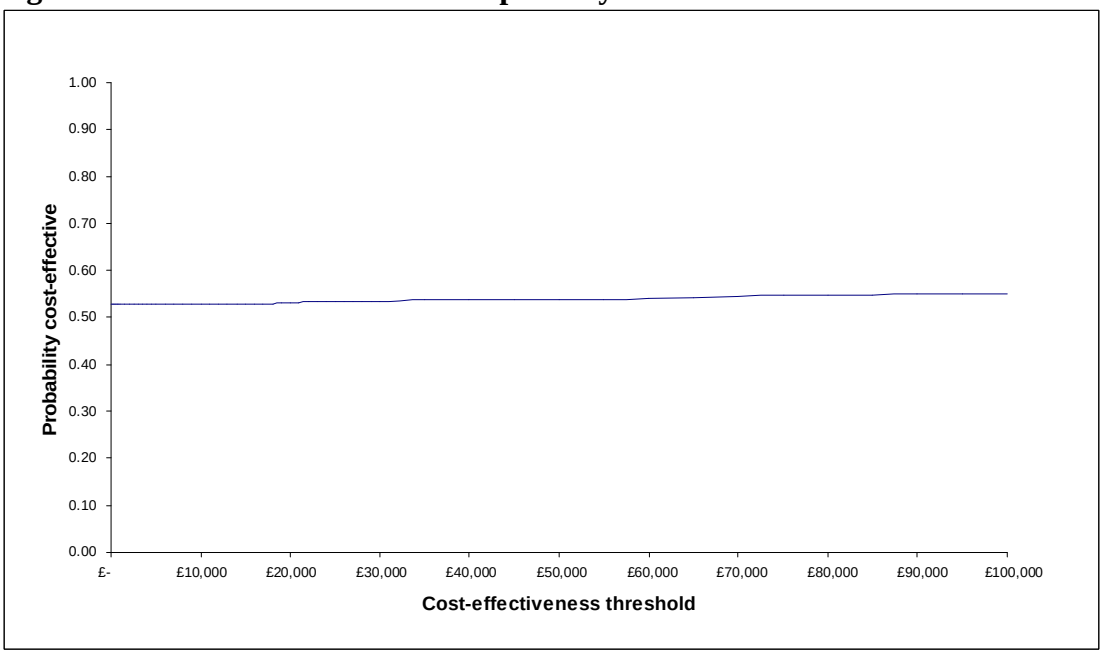
The incremental cost effectiveness plane illustrates the high degree of uncertainty around the central estimates (Figure 8). NIV has the potential to be more effective and less costly than usual care but the risk of NIV being more costly and less effective is also high. The Figure as shown does not actually show all observations – some are beyond the scale of the figure.

Figure 8: Incremental cost-effectiveness plane



The probability of NIV being cost-effective is close to 50% regardless of the value placed on health benefits. The CEAC is unusually flat, again reflecting the very high degree of uncertainty in the data.

Figure 9: Cost-effectiveness acceptability curve



6.4 Discussion

The central estimate of the cost-effectiveness of NIV compared to usual care indicates that NIV is a cost-effective alternative. However, there is immense uncertainty around this estimate. Within the existing model, the main reason for this uncertainty is the hospitalisation data; the impact on hospitalisation is quite small yet the variability is extremely large (SD = 33 days in the usual care group). Better information on the impact of NIV on hospitalisation would help in producing more robust estimates of cost-effectiveness.

Of greater concern than the statistical uncertainty surrounding hospitalisations is the appropriateness of the data in the Clini study. Clinical opinion is that the patterns of care in the Italian healthcare system for this patient group are totally unrepresentative of UK practice (Mark Elliot, Personal Communication). Therefore, our central estimate of cost-effectiveness is likely to be misleading.

The other key factor in producing a small, but highly uncertain ICER is that domiciliary NIV is relatively cheap at around £1,500 per annum (1999/2000 prices). At such low levels, small improvements in QOL produce low ICERS and small reductions in hospitalisation reduce them further or produce cost-savings. The NIV costs are taken from a single study (Tuggey et al., 2003[36]) and if higher estimates are thought to be more reasonable, these will increase the ICER. For example, more complex and expensive machines are now available, which cost around £8,000 (David Black, Personal Communication).

There are other, less important issues that will have an impact on the results produced. Firstly, mortality differences have not been factored into the model. This would be possible, but the evidence on this matter is also highly uncertain, and so it was thought best not to include this information.

Secondly, data on other NHS costs have not been included, such as outpatient and GP attendances. Once again, whilst estimates are available from other sources, they are considered to be particularly accurate, and due to their magnitude, will have very little impact on the ICER.

Thirdly, in order to undertake the PSA, assumptions had to be made regarding the shape of the distribution around the mean estimates. It is possible that alternative distributions may reduce the estimated uncertainty around the estimates produced. The best way to do this would be to gain access to underlying trial data so that we could sample directly from the patient data, or alternatively, we might run sensitivity analyses using different distribution types. It would also be possible to use local data that characterises hospitalisations in region, although the down-side of this is that it would reduce the internal validity of the analysis as it stands.

The fundamental weaknesses in the economic analysis are the reliance on one small study for effectiveness data, and our reliance on the only useable RCT which was based in Italy. Consequently, we can not conclude that these results as reliable estimates of the cost-effectiveness of domiciliary NIV. The analysis does, however provide a framework for future analyses, and includes utility estimates for the key health states used. It also, shows that domiciliary NIV has the potential to be extremely cost-effective if modest reductions in hospitalisation can be achieved.

For more reliable results to be produced, it is essential that UK based hospitalisation data are identified, evidence of effectiveness obtained from good quality sources, and a full range of NIV machine costs used.

Appendix 1: Additional background information concerning treatment

Non-invasive Methods:

- **Positive Pressure Ventilation: Mouth and/or Nose**

Positive pressure ventilation delivers air (and sometimes extra oxygen when medically necessary) to the patient through a face mask, mouthpiece, or nasal mask. Patients who can be independent of the ventilator for portions of the day may use non-invasive positive-pressure ventilation to assist night time breathing.

- **Negative Pressure Ventilation**

Entry of air into the lungs is assisted by applying intermittent negative pressure (like a vacuum) to the chest and abdomen by means of a body tank (iron lung), a chest shell, or a body jacket.

- **Rocking Bed**

A bed with rocking motion assists ventilation by intermittently causing the diaphragm to move up and down, creating a "pumping" motion in the chest, and thus, helping air to go in and out of the lungs.

- **Pneumobelt**

An inflatable band around the abdomen presses on the abdomen and forces air in and out of the lungs. The pneumobelt may be used in combination with other non-invasive methods of ventilation. It may not be suitable for some patients—for example, patients who are excessively underweight or overweight. The patient must be sitting up for this device to work. It is often used by patients in a wheelchair.

- **Diaphragm Pacing**

An electronic pacer stimulates the diaphragm to contract, thus assisting breathing by "bellows" motion of the diaphragm. This method is used by patients who have high (C1-C2) spinal cord injury, and with tracheostomy in some children who cannot breathe spontaneously because of a problem with central control of breathing.

- **Glossopharyngeal Breathing**

Sometimes called "frog" breathing—a technique in which the patient learns to "gulp" air into the lungs. Some patients use this technique in order to spend more time off the ventilator and to have "free" time in case of ventilator failure.

- **Manually Assisted Coughing**

A caregiver helps the patient to exhale and clear mucus from the lungs by delivering a thrust similar to a Heimlich manoeuvre. Thorough training of the patient and caregivers is required to make this technique effective and to avoid injury to the patient.

Invasive Methods:

Invasive methods may be needed for patients who are unable to use non-invasive methods. Invasive mechanical ventilation requires a tracheostomy for placement of a tracheostomy tube into the windpipe to deliver air directly into the lungs. The patient and caregivers are trained in care of the tracheostomy and tube to prevent complications such as infection around the tracheostomy tube or clogging of the tube.

The following information was extracted from:
http://www.patienthealthinternational.com/article/501995.aspx

What is COPD?
Chronic obstructive pulmonary disease (COPD) is a progressive disease which is characterised by airflow limitation that is not fully reversible. The airflow limitation is associated with inflammation in the lungs caused primarily by tobacco smoke, but also by air pollution or other noxious particles or gases.

COPD is one of the world's most common chronic diseases, with an estimated 600 million sufferers worldwide.

How do you get COPD?
The most common cause of COPD is cigarette smoking, with other types of tobacco smoking also being strong risk factors. Other causes include heavy exposure to occupational dusts and chemicals (vapours, irritants and fumes) and indoor and outdoor air pollution.

How serious is COPD?
The airflow limitation in COPD patients is progressive and often becomes debilitating, or even life-threatening.

Symptoms of COPD include breathlessness, dyspnoea (difficulty breathing), cough, chest tightness and increased secretion of sputum. Many patients are kept awake at night by their symptoms.

In addition to their everyday symptoms, patients with more severe COPD suffer acute exacerbations of symptoms or episodes of worsening of symptoms requiring medical intervention which often require hospitalisation. Infection and air pollution are the most common causes of an exacerbation.

The main symptom of an exacerbation is increased breathlessness, often accompanied by wheezing, chest tightness, increased cough and sputum, and fever. Exacerbations may also be accompanied by non-specific complaints such as malaise, insomnia, fatigue, depression, and confusion. Exacerbations tend to result in worsening of baseline symptoms, with some patients never completely recovering from an exacerbation.

GOLD - the Global Initiative for Chronic Obstructive Lung Disease, endorsed by the World Health Organisation and the US National Heart, Lung and Blood Institute - identifies four stages of COPD:

- Stage 0 refers to people at risk of COPD. At this stage, individuals have normal lung function, but suffer chronic cough and sputum production.
- Stage 1 refers to mild COPD. At this stage, there is mild airflow limitation, but patients may be unaware that their lung function is abnormal.
- Stage 2 refers to moderate COPD. By this stage the airflow limitation is causing symptoms like shortness of breath on exertion. Patients usually seek medical attention at this stage.
- Stage 3 refers to severe COPD. By this stage, airflow limitation is severe, symptoms are severe and exacerbations may be life threatening.

How long does COPD last?
There is no cure for COPD, but treatment can help patients manage their condition. The average stay in hospital for an acute exacerbation is approximately ten days.

How is COPD treated?
Management of COPD requires a long-term therapeutic approach:

- Stopping smoking is the single most effective step in slowing the progression of the disease.
- Other risk factors should also be avoided.
- Drugs help to control symptoms, while rehabilitation programs and physiotherapy may be useful to clear sputum and improve exercise tolerance and health-related quality of life.
- Patients with severe disease often require a variety of treatment approaches.

GOLD recommends that patients with mild (Stage 1) COPD should be treated with a bronchodilator on an as-needed basis to reduce symptoms. Patients with moderate-to-severe COPD (Stages 2 and 3) should receive a bronchodilator, plus inhaled glucocorticosteroids if they have a lung function response to glucocorticosteroids, or repeated exacerbations requiring medical intervention.

Appendix 2: Search strategies and databases

Search strategies
Electronic bibliographic databases

BIOSIS previews 1985 -
1. chronic obstructive pulmonary disease
2. copd
3. obstructive lung disease
4. chronic airflow obstruction
5. chronic obstructive airway disease
6. coad
7. (chronic obstructive airway disease) or (chronic airflow obstruction) or (obstructive lung disease) or (copd) or (chronic obstructive pulmonary disease) or (coad)
8. nasal ventilat*
9. nasal
10. mechanical
11. non-invasive
12. non invasive
13. non-invasive
14. positive pressure
15. positive-pressure
16. ventilat* support
17. intermittent positive pressure
18. airway* pressure
19. pressure-controlled
20. volume-controlled
21. ventilat*
22. bi-level positive pressure
23. NIPPV
24. NPPV
25. NIV
26. NIMV
27. (NPPV) or (NIPPV) or (bi-level positive pressure) or (ventilat*) or (mechanical) or (nasal) or (nasal ventilat*) or (volume-controlled) or (pressure-controlled) or (airway* pressure) or (intermittent positive pressure) or (ventilat* support) or (positive-pressure) or (positive pressure) or (noninvasive) or (non invasive) or (non-invasive) or (NIMV) or (NIV)
28. ((chronic obstructive airway disease) or (chronic airflow obstruction) or (obstructive lung disease) or (copd) or (chronic obstructive pulmonary disease) or (coad)) and ((NPPV) or (NIPPV) or (bi-level positive pressure) or (ventilat*) or (mechanical) or (nasal) or (nasal ventilat*) or (volume-controlled) or (pressure-controlled) or (airway* pressure) or (intermittent positive pressure) or (ventilat* support) or (positive-pressure) or (positive pressure) or (noninvasive) or (non invasive) or (non-invasive) or (NIMV) or (NIV))
29. domiciliary
30. domicilliary
31. home-setting
32. discharged

33. nursing home*
34. residential home*
35. home*
36. (home*) or (residential home*) or (nursing home*) or (domicilliary) or (discharged) or (domiciliary) or (home-setting)
37. ((home*) or (residential home*) or (nursing home*) or (domicilliary) or (discharged) or (domiciliary) or (home-setting)) and (((chronic obstructive airway disease) or (chronic airflow obstruction) or (obstructive lung disease) or (copd) or (chronic obstructive pulmonary disease) or (coad)) and ((NPPV) or (NIPPV) or (bi-level positive pressure) or (ventilat*) or (mechanical) or (nasal) or (nasal ventilat*) or (volume-controlled) or (pressure-controlled) or (airway* pressure) or (intermittent positive pressure) or (ventilat* support) or (positive-pressure) or (positive pressure) or (noninvasive) or (non invasive) or (non-invasive) or (NIMV) or (NIV)))

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to December Week 2 2005>

1 Lung Diseases, Obstructive/
2 chronic obstructive pulmonary disease$.tw.
3 copd.tw.
4 obstructive lung disease$.tw.
5 chronic airflow obstruction.tw.
6 chronic obstructive airflow disease$.tw.
7 coad.tw.
8 chronic obstructive airway$ disease$.tw.
9 or/1-8
10 Ventilation, Mechanical/
11 non-invasive ventilation.tw.
12 non invasive ventilation.tw.
13 nasal ventilat$.tw.
14 nasal.tw.
15 mechanical.tw.
16 non-invasive.tw.
17 non invasive.tw.
18 Positive Pressure Ventilation/
19 positive pressure.tw.
20 positive-pressure.tw.
21 ventilat$ support.tw.
22 Intermittent Positive Pressure Ventilation/
23 intermittent positive pressure.tw.
24 Airway Pressure/
25 airway$ pressure.tw.
26 pressure controlled.tw.
27 volume-controlled.tw.
28 ventilat$.tw.
29 Noninvasive Procedures/
30 bi-level positive pressure.tw.
31 NIPPV.tw.
32 NPPV.tw.
33 NIV.tw.

34 NIMV.tw.
35 or/10-34
36 9 and 35
37 domiciliary.tw.
38 domicillary.tw.
39 Home Health Care/
40 home.tw.
41 home-setting.tw.
42 discharged.tw.
43 exp Nursing Homes/
44 nursing home$.tw.
45 residential home$.tw.
46 Residential Facilities/
47 or/37-46
48 36 and 47

Filters were utilised with the CINAHL search to retrieve guidelines, systematic reviews, randomised controlled trials and economic evaluations.

Database: EMBASE <1980 to 2005 Week 51>

1 exp *Chronic Obstructive Lung Disease/
2 chronic obstructive pulmonary disease$.tw.
3 copd.tw.
4 obstructive lung disease$.tw.
5 chronic airflow obstruction.tw.
6 chronic obstructive airflow disease$.tw.
7 coad.tw.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 artificial ventilation/
10 Assisted Ventilation/
11 non-invasive ventilation.tw.
12 non invasive ventilation.tw.
13 nose breathing/
14 nasal ventilat$.tw.
15 mechanical.tw.
16 non-invasive.tw.
17 non invasive.tw.
18 noninvasive.tw.
19 positive end expiratory pressure/
20 positive pressure.tw.
21 positive-pressure.tw.
22 intermittent positive pressure ventilation/
23 airway pressure/
24 airway$ pressure.tw.
25 pressure-controlled.tw.
26 volume-controlled.tw.
27 ventilat$.tw.
28 bi-level positive pressure.tw.
29 ventilat$ support.tw.
30 NIPPV.tw.

31 NPPV.tw.
32 NIV.tw.
33 NIMV.tw.
34 or/9-33
35 8 and 34
36 home care/
37 domiciliary.tw.
38 domicilliary.tw.
39 home.tw.
40 home-setting.tw.
41 discharged.tw.
42 nursing home/
43 nursing home$.tw.
44 residential home/
45 residential home$.tw.
46 or/36-45
47 35 and 46

Filters were utilised with the Embase search to retrieve guidelines, systematic reviews, randomised controlled trials and economic evaluations.

Ovid MEDLINE(R) <1966 to November Week 3 2005>

1 exp *Pulmonary Disease, Chronic Obstructive/
2 chronic obstructive pulmonary disease$.tw.
3 copd.tw.
4 *Lung Diseases, Obstructive/
5 obstructive lung disease$.tw.
6 chronic airflow obstruction.tw.
7 chronic obstructive airflow disease$.tw.
8 coad.tw.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp *Respiration, Artificial/
11 non-invasive ventilation.tw.
12 non invasive ventilation.tw.
13 nasal ventilat$.tw.
14 nasal.tw.
15 Ventilators, Mechanical/
16 mechanical.tw.
17 non-invasive.tw.
18 non invasive.tw.
19 noninvasive.tw.
20 exp Positive-Pressure Respiration/
21 positive pressure.tw.
22 positive-pressure.tw.
23 ventilatory support.tw.
24 exp Intermittent Positive-Pressure Ventilation/
25 intermittent positive pressure.tw.
26 airway$ pressure.tw.
27 pressure-controlled.tw.
28 pressure controlled.tw.

29 volume-controlled.tw.
30 volume controlled.tw.
31 ventilat$.tw.
32 bi-level positive pressure.tw.
33 ventilation support.tw.
34 NIPPV.tw.
35 NPPV.tw.
36 NIV.tw.
37 NIMV.tw.
38 or/10-37
39 9 and 38
40 home care services/ or home care services, hospital-based/
41 domicilary.tw.
42 domicillary.tw.
43 home.tw.
44 home-setting.tw.
45 exp Nursing Homes/
46 nursing home$.tw.
47 residential facilities/ or homes for the aged/
48 residential home$.tw.
49 discharged.tw.
50 or/40-49
51 39 and 50

Filters were utilised with the Medline search to retrieve guidelines, systematic reviews, randomised controlled trials and economic evaluations.

Review databases:
CRD databases – DARE, NHSHTA and NHSEED.
(copd OR chronic obstructive pulmonary disease)/All fields AND (domiciliary OR home OR home-setting OR discharged OR nursing home OR residential home) /All fields AND (ventilat OR non invasive OR NIPPV OR NPPV OR NIV OR NIMV)/All fields -

Citation Indexes – Science and Scoial Science Citation Indexes
1. TS=(chronic obstructive pulmonary disease* OR COPD)
2. TS=(nasal ventilat* OR nasal OR mechanical OR non-invasive OR noninvasive OR non invasive OR positive pressure OR positive-pressure OR ventilat* support OR intermittent positive pressure OR airway* pressure OR pressure-controlled OR volume-controlled OR ventilat* OR bi-level positive pressure OR NIPPV OR NPPV OR NIV OR NIMV)
3. TS=(domiciliary OR domicilliary OR home OR home-setting OR discharged OR nursing home* OR residential home*)
4. #3 AND #2 AND #1

Cochrane Library:
Cochrane Controlled Trials Register (CCTR),
Cochrane Database of Systematic Reviews (CDSR), DARE, NHSEED, NHSHTA, Cochrane Airways Group COPD trial register

1. MeSH descriptor Pulmonary Disease, Chronic Obstructive explode all trees in MeSH products
2. copd in Record Title or copd in Abstract in all products
3. chronic obstructive pulmonary disease* in Record Title or chronic obstructive pulmonary disease* in Abstract in all products
4. MeSH descriptor Airway Obstruction explode all trees in MeSH products
5. chronic obstructive airflow disease* in Record Title or chronic obstructive airflow disease* in Abstract in all products
6. chronic obstructive airway* disease* in Record Title or chronic obstructive airway* disease* in Abstract in all products
7. coad in Record Title or coad in Abstract in all products
8. MeSH descriptor Lung Diseases, Obstructive explode all trees in MeSH products
9. obstructive lung disease* in Record Title or obstructive lung disease* in Abstract in all products
10. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
11. MeSH descriptor Respiration, Artificial explode all trees in MeSH products
12. non-invasive ventilat* in Record Title or non-invasive ventilat* in Abstract in all products
13. non invasive ventilat* in Record Title or non invasive ventilat* in Abstract in all products
14. nasal ventilat* in Record Title or nasal ventilat* in Abstract in all products
15. mechanical in Record Title or mechanical in Abstract in all products
16. non invasive in Record Title or non invasive in Abstract in all products
17. non invasive in Record Title or non invasive in Abstract in all products
18. noninvasive in Record Title or noninvasive in Abstract in all products
19. positive pressure in Record Title or positive pressure in Abstract in all products
20. positive-pressure in Record Title or positive-pressure in Abstract in all products
21. ventilat* support in Record Title or ventilat* support in Abstract in all products
22. intermittent positive pressure in Record Title or intermittent positive pressure in Abstract in all products
23. airway* pressure in Record Title or airway* pressure in Abstract in all products
24. pressure-controlled in Record Title or pressure-controlled in Abstract in all products
25. volume-controlled in Record Title or volume-controlled in Abstract in all products
26. ventilat* in Record Title or ventilat* in Abstract in all products
27. MeSH descriptor Intermittent Positive-Pressure Ventilation explode all trees in MeSH products
28. bi-level positive pressure in Record Title or bi-level positive pressure in Abstract in all products
29. NIPPV in Record Title or NIPPV in Abstract in all products
30. NIPPV in Record Title or NIPPV in Abstract in all products
31. NPPV in Record Title or NPPV in Abstract in all products
32. NIV in Record Title or NIV in Abstract in all products
33. NIMV in Record Title or NIMV in Abstract in all products
34. (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33)
35. (#10 AND #34)
36. MeSH descriptor Home Care Services explode all trees in MeSH products
37. domiciliary in Record Title or domiciliary in Abstract in all products

38. domicilliary in Record Title or domicilliary in Abstract in all products
39. home in Record Title or home in Abstract in all products
40. home-setting in Record Title or home-setting in Abstract in all products
41. discharged in Record Title or discharged in Abstract in all products
42. MeSH descriptor Nursing Homes explode all trees in MeSH products
43. nursing home* in Record Title or nursing home* in Abstract in all products
44. MeSH descriptor Residential Facilities explode all trees in MeSH products
45. residential home* in Record Title or residential home* in Abstract in all products
46. (#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #45)
47. (#35 AND #46)

OHE HEED

(chronic obstructive pulmonary disease OR copd) AND (home-setting OR home OR domiciliary OR discharged OR nursing home OR residential home) AND ventilat* OR mechanical OR NIPPV OR NPPV OR NIV OR NIMV)

Appendix 3: Ongoing clinical trials concerning the evaluation of NIV in the domiciliary setting for patients with COPD

Author/Country/Trial	Summary
AVCAL: Australian trial of Ventilation in Chronic Airflow Limitation Australia RCT	• Trial concerning nocturnal NIV in hypercapnic chronic COPD patients is currently being conducted across four centres in Australia • Survival is the primary outcome of interest • 135 have been enrolled into the study over last 4 years • Doug McEvoy has been contacted by ScHARR. The results are currently being written for publication • Some of the results were presented recently at a plenary session of the Asia Pacific Society of Respirology in Guangzhou, China
German Multicentre Study on NIV in Patients with Severe COPD and Emphysema Köhnlein et al. (2004[37]) Germany RCT	• National Task Force for Non-invasive ventilation and weaning aims to study patients with severe COPD and hypercapnic ventilatory pump insufficiency • It is a prospective, randomised, multi-centre clinical trial over one year • In the intervention group, NIV will be used for at least six hours per day in addition to standard COPD treatment • Main purpose of mechanical ventilation will be a reduction of $PaCO_2$ during spontaneous breathing by at least 20 %, or until a normal range is obtained • Primary outcome measure is mortality • Secondary outcome measures are consumption of medical resources, course of disease, exercise capacity and QOL • Sample size is estimated to be 300 patients (150 intervention group, 150 control group) • Study will take approximately three years
Does Chronic Ventilatory Support Improve the Outcomes of Rehabilitation in Hypercapnic Patients With COPD? Peter J Wijkstra Marieke L Duiverman The Netherlands RCT	• Purpose of study is to investigate whether non-invasive ventilation by nose mask during night has additional benefits with to pulmonary rehabilitation in patients with severe hypercapnic COPD • Hypothesis: long-term NPPV in hypercapnic patients with COPD may improve effects of rehabilitation at home regarding health status, ADL function, dyspnoea and exercise tolerance • Comparison: patients who receive non-invasive ventilation during night while following a pulmonary rehabilitation program with patients who only follow a rehabilitation program without receiving non-invasive ventilation • Treatment, Randomized, Open Label, Dose Comparison, Parallel Assignment, Safety/Efficacy Study • Primary Outcomes: HRQOL measured by the Chronic Respiratory Questionnaire • Secondary Outcomes: Activities of daily

	Living; Dyspnea (Medical Research Council Scale [MRC], baseline dyspnea index [BDI], Borg); Exercise tolerance (Cycle ergometer test, 6-minute walk distance [6-MWD], incremental shuttle walking test [ISWT], endurance shuttle walking test [ESWT]); Pulmonary function testing; Sleep quality (polysomnography); Respiratory muscle activity (endurance shuttle walking test [EMG]); Respiratory muscle strength (PImax, PEmax) • Expected Total Enrollment: 100 patients • Study start: November 2004 • Expected completion: November 2008 • Last follow-up: September 2008 • Data entry closure: October 2008

Appendix 4: Studies concerned with the economic analysis of non-invasive ventilation in domiciliary setting for COPD patients

Author	Source	Type	Summary
Tuggey, Plant, & Elliott (2003)[36]	Thorax	Cost and consequences analysis	• Evaluated economic data concerning impact of domiciliary NIV on admission to hospital and attendant costs • Examined domiciliary NIV based on before and after case note audit in 13 patients with recurrent acidotic exacerbations of COPD who tolerated and responded well to NIV • Primary outcome measure was total cost incurred per patient per year • Provision of home NIV service resulted in mean saving of £8254 (£4013 to £12,495) per patient per year • Significant decrease of: mean (SD) days in hospital 78 (51) to 25 (25); number of admissions 5 (3) to 2 (2); and ICU days 25 to 4 • Domiciliary NIV for selected group of COPD patients appears effective at reducing admissions and costs from perspective of an acute hospital
Tuggey, Plant, & Elliott (2001)[88]	Thorax	Cost minimisation analysis: retrospective case note audit,	• Investigated if home NIV is cost-effective at reducing admission rates • All patients had commenced home ventilation for recurrent admissions with acidotic exacerbations of COPD in 7 years • Evaluated the costs of admissions (ward and intensive care) and cost of domiciliary NIV service (equipment, staff) • Net saving to £10,8785 per year to the acute Trust by providing home NIV for 13 patients with sever COPD (i.e, £8,368 saved per patient per year) • Significant differences found between before NIV and home NIV in terms of admission, days in hospital and admission length • Overall, Home NIV reduced costs for a highly selected group of patients with COPD and recurrent admissions requiring acute NIV
Turner, Cooper, Watson, Britton, Wharton, & Kinnear (2003)[89]	Thorax	Letter to Editor	• Nottingham Assisted Ventilation Group (NAVG) provides home NIV for approximately two million patients • In many countries patients with COPD account for a large proportion of those on home NIV

			• Trial data suggest the beneficial effects are probably small • The numbers of patients with COPD using NAVG is small but, if evidence emerges of a long term survival benefit with NIV, this would have large resource implications • Mean increase in number of patients on home NIV was 8.8 per year • Mean (SD) age of the patients in 2002 was 54.6 (17.1) years (male:female ratio = 1:1.7) • Estimated first year equipment costs of NAVG service based on an average of 8.8 patients on home NIV would be £26,400 for ventilators and £2200 for masks/circuits. • After 5 years £11 000 is needed for masks/circuits in 44 patients at home • After 10 years ventilator costs double because need to replace ventilators over 7 years old, and for 88 patients at home total cost is £74 800 • Therefore equipment costs for home NIV service are substantial

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