

# Cost-effectiveness of domiciliary non-invasive ventilation in patients with chronic obstructive pulmonary disease

Hall, James; Turner, Alice; Dretzke, Janine; Moore, David; Jowett, Sue

DOI:

[10.1136/thoraxjnl-2021-217463](https://doi.org/10.1136/thoraxjnl-2021-217463)

License:

Creative Commons: Attribution-NonCommercial (CC BY-NC)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Hall, J, Turner, A, Dretzke, J, Moore, D & Jowett, S 2021, 'Cost-effectiveness of domiciliary non-invasive ventilation in patients with chronic obstructive pulmonary disease', *Thorax*. <https://doi.org/10.1136/thoraxjnl-2021-217463>

[Link to publication on Research at Birmingham portal](#)

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.



OPEN ACCESS

Original research

# Cost-effectiveness of domiciliary non-invasive ventilation in patients with chronic obstructive pulmonary disease

James Hall <sup>1</sup>, Alice Margaret Turner <sup>2</sup>, Janine Dretzke,<sup>2</sup> David Moore,<sup>2</sup> Sue Jowett <sup>1</sup>

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2021-217463>).

<sup>1</sup>Health Economics Unit, Institute of Applied Health Research, University of Birmingham, Birmingham, UK  
<sup>2</sup>Institute of Applied Health Research, University of Birmingham, Birmingham, UK

## Correspondence to

Professor Sue Jowett, Health Economics Unit, Institute of Applied Health Research, University of Birmingham, Birmingham, UK; [s.jowett@bham.ac.uk](mailto:s.jowett@bham.ac.uk)

Received 15 April 2021  
Accepted 14 October 2021

## ABSTRACT

**Background** Chronic obstructive pulmonary disease (COPD) is a chronic disease associated with recurring exacerbations, which influence morbidity and mortality for the patient, while placing significant resource burdens on healthcare systems. Non-invasive ventilation (NIV) in a domiciliary setting can help prevent admissions, but the economic evidence to support NIV use is limited.

**Methods** A Markov model-based cost-utility analysis from the UK National Health Service perspective compared the cost-effectiveness of domiciliary NIV with usual care for two end-stage COPD populations; a stable COPD population commencing treatment with no recent hospital admission; and a posthospital population starting treatment following admission to hospital for an exacerbation. Hospitalisation rates in patients receiving domiciliary NIV compared with usual care were derived from randomised controlled studies in a recent systematic review. Other model parameters were updated with recent evidence.

**Results** At the threshold of £20 000 per quality-adjusted life-year (QALY) domiciliary NIV is 99.9% likely cost-effective in a posthospital population, but unlikely (4%) to be cost-effective in stable populations. The incremental cost-effective ratio (ICER) was £11 318/QALY gained in the posthospital population and £27 380/QALY gained in the stable population. Cost-effectiveness estimates were sensitive to longer-term readmission and mortality risks, and duration of benefit from NIV. Indeed, for stable Global Initiative for Chronic Obstructive Lung Disease (GOLD) for stage 4 patients, or with higher mortality and exacerbation risks, ICERs were close to the £20 000/QALY threshold.

**Conclusion** Domiciliary NIV is likely cost-effective for posthospitalised patients, with uncertainty around the cost-effectiveness of domiciliary NIV in stable patients with COPD on which further research should focus.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease often accompanied by recurring exacerbations, that lead to clinical deterioration, and when severe, require hospitalisation.<sup>1</sup> When comparing non-invasive ventilation (NIV) with either no ventilation or invasive mechanical ventilation in hospital settings, in the context of type two respiratory failure/acute hypercapnic respiratory failure (AHRF), but not the absence of type 2 respiratory failure (T2RF), various study

## Key messages

### What is the key question?

► Taking into account recently published evidence on effectiveness, what is the longer-term cost-effectiveness of domiciliary non-invasive ventilation (NIV) in posthospitalised and stable patients.

### What is the bottom line?

► Health economic decision modelling found that domiciliary NIV is highly, likely to be cost-effective in posthospitalised patients, but unlikely to be cost-effective in stable patients, compared with usual care.

### Why read on?

► Currently, there is uncertainty surrounding the effectiveness and cost-effectiveness of domiciliary NIV, and commissioning of this intervention varies across and within countries (including the UK). This paper reports an updated model-based analysis of the cost-effectiveness of domiciliary NIV for end stage COPD, incorporating new effectiveness evidence.

designs have consistently shown better outcomes for NIV in the form of reduced inpatient mortality and length of stay.<sup>2-6</sup>

NIV may also be administered at home with or without oxygen therapy. Based on randomised controlled trials (RCTs), a previous systematic review<sup>7</sup> found no evidence for a survival benefit and limited evidence for fewer hospitalisations in stable populations. A survival benefit was also not demonstrated for posthospitalised patients (those recently discharged from admission to hospital for an exacerbation) with inconsistent findings on hospital readmissions.

We have previously demonstrated in a model-based cost-effectiveness analysis considerable uncertainty regarding cost-effectiveness of domiciliary NIV for both stable and posthospital patients.<sup>7</sup> The analysis was sensitive to assumptions regarding the strength and duration of treatment effect. As a consequence of the uncertainty over evidence, commissioning of domiciliary NIV varies across and within countries (including the UK), and a robust



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Hall J, Turner AM, Dretzke J, et al. *Thorax* Epub ahead of print: [please include Day Month Year]. doi:10.1136/thoraxjnl-2021-217463

model could aid formation of national guidance and streamline processes surrounding this treatment in the UK.

There is growing evidence relating to the effectiveness of domiciliary NIV in COPD.<sup>1</sup> This paper reports an analysis of the cost-effectiveness of domiciliary NIV for end-stage COPD updating our previously published model<sup>7</sup> with estimates of clinical effectiveness including recent and previously missed evidence.<sup>8</sup> Other model parameters are updated using real-life COPD data from the UK, including the National COPD audit<sup>9</sup> and Clinical Practice Research datalink,<sup>10</sup> which provide robust UK baselines of COPD outcomes for an untreated population.

## METHODS

Two cost-utility analyses were undertaken comparing domiciliary NIV with usual care for two COPD populations:

- ▶ Patients starting domiciliary NIV in a stable state, where they had no recent exacerbations, hospital admissions or other major change in clinical parameters over a defined period (4 or more weeks).<sup>7</sup>
- ▶ Patients starting domiciliary NIV immediately following admission to hospital for an exacerbation.

A Markov cohort model was constructed in TreeAge Pro (TreeAge Software, 2019) to estimate quality-adjusted life years (QALYs) and costs from the UK National Health Service (NHS) perspective. A 10-year time horizon was selected owing to high mortality in this patient population, with monthly time cycles. QALYs and costs were discounted at 3.5% as per UK guidance<sup>11</sup> with half-cycle correction performed. Model results are predicated on the benefit of NIV being accrued via a reduced risk of hospitalisation and associated cost-savings, life years gained and utility improvements.

## Model population

The stable model population was reflective of stable patients included in RCTs from the clinical effectiveness systematic review.<sup>8</sup> The mean age was 67, 54% were female, and 52% smokers (online supplemental appendix 1). Distribution

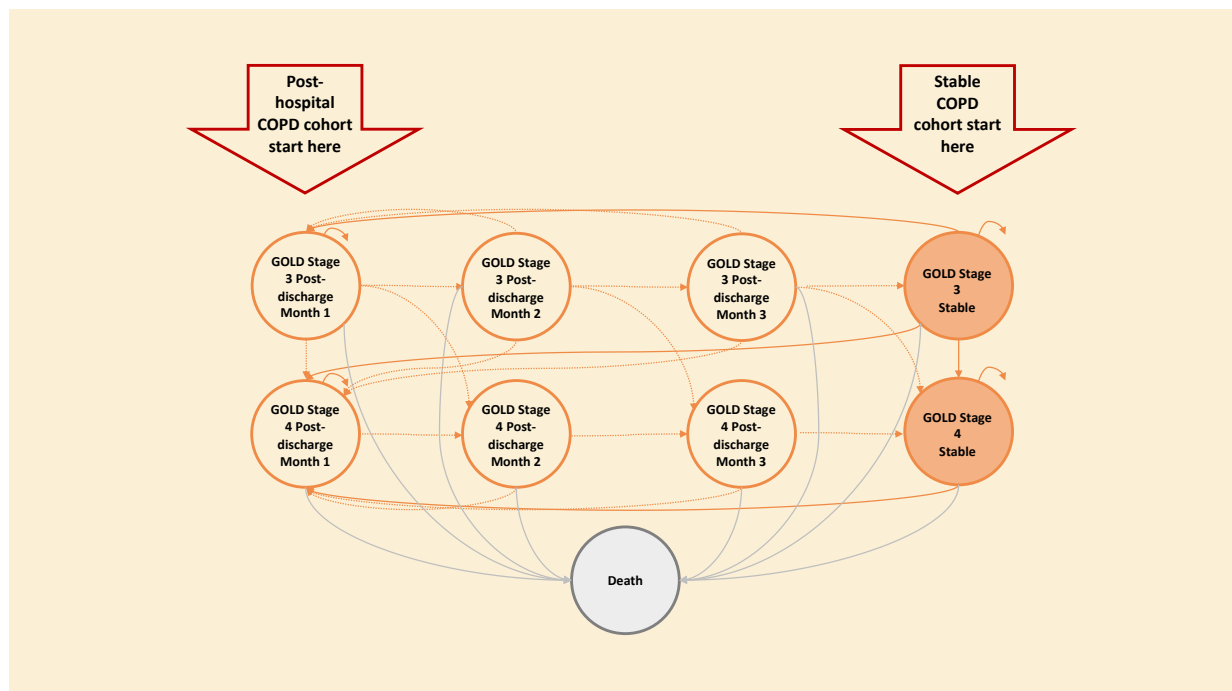
between 2011 GOLD stages was not commonly reported, therefore an assumption was made that 50% were in Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity stage 3% and 50% in stage 4, and domiciliary NIV would not be required in earlier disease stages, or where significant comorbid disease contributed to the underlying respiratory failure. COPD stage was defined according to 2011 GOLD classifications; GOLD stage 3 had a predicted forced expiratory volume in one second (FEV<sub>1</sub>)  $\geq 30\%$ ,  $< 50\%$  and GOLD stage 4 a predicted FEV<sub>1</sub>  $\leq 30\%$ . As real-world information was available for post-hospital patients, the model population was reflective of patients in the 2017 National UK COPD audit,<sup>9</sup> mean age 73, 47% female, 31% smokers, with an assumed 50% in GOLD stage 3 and 4 (online supplemental appendix 1). Online supplemental appendix 2 details all model assumptions.

## Model structure

Figure 1, adapted from Dretzke *et al*,<sup>7</sup> shows the model composition. The same structure was used for both populations, although posthospitalised patients started in 'postdischarge month 1', while stable patients began in stable states. The model used tunnel states to represent increased risk of mortality and readmission, lower quality of life, and higher costs, in those discharged after admission for an exacerbation. Accordingly, patients could not remain in postdischarge states by definition. Posthospitalised patients moved to stable health states after the postdischarge period, and stable patients moved to a posthospital state if they experienced an exacerbation requiring hospitalisation. There was a differing mortality risk in each state, according to population and health state. Patients could transition from GOLD stage 3–4, although not 4–3 as the disease is progressive. Online supplemental appendix 3 provides further detail.

## Model parameter estimates

Table 1 presents the model parameters for hospitalisation, mortality and discontinuation.



**Figure 1** State-transition schematic. GOLD, Global Initiative for Chronic Obstructive Lung Disease.

**Table 1** Hospitalisation, mortality and discontinuation parameters

Mortality and hospitalisation in postadmission states				
Definition	Probability	Beta distribution, $\alpha$ , $\beta$		Source
COPD-related death during admission				
Men	0.046	654, 13 552		2017 National UK COPD audit <sup>9</sup>
Women	0.035	570, 15 514		
COPD-related 90-day death post admission				
Men	0.073	1043, 13 163		2017 National UK COPD audit <sup>9</sup>
Women	0.066	1058, 15 027		
90-day COPD-related readmission				
Men	0.171	2423, 11 784		2017 National UK COPD audit <sup>9</sup>
Women	0.162	2609, 13 476		
All-cause COPD mortality post admission				
90-day men	0.046	650, 13 556		2017 National UK COPD audit <sup>9</sup>
90-day women	0.041	660, 15 425		
Hospitalisation rate and risk of non-COPD-related mortality in the stable health state for the post hospital population				
Definition	Rate	Sample size	Source	
Base case				
COPD admissions per year	1.6	340	Garcia-Aymerich <i>et al</i> <sup>12</sup>	
Non-COPD-related mortality	0.071	340		
Lowest rates				
COPD admissions per year	0.47	464	Bucknall <i>et al</i> <sup>14</sup>	
Non-COPD-related mortality	0.194	464		
Highest rates				
Base case risks multiplied by 2				
Treatment and exacerbation rates for stable population				
Severity stage	Annual exacerbation rate	Proportion of exacerbations hospitalised		Source
		%	Beta distribution, $\alpha$ , $\beta$	
GOLD 3	2.356	10.2	2267, 22 062	Rothnie <i>et al</i> <sup>10</sup>
GOLD 4	2.914	13.4	862, 6429	Rothnie <i>et al</i> <sup>10</sup>
Base case rate ratios for admission to domiciliary NIV relative to usual care				
		Rate Ratio (95% CI)*	Source	
<b>All studies estimates</b>				
Posthospital population				
Pooled mean		0.494 (0.382 to 0.638)	Pooled result of 11 RCTs <sup>8</sup>	
Best-case NIV		0.333 (0.187 to 0.596)	Li <i>et al</i> <sup>20</sup>	
Worst-case NIV		1.372 (1.067 to 1.763)	Struik <i>et al</i> <sup>21</sup>	
Stable population				
Pooled mean		0.606 (0.482 to 0.760)	Pooled result of 10 RCTs <sup>8</sup>	
Best-case NIV		0.346 (0.276 to 0.433)	Luyang <i>et al</i> <sup>22</sup>	
Worst-case NIV		1.166 (0.601 to 2.264)	Kamiński <i>et al</i> <sup>33</sup>	
<b>Western setting estimates†</b>				
Posthospital population				
Pooled mean		0.728 (0.212 to 2.504)	Pooled result of 2 RCTs <sup>8</sup>	
Best-case NIV		0.389 (0.321 to 0.470)	Murphy <i>et al</i> <sup>1</sup>	
Worst-case NIV		1.372 (1.067 to 1.763)	Struik <i>et al</i> <sup>21</sup>	
Stable population				
Pooled mean		0.718 (0.617 to 0.836)	Pooled result of 4 RCTs <sup>8</sup>	
Best-case NIV		0.643 (0.432 to 0.956)	Clini <i>et al</i> <sup>24</sup>	
Worst-case NIV		1.166 (0.601 to 2.264)	Kaminski <i>et al</i> <sup>33</sup>	

Continued

Table 1 Continued

Discontinuation			
Health state	Discontinuation Rate	Normal distribution, 95% CI	Source
All patients	15%	10% to 20%	Assumption and Dretzke <i>et al</i> <sup>8</sup>

\*Western settings included studies from Italy, Poland, the Netherlands, Germany and the UK. Non-Western studies contributing to meta-analyses are set in China.

†Natural log rate ratios and standard errors used in the probabilistic sensitivity analysis are shown in online supplemental appendix 6.

GOLD, Global Initiative for Chronic Obstructive Lung Disease; NIV, non-invasive ventilation; RCT, randomised controlled trial.

### Hospitalisation and mortality in postadmission health states

Transition probabilities for mortality and readmission for post-discharge states in both populations were obtained from the most recent UK audit of patients with COPD admitted to hospital.<sup>9</sup> Risk of readmission and mortality were assumed (1) to be evenly distributed over the 3-month period, and (2) to not to differ by GOLD stage as there is no evidence on a differentiated risk.<sup>7</sup>

### Hospitalisation and mortality risks for the posthospitalised population

Beyond the postdischarge period for the posthospitalised population, there was greater uncertainty regarding admission rates and mortality. Four studies<sup>12–15</sup> were identified which reported long-term admission rates and mortality. Highest and lowest rates were used in sensitivity analyses, with mid-range rates used for the base case.

COPD-related mortality was captured via the risk of a COPD-related death either during admission or in the 3-month post-discharge period.<sup>9</sup> These risks in combination with the all-cause mortality risk reported in Garcia-Aymerich *et al*<sup>12</sup> were assumed to stay constant over the cohort lifetime.

### Exacerbation and hospitalisation risk in stable health states

For the stable population, data on exacerbation and hospital admissions in the stable health states were drawn from a large UK study (n=12830) with long-term follow-up of a COPD general practice population.<sup>9</sup>

### Mortality risks for the stable population

For health states for the stable population, Office for National Statistics life tables were used to populate age and gender-specific all-cause mortality probabilities, adjusted to avoid double counting of COPD-related mortality (online supplemental appendix 4).

### Discontinuation rate

After an initial period, it was assumed a proportion of patients starting domiciliary NIV would discontinue treatment. Non-adherence and discontinuation rates vary across both populations,<sup>8</sup> therefore it was assumed that 15% of patients would discontinue after 3 months. Patients who discontinued NIV were assumed to incur costs but not benefits of NIV in the initial 3 months, and neither costs nor benefits of NIV beyond 3 months.

### Disease progression in stable and posthospitalised population

Baseline risks of hospital admission and mortality need to be extrapolated beyond the follow-up duration in source studies. Accordingly, to capture long-term prognosis, patients were allowed to move between GOLD stages. Probabilities associated with moving to GOLD stage 4 were sourced from a previously published model<sup>16</sup> and applied to GOLD stage 3 states for both populations (online supplemental appendix 5).

### Effectiveness of domiciliary NIV

Hospital admission data were taken from our meta-analysis of absolute differences<sup>8</sup> and converted to rate ratios by estimating the number of events and total time at risk (assuming complete follow-up) from relevant RCTs. The rate ratio and SE were calculated using Poisson regression, rate ratios with 95% CIs (table 1).

The base case analysis considered all studies in the review; however, to account for differences between healthcare systems, a sensitivity analysis was also performed on studies in Western/high-income settings. Further sensitivity analyses used individual studies with the best-case and worst-case rate ratios for the effect of NIV on hospital admissions.

Given that hospital admission is associated with increased mortality risk, the model produces an improvement in mortality for NIV indirectly by preventing admissions. To assess external validity, the extent to which the model reflects the real-world, model survival rates were contrasted with those found in the RCTs in the clinical effectiveness systematic review.<sup>8</sup>

Following consultation with clinicians involved with treating patients with NIV, it was assumed that the effect of NIV in reducing admissions would last 5 years in both patient groups, with alternative periods of efficacy tested in sensitivity analysis.

### Utility values

Utility values were obtained for each stable GOLD stage 3 and 4 from EQ-5D-5L (the five level EuroQol five dimensions) values for 336 participants with a confirmed diagnosis of COPD from a UK cohort study,<sup>17</sup> table 2. No effect on quality of life is assumed above that of the impact NIV has on exacerbations and mortality, this assumption is tested in sensitivity analyses.

In line with previous COPD models,<sup>18–20</sup> disutility values associated with moderate or severe exacerbation were taken from Rutten-van Mólken *et al*.<sup>21</sup> A disutility of 15% for a moderate exacerbation was assigned for a period of 1 month, with a 50% loss in the first month of a severe exacerbation and a 25% loss in second and third months.

### Costs

Costs were presented in 2019/2020 pounds sterling and inflated to current value using hospital and community health services index and NHS cost inflation index.<sup>22</sup> Costs were subdivided into three components, (1) routine COPD care, (2) treatment of exacerbations, and (3) provision of domiciliary NIV.

All detailed cost calculations for each component can be found in online supplemental appendix 7, with table 2 providing headline costs, as well as the methodology for estimating the cost of providing domiciliary NIV, estimated at £1698.18 in the first year and £1086 in subsequent years (further details in online supplemental appendix 7).

**Table 2** Utility scores and costs for stable GOLD states, and costs of providing a domiciliary NIV service

	Utility GOLD stage 3	Utility GOLD stage 4	
Sample size	299	37	
Mean utility score (SE)	0.678 (0.015)	0.601 (0.042)	
<b>Type of healthcare</b>	<b>Cost GOLD stage 3</b>	<b>Cost GOLD stage 4</b>	
Routine healthcare	£39.91/month	£77.33/month	
Routine pharmacotherapy	£50.42/month	£54.71/month	
Moderate exacerbation	£140.40 per episode		
Severe exacerbation	£2283.18 per episode		
<b>Estimation of the cost of providing a domiciliary NIV service</b>			
Cost type	Cost	Unit cost source	Resource use source
<b>Equipment costs</b>			
NIV equipment for domiciliary use	£2939.69	Supplier estimates	Clinician estimates of use of machines and cost estimate from firms
NIV equipment for domiciliary use monthly cost	£48.99	Depreciated over 5 years	
<b>Set-up costs</b>			
NIV set-up and assessment month 1	£482.82	National Tariff Payment System 2019/20 <sup>35</sup>	Expert opinion
NIV Follow-up in m3: 1 × Consultant led outpatient app+1 × Blood gas test	£157.16 + £194	NHS reference costs 2018/2019 <sup>36</sup>	Expert opinion
<b>Annual costs therefore</b>			
2 × blood gas test conducted at routine follow-up	2 × £194	NHS reference costs 2018/2019 <sup>36</sup>	Expert opinion
1 × annual NIV assessment and consumable provision	£650	Estimate	Expert opinion
<b>Monthly costs</b>			
First 3 months	£294.32	Includes equipment and set-up costs	
>3 months	£90.58	Includes equipment and annual monitor and service costs	

GOLD, Global Initiative for Chronic Obstructive Lung Disease; NHS, National Health Service; NIV, Non-Invasive ventilation.

## Analyses

A cost-utility analysis was undertaken to estimate incremental cost-effectiveness ratios (ICERs), the difference in costs divided by the difference in QALYs of two strategies, with results presented as cost-per-QALY gained. Cost-effectiveness was considered in relation to the lower NICE threshold of £20 000 per-QALY gained.<sup>23</sup> Each result reflects mean costs and QALYs as an average of 10 000 model iterations generated by probabilistic sensitivity analysis, used to account for parameter uncertainty. Where possible, distributions were attached to probabilities, utilities and costs in the model. Beta distributions were attached to transition probabilities and utilities, with natural logs of rate ratios sampled normally and exponentiated.<sup>24</sup> The model results were expressed as a cost-effectiveness acceptability curve (CEAC) showing graphically the probability of cost-effectiveness of domiciliary NIV across a range of cost-per-QALY thresholds.<sup>24</sup> Deterministic sensitivity analyses were used to assess the individual impact of varying model parameters on cost-effectiveness results.

## Expected value of perfect information (EVPI)

EVPI is a quantitative method of assessing the marginal value of further studies, and in essence helps consider whether it is worth conducting more research.<sup>25</sup> In order to calculate the population EVPI the size of population expected to benefit must be calculated. We estimated this to be 661 199 for stable patients and

190 049 for posthospital patients over a 10-year time horizon (calculations in online supplemental appendix 8).

## RESULTS

### Posthospital population

#### Base case for the posthospital population

In the base case analysis for the posthospital population domiciliary NIV was £4799 more costly, delivering 0.424 more QALYs, making the ICER £11 318/QALY gained. This was 99.9% likely to be cost-effective at the £20 000/QALY threshold (table 3).

Using hospitalisation rates from Western studies, QALY gains reduced to 0.168 for £4765 additional cost, increasing the ICER to £28 430/QALY with domiciliary NIV only 46.9% likely to be cost-effective.

The base case cost-effectiveness plane in figure 2 shows NIV is more effective and costly in all model iterations (hence all iterations in the north-east quadrant). The corresponding CEAC (figure 3) demonstrates domiciliary NIV is very likely to be cost-effective over thresholds of about £12 500/QALY and is always cost-effective between £20 000/QALY and £30 000/QALY.

### Sensitivity analysis

Table 4 shows the impact of alternate parameter values on cost-effectiveness in posthospital patients. Applying the rate ratio for hospital admissions from the worst-case study results in NIV being dominated, that is both more costly with worse

**Table 3** Base case analyses posthospital population

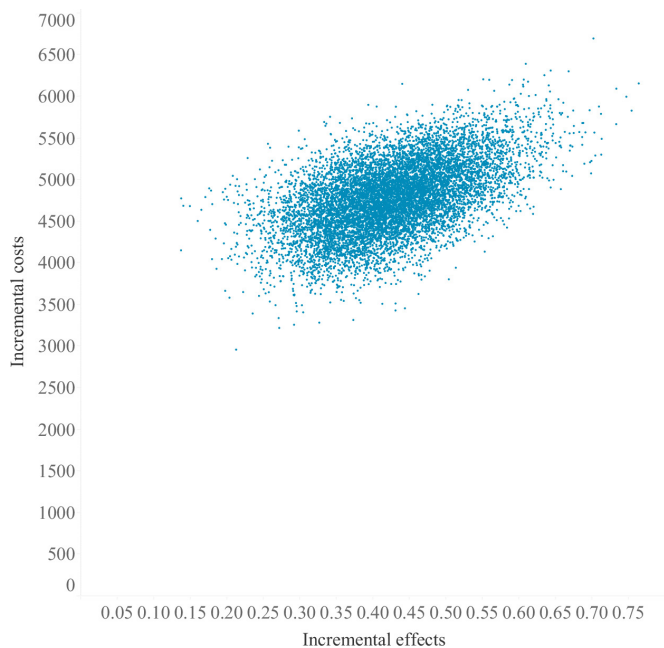
Strategy	Mean cost (£)	Mean QALY	ICER (£/QALY)	Probability cost-effective*
Base case posthospital population, all studies, pooled mean rate ratio				
Domiciliary NIV	£19 876	2.391	£11 318	99.9%
Usual care	£15 081	1.967		
Incremental difference	£4799	0.424		
Posthospital population, 'Western' settings†, pooled mean rate ratio				
Domiciliary NIV	£19 840	2.136	£28 430	46.9%
Usual care	£15 075	1.969		
Incremental difference	£4765	0.168		

\*Cost-effective at £20 000/QALY.

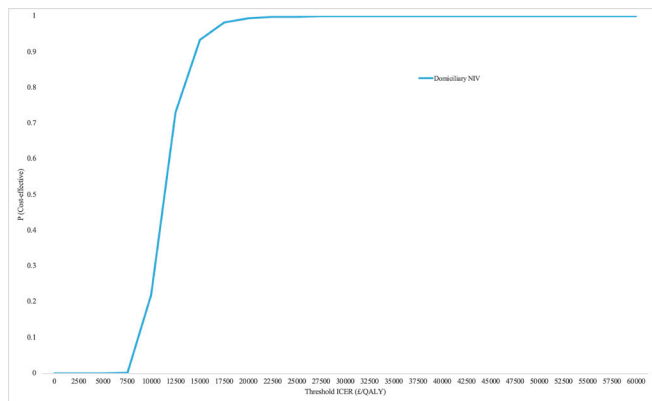
†Western studies included studies reporting hospitalisations from Italy, Poland, the Netherlands, Germany and the UK.

ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

health outcomes in all study settings. Assuming the duration of effect of domiciliary NIV in reducing hospital admissions is only 2 years, gives a higher ICER of £22 078/QALY, with likely cost-effectiveness reduced to 26%. However, it would take a 0.10 reduction in utility on NIV to significantly impact the likely



**Figure 2** Base case cost-effectiveness plane for domiciliary NIV for posthospitalised patients. Incremental costs and effectiveness reflect the sum of mean costs and quality-adjusted life years (QALYs) of domiciliary non-invasive ventilation (NIV) minus those of usual care. Results are generated from probabilistic sensitivity analysis, where 10 000 unique Monte Carlo simulations sample from the known distributions of model parameters. Accordingly, each dot reflects the incremental costs and QALYs for each one of the 10 000 model iterations. Notice, all dots lie above 0 for incremental effectiveness indicating NIV is more effective, and all points above 0 for incremental costs indicating NIV is more expensive. The size of the cloud of dots reflect the range of incremental costs and QALYs that the model results could take, given the uncertainty in the model parameters.



**Figure 3** Base case cost-effectiveness acceptability curve. The graph plots the probability that domiciliary NIV is cost-effective at various UK thresholds for willingness to pay for 1 QALY (£/QALY). Between the commonly used UK thresholds of £20 000 to £30 000 per QALY, it can be seen NIV is consistently 99%–100% likely to be cost-effective. ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; P, probability; QALY, quality-adjusted life year.

cost-effectiveness, resulting in an ICER of £35 526/QALY and only 5% likely to be cost-effective.

Changing baseline hospitalisation and mortality data to lower estimates<sup>14</sup> increased the ICER to £21 473/QALY and reduced the probability of NIV being cost-effective to 39%. However, increasing all mortality risks by a factor of two decreased costs and outcomes owing to shorter survival, reducing the ICER to £9883/QALY.

Varying the time horizon did not impact cost-effectiveness significantly, neither did analyses on various machine costs, lifespans, maintenance cost of NIV (online supplemental appendix 9) or different population subgroups (online supplemental appendix 10).

In terms of model validity, base case estimated mortality at 2 years was 43.5% on usual care and 36% on NIV, this is similar to an RCT which reported 2-year mortality at 40% in posthospitalised patients receiving NIV.<sup>26</sup> Moreover, the relative risk of mortality on NIV compared with usual care of 0.83 is statistically similar to the relative risk of mortality for the posthospitalised population found in RCTs in the systematic review 0.78 (0.60–1.03).<sup>8</sup>

**EVPI for the posthospital population**

The EVPI for the posthospital population was estimated to be £3.25 per patient, reflecting low uncertainty in the base case analysis at a threshold of £20 000/QALY. The estimated population EVPI over the next 10 years was estimated at £617 659.

**Stable population**

**Base case**

In the base case analysis for the stable population, domiciliary NIV was £8488 more costly but gave 0.310 additional QALYs, for an ICER of £27 380/QALY, only 4% likely to be cost-effective at the £20 000/QALY threshold (table 5). Using a rate ratio estimate from 'Western' settings, saw a smaller QALY gain of 0.14 for £8400 additional cost, increasing the ICER to £60 000/QALY. The likely cost-effectiveness was 25% due to uncertainty in the effectiveness estimate.

The base case cost-effectiveness plane (figure 4) shows NIV was more effective and costly in most model iterations. The corresponding CEAC (figure 5) demonstrates QALY increases

**Table 4** One-way sensitivity analysis in the posthospital population

	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective*
<b>Varying the rate ratio</b>				
Best-case NIV	+£4855	+0.596	£8146	100%
Worst-case NIV	+£4715	-0.220	Dominated	1.1%
Base case	+£4799	+0.424	£11 318	99.9%
Best case 'Western' settings NIV†	+£4765	+0.539	£8979	100%
Worst-case 'Western' settings NIV†	+£4687	-0.215	Dominated	0%
<b>Change in utility on NIV</b>				
+0.20 utility	+£4799	+1.005	£4763	100%
+0.10 utility	+£4799	+0.714	£6707	100%
+0.05 utility	+£4799	+0.571	£8385	100%
-0.05 utility	+£4799	+0.280	£17 104	71.1%
-0.10 utility	+£4799	+0.135	£35 526	5.4%
-0.20 utility	+£4799	-0.158	Dominated	0%
<b>Varying duration of effect</b>				
2 years	+£4813	+0.218	£22 078	26.0%
5 years (base case)	+£4799	+0.424	£11 318	99.9%
10 years (model horizon)	+£4172	+0.535	£7798	99.9%
<b>Alternate model time horizon</b>				
2 years	+£919	+0.073	£12 589	78.9%
5 years	+£2187	+0.260	£8408	99.5%
10 years (base case)	+£4799	+0.424	£11 318	99.9%
20 years	+£5763	+0.484	£11 914	99.4%
<b>Alternate Mortality and readmission risk</b>				
Lower risks from Bucknell <i>et al</i> <sup>14</sup>	+£3715	+0.173	£21 473	39.34%
Doubling all mortality risks <sup>13 15</sup>	+£3953	+0.400	£9883	99.9%

\*Cost-effective at £20 000/QALY.

†Western studies included studies from Italy, Poland, the Netherlands, Germany, and the UK.

ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

come at a high cost, with domiciliary NIV only likely to be cost-effective over thresholds of £40 000/QALY.

### Sensitivity analyses

Table 6 shows sensitivity analyses for stable patients. When using alternate rate ratios, NIV is almost certain to be

cost-effective at £20 000/QALY in the best case all studies estimate, whereas the best-case Western study only gives an ICER of £31 196/QALY. Cost-effectiveness was very sensitive to changes in utility, with a +0.05 gain in utility on NIV reducing the ICER to below £20 000/QALY. While assuming the effect of NIV lasted for a 10-year time horizon also reduced the ICER to £19 119/QALY.

Domiciliary NIV is more cost-effective in patients with higher baseline hospitalisation and mortality risks. Higher baseline hospitalisation and mortality risks<sup>12</sup> reduced the ICER to £20 797/QALY, increasing the probability of NIV being cost-effective to 44%.

Sensitivity analyses on alternative machine cost, lifespan and annual NIV maintenance cost did not influence cost-effectiveness (online supplemental appendix 9).

Choice of GOLD stage starting cohort also influenced the likely cost-effectiveness, the ICER fell to £21 132/QALY with a 43% probability of being cost-effective when only GOLD stage 4 patients were considered. Results for other subgroups were similar to the base case (online supplemental appendix 10).

### EVPI analysis for the stable population

The EVPI per patient for the posthospital population was estimated to be £18.01 per patient and over the next 10 years generated population EVPI of £11 908 194.

**Table 5** Base case analyses stable population

Strategy	Mean cost (£)	Mean QALY	ICER (£/QALY)	Probability cost-effective*
<b>Base case stable population, all studies, pooled mean rate ratio</b>				
Domiciliary NIV	£25 461	4.177	£27 380	4%
Usual care	£16 973	3.867		
Incremental difference	£8488	0.310		
<b>Stable population, 'Western' settings†, pooled mean rate ratio</b>				
Domiciliary NIV	£25 373	4.007	£60 000	25%
Usual care	£16 973	3.867		
Incremental difference	£8400	0.14		

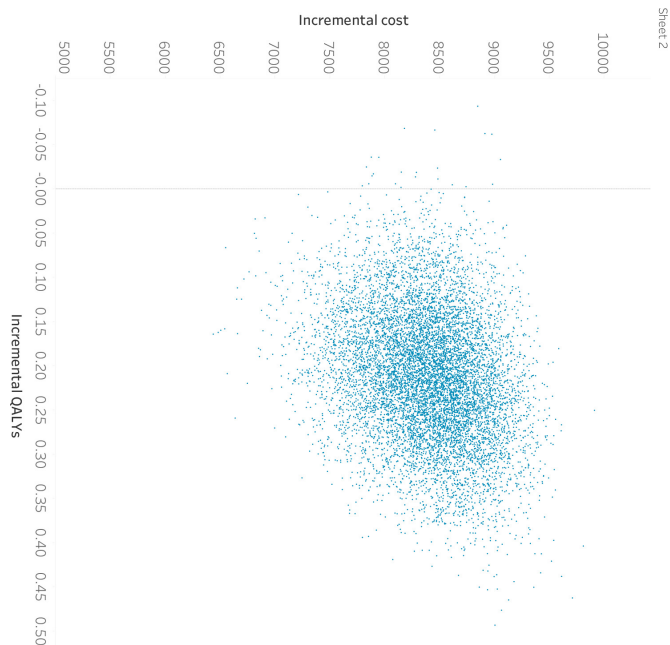
\*Cost-effective at £20 000/QALY.

†Western studies included studies reporting hospitalisations from Italy, Poland, the Netherlands, Germany and the UK.

ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; QALY, quality-adjusted life year.



## Chronic obstructive pulmonary disease



**Figure 4** Base case cost-effectiveness plane for domiciliary NIV for stable patients. Incremental costs and effectiveness reflect mean the sum of mean costs and quality-adjusted life years (QALYs) of domiciliary non-invasive ventilation (NIV) minus those of usual care. Results are generated from probabilistic sensitivity analysis, where 10 000 unique Monte Carlo simulations sample from the known distributions of model parameters. Accordingly, each dot reflects the incremental costs and QALYs for each one of the 10 000 model iterations. Notice, all dots lie above 0 for incremental effectiveness indicating NIV is more effective, and all points above 0 for incremental costs indicating NIV is more expensive. The size of the cloud of dots reflect the range of incremental costs and QALYs that the model results could take, given the uncertainty in the model parameters.

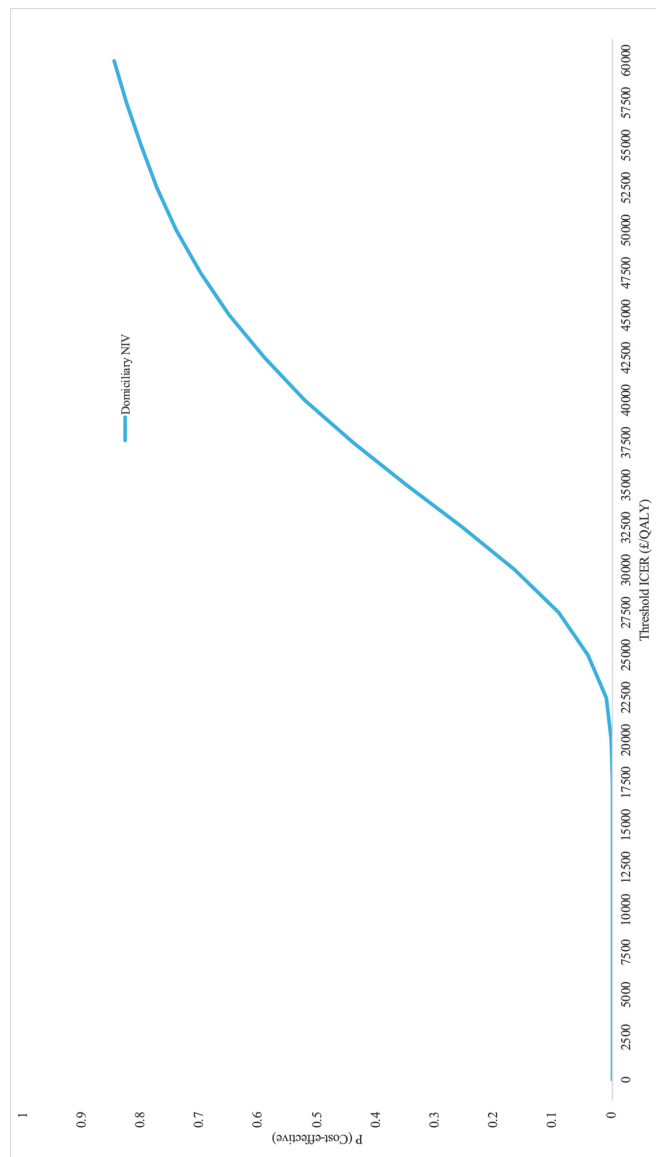
### DISCUSSION

This updated and enhanced economic model for domiciliary NIV in severe patients with COPD provides evidence on the likely cost-effectiveness of domiciliary NIV in a posthospital population. The high likelihood of cost-effectiveness in the posthospitalised population is driven by favourable new evidence on hospital admissions from recently published RCTs, and those conducted in China not included in previous systematic reviews.<sup>8</sup> However, caution is required for generalisation to the UK, as the likely cost-effectiveness is below 50% when applying estimates of NIV effect from ‘Western’ studies. While NIV for those with more stable disease is unlikely to be cost-effective, the ICER for stable patients in GOLD stage 4 and with higher exacerbation risks was only just over the £20 000/QALY threshold.

#### Are there settings in which domiciliary NIV is more cost-effective?

Cost-effectiveness and clinical effectiveness are related, in that groups with the most clinical benefit will usually incur lower costs, and this is the case with domiciliary NIV. Analyses on admissions and mortality risks demonstrated that posthospitalised patients, who have inherently higher admission and mortality risks, are more likely to benefit from domiciliary NIV.

The rate ratio in posthospitalised populations in ‘Western’ settings, derived from fewer studies, was also higher than the all-studies estimate and lowered the likely cost-effectiveness



**Figure 5** Base case cost-effectiveness acceptability curve. The graph plots the probability that domiciliary NIV is cost-effective at various UK thresholds for willingness to pay for 1 QALY (£/QALY). Above thresholds of £40 000 per QALY, it can be seen NIV emerges as likely to be cost-effective. ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; P, probability; QALY, quality-adjusted life years.

somewhat, suggesting other factors might be influencing outcomes independently of NIV in ‘Western’ settings. Assuming that NIV only impacts hospital admissions for a duration of 2 years also raises the ICER over the £20 000/QALY threshold. Long-term registry-based studies of domiciliary NIV might assist in generating the data to estimate how long the true effect lasts.

Domiciliary NIV for stable populations is not likely to be cost-effective at the £20 000/QALY threshold. However, there is evidence that patients with a higher risk of mortality and admission are more likely to benefit from domiciliary NIV, and it remains possible that stable populations such as those with a high blood CO<sub>2</sub> level<sup>27</sup> would benefit more. However, sensitivity analyses based on severe hypercapnia, or change in hypercapnia with treatment, were not possible because of poor reporting, and a lack of studies targeting appropriate patients.

**Table 6** One-way sensitivity analysis for stable population

	Cost difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective*
<b>Varying the rate ratio</b>				
Best-case NIV	+£8804	+0.562	£15 665	99.2%
Worst-case NIV	+£8112	-0.111	Dominated	0%
Base case	+£8488	+0.310	£27 380	4%
Best-case 'Western' setting NIV†	+£8812	+0.271	£31 196	8%
Worst-case 'Western', setting NIV†	+£8112	-0.111	Dominated	0%
<b>Change in utility on NIV</b>				
+0.20 utility	+£8488	+1.147	£7401	100%
+0.10 utility	+£8488	+0.72	£11 597	100%
+0.05 utility	+£8488	+0.514	£16 514	82.4%
Base case	+£8488	+0.310	£27 380	4%
-0.05	+£8488	+0.097	£87 505	0%
<b>Varying duration of effect</b>				
2 years	+£8488	+0.150	£56 153	0%
10 years (model horizon)	+£7896	+0.413	£19 119	58%
<b>Alternate model time horizon</b>				
2 years	+£2057	+0.033	£62 333	0%
15 years	+£10 696	+0.392	£27 286	3%
20 years	+£11 750	+0.429	£27 389	3%
<b>Alternate mortality and readmission risk</b>				
Higher risks from Garcia-Aymerich <i>et al</i> <sup>12</sup>	+£5137	+0.247	£20 797	44%

\*Cost-effective at £20 000/QALY.

†Western studies included studies reporting hospitalisations from Italy, Poland, The Netherlands, Germany and the UK  
ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

### How certain are the results?

The probability of cost-effectiveness in posthospital populations is close to 100% at the £20 000 per QALY threshold; however, there is more uncertainty in stable patients. Cost-effectiveness of NIV in the posthospital population is higher (99.9%) than in our original model (72%) reflecting reduced uncertainty. However, the ICER is actually higher (£11 318/QALY vs £10 107/QALY) as the time horizon and NIV effect duration were lowered to 10 years and 5 years, respectively, reflecting greater knowledge of long-term outcomes. The result in the stable population is sensitive to assumptions, for example, applying an increase in utility of 0.05 on NIV lowers the ICER below the £20 000/QALY threshold, and using the best-case rate ratio estimate results in the intervention being close to 100% cost-effective at the £20 000/QALY threshold.

### What studies should be done next?

One of the limitations of our study concerns the pooling of data from potentially heterogeneous patients with COPD, and clearly given the sensitivity to variation in clinical risk there could be real value in exploring the effect of NIV in these subgroups. In particular, the estimate for the value of further research in the stable population is substantial, reflecting the sizeable population expected to benefit. However, uncertainty regarding mortality and readmission rates, which are shown to influence cost-effectiveness in both populations, is not parameterised in this model (and therefore excluded from the EVPI) owing to the lack of consistency, and ought to be a target for further research. More nuanced studies enrolling subgroups of patients with COPD in the stable state, for example, studies targeting specific subgroups within a stable population, for example, severely hypercapnic

patients (eg,  $p\text{CO}_2 > 7.5$  kPa), and studies using higher pressure settings<sup>28</sup> and longer-term follow-up could reduce uncertainty in future cost-effectiveness evaluations. Moreover, research will be required to understand the long-term impact of the COVID-19 pandemic on patient with COPD outcomes and treatment patterns, and may require updated modelling to reflect the new normal.

### Strengths and limitations

Key strengths of this analysis derive from the original model design, which considers stable and posthospital patients with COPD separately, allowing for appropriate risk estimates for each population. Moreover, the utilisation of postadmission health states allows higher risks of readmission and mortality in patients with COPD immediately after discharge. Results are strengthened by the updating of model parameters using recently published data.

Moreover, the use of more robust assessment of clinical effectiveness evidence has decreased the uncertainty regarding the treatment effect of NIV (hospital admissions) in posthospital patients. This has arisen from the incorporation of a large number of additional studies and the decision to use a pooled effect estimate, despite some evidence of heterogeneity. This was felt to be a reasonable decision in this case as the direction of effect was consistent (bar one study), unlike the original analysis which was limited to three studies with substantial uncertainty around direction of effect. The degree of uncertainty regarding the pooled estimate in the stable population has also been reduced, driven by the inclusion of previously unidentified studies conducted in China. The inclusion of evidence from studies conducted world-wide strengthens the

overall cost-effectiveness findings, although the generalisability of these findings to different healthcare settings needs further evaluation.

However, the analyses cannot overcome uncertainties in parameters, in particular for the longer-term risks where there is only limited evidence. Nonetheless, this analysis provided extensive sensitivity analyses to illuminate the implications of this uncertainty wherever possible.

It is possible our dichotomisation of stable and posthospital patients reflects more the pathway by which hypercapnia is identified than different populations, further research is required. Importantly, patients with COPD are mainly monitored for respiratory failure using oxygen saturations, and rarely blood gases, when stable. This may lead to late identification of stable hypercapnia, whereby it is only deterioration with resultant acidosis and hospital admission that leads to blood gas being taken during admission and at follow-up. Research to date to identify factors predicting hypercapnia has been unable to identify accurately all those who might require blood gas testing, but those with severe disease and with a prior admission (even if not requiring NIV) may be an important group.<sup>29</sup> Alternatively, they may be truly different due to medical optimisation while admitted, or other as yet unknown factors.

## CONCLUSION

Domiciliary NIV appears to be cost-effective when started immediately after or within 4–6 weeks of a hospital admission in which NIV was required. Cost-effectiveness is greater in more severely ill patients, and in those with a higher risk of mortality or subsequent admission. Uncertainty remains around the cost-effectiveness of domiciliary NIV in stable patients with COPD, as well as patients within a stable population that might benefit most, and further research should focus on this area.

**Twitter** James Hall @JamesHall795 and Sue Jowett @SusieJ71

**Acknowledgements** We would like to acknowledge the contribution of Rahul Mukherjee in assisting with the pricing of the various non-invasive ventilation machines, as well as providing information for JH and SJ on the use of the machines in clinical practice. We would also like to acknowledge the contribution of Malcolm Price, for statistical guidance.

**Contributors** JH edited the existing model, updated model parameters, conducted statistical analyses, performed the economic analysis and wrote the paper with guidance from SJ, AMT, JD and DM. SJ designed the original health economic analyses, supervised the economic modelling and contributed to writing the paper. AMT provided clinical guidance on and identified the updated model parameters and contributed to writing the paper. JD and DM designed the systematic review from which the hospitalisation data was drawn, advised on use of parameters in the economic model and contributed to the writing of the paper. JD led and undertook the systematic review. SJ is the guarantor and accepts full responsibility for the work and the conduct of the study, and controlled the decision to publish.

**Funding** This study was funded by a non-commercial grant from ResMed and Phillips. The funders had no input to the study design, conduct or interpretation of the results.

**Competing interests** AMT has received grant funding to her institution for the work contained in the manuscript from ResMed/Phillips, which funded JH and JD, as well as contributions for oversight from DM and SJ. She has also received grant funding and/or honoraria from several companies involved in treatment of COPD, specifically AstraZeneca, Chiesi, GSK and Boehringer Ingelheim.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## ORCID iDs

James Hall <http://orcid.org/0000-0001-8024-5427>

Alice Margaret Turner <http://orcid.org/0000-0002-5947-3254>

Sue Jowett <http://orcid.org/0000-0001-8936-3745>

## REFERENCES

- Murphy PB, Rehal S, Arbane G, *et al*. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA* 2017;317:2177–86.
- Brochard L, Mancebo J, Wysocki M, *et al*. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995;333:817–22.
- Bott J, Carroll MP, Conway JH, *et al*. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993;341:1555–7.
- Lindenauer PK, Stefan MS, Shieh M-S, *et al*. Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease. *JAMA Intern Med* 2014;174:1982–93.
- Osadnik CR, Tee VS, Carson-Chahhoud KV, *et al*. Non-Invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017;7:CD004104.
- Shah NM, D'Cruz RF, Murphy PB. Update: non-invasive ventilation in chronic obstructive pulmonary disease. *J Thorac Dis* 2018;10:S71–9.
- Dretzke J, Blissett D, Dave C. *The cost-effectiveness of domiciliary non-invasive ventilation in patients with end-stage chronic obstructive pulmonary disease: a systematic review and economic evaluation*. Southampton, UK: NIHR Journals Library, 20152015.
- Dretzke J, Wang J, Yao M. The effect of domiciliary non-invasive ventilation on stable and recently hospitalized patients with COPD: a systematic review using English and Chinese language sources and meta-analysis of studies 2021. Manuscript in Preparation.
- Hurst J, Stone RA, McMillan V. *COPD: National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme (NACAP) Outcomes of patients included in the 2017 COPD clinical audit (patients with COPD exacerbations discharged from acute hospitals in England and Wales between February and September 2017)*. Audit report. London: RCP, May, 2019.
- Rothnie KJ, Müllerová H, Smeeth L, *et al*. Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018;198:464–71.
- National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013*. London: National Institute for Health and Clinical Excellence, 2013.
- García-Aymerich J, Ferrero E, Féliz MA, *et al*. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003;58:100–5.
- Budweiser S, Hitzl AP, Jörres RA, *et al*. Impact of noninvasive home ventilation on long-term survival in chronic hypercapnic COPD: a prospective observational study. *Int J Clin Pract* 2007;61:1516–22.
- Bucknall CE, Miller G, Lloyd SM, *et al*. Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD: randomised controlled trial. *BMJ* 2012;344:e1060.
- Heinemann F, Budweiser S, Jörres RA, *et al*. The role of non-invasive home mechanical ventilation in patients with chronic obstructive pulmonary disease requiring prolonged weaning. *Respirology* 2011;16:1273–80.
- Atsou K, Chouaid C, Hejblum G. Simulation-Based estimates of effectiveness and cost-effectiveness of smoking cessation in patients with chronic obstructive pulmonary disease. *PLoS One* 2011;6:e24870.
- Adab P, Fitzmaurice DA, Dickens AP, *et al*. Cohort profile: the Birmingham chronic obstructive pulmonary disease (COPD) cohort study. *Int J Epidemiol* 2017;46:23.
- Lambe T, Adab P, Jordan RE, *et al*. Model-Based evaluation of the long-term cost-effectiveness of systematic case-finding for COPD in primary care. *Thorax* 2019;74:730–9.
- Miravittles M, Marín A, Huerta A, *et al*. Estimation of the clinical and economic impact of an improvement in adherence based on the use of once-daily Single-Inhaler triple therapy in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2020;15:1643–54.
- Rajagopalan K, Bloudek L, Marvel J, *et al*. Cost-effectiveness of twice-daily indacaterol/glycopyrrolate inhalation powder for the treatment of moderate to severe COPD in the US. *Int J Chron Obstruct Pulmon Dis* 2018;13:3867–77.
- Rutten-van Mölken MPMH, Oostenbrink JB, Miravittles M, *et al*. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. *Eur J Health Econ* 2007;8:123–35.
- Personal Social Services Research Unit (PSSRU). Unit costs of health and social care 2019, 2020. Available: <https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019> [Accessed 17 Nov 2020].

- 23 Appleby J, Devlin N, Parkin D. Nice's cost effectiveness threshold. *BMJ* 2007;335:358–9.
- 24 Briggs A, Claxton K, Sculpher M. *Decision modelling for health economic evaluation*. New York: Oxford University Press, 2006.
- 25 Wilson ECF. A practical guide to value of information analysis. *Pharmacoeconomics* 2015;33:105–21.
- 26 Xiang P-chao, Zhang X, Yang J-nan, *et al.* [The efficacy and safety of long term home noninvasive positive pressure ventilation in patients with stable severe chronic obstructive pulmonary disease]. *Zhonghua Jie He He Hu Xi Za Zhi* 2007;30:746–50.
- 27 Köhnlein T, Windisch W, Köhler D, *et al.* Non-Invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2:698–705.
- 28 Dreher M, Storre JH, Schmoor C, *et al.* High-Intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. *Thorax* 2010;65:303–8.
- 29 Dave C, Wharton S, Mukherjee R, *et al.* Development and relevance of hypercapnia in COPD. *Can Respir J* 2021;2021:6623093.
- 30 Li Zhancheng ZQ, Xiangjie Z, *et al.* The clinical value of family noninvasive positive pressure ventilation for severe COPD during the stable period. *Chinese Journal Of Modern Drug Application* 2009;3:51–3.
- 31 Struik FM, Sprooten RTM, Kerstjens HAM, *et al.* Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 2014;69:826–34.
- 32 Han L. Analysis of the efficacy of family noninvasive positive pressure ventilation together with tiotropium bromide and budesonide formoterol in patients with COPD. *Journal of Shandong Medical College* 2019;41:111–2.
- 33 Kamiński D, Sliwiński P, Bieleń P, *et al.* [Noninvasive positive pressure ventilation in COPD patients with hypercapnic respiratory failure]. *Pneumonol Alergol Pol* 1999;67:45–52.
- 34 Clini EM, Magni G, Crisafulli E, *et al.* Home non-invasive mechanical ventilation and long-term oxygen therapy in stable hypercapnic chronic obstructive pulmonary disease patients: comparison of costs. *Respiration* 2009;77:44–50.
- 35 NHS Improvement. National tariff payment system, 2019. Available: <https://improvement.nhs.uk/resources/national-tariff/#h2-201920-national-tariff-payment-system> [Accessed 28 Jun 2020].
- 36 Department of Health. *Nhs 2018–19 reference costs*. London: Department of Health, 2019.

**APPENDIX 1 MODEL POPULATION****Table A1****Model population**

<b>Population</b>	<b>Stable</b>	<b>Post-hospital</b>
Age (median)	67	73
Sex (% male)	53.9	46.9
Smoking status (% current smokers)	52.2	31.3
GOLD stage (% GOLD 3/ % GOLD 4)	50/50	50/50
Source	Studies included in systematic review [8]	2017 National UK COPD audit [9]

## APPENDIX 2 MODEL ASSUMPTIONS

### Model Assumptions

The starting cohort for the stable population was assumed to contain 50% with GOLD stage 3 and the remainder with GOLD stage 4 populations.

An estimate was applied for the utility loss from a cohort study of patients admitted to hospital followed up for 1 year.

The costs of usual care, NIV, and treating exacerbations were estimated with reference to best practice guidance and expert opinion.

No additional improvement in baseline utility was applied to either the stable or post-hospital population.

The effect of domiciliary NIV was assumed to last for up to 5 years and be driven primarily by a reduced risk of hospital admission and indirectly the associated reduction in mortality risk.

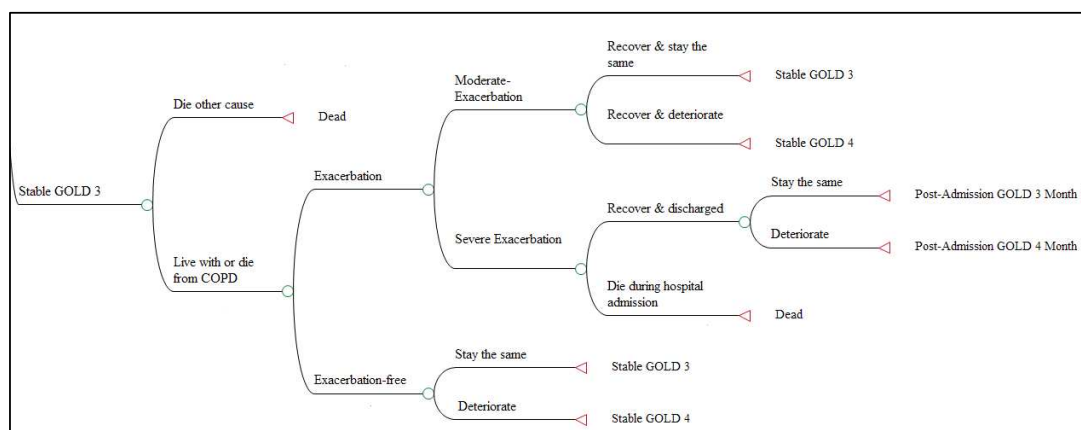
15% of patients were assumed to discontinue using domiciliary NIV after 3 months. These patients were assumed to incur costs but no benefits in the first 3 months and neither costs nor benefits beyond 3 months.

## APPENDIX 3 MODEL TRANSITIONS

Both populations face risks of both moderate and severe exacerbation, and their routes through the model are slightly different, with entirely unique probabilities of moving between health states.

### Stable health state transitions

As figure A1 shows in stable states patients can die from a disease-free mortality rate, live without an exacerbation, or experience an exacerbation.

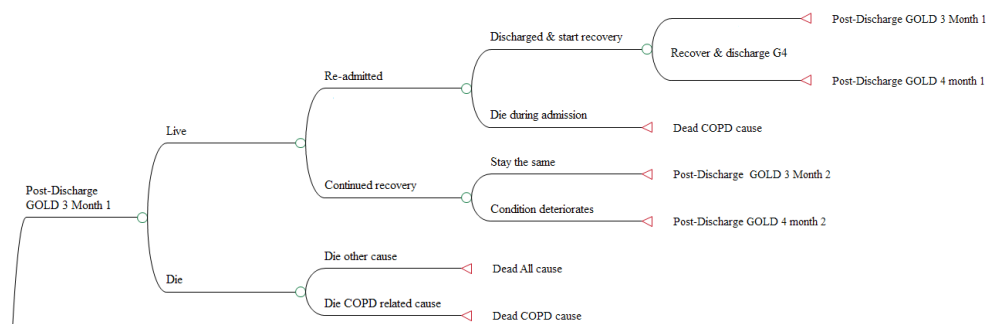


**Figure A1** Stable health state transitions

The exacerbation may either be moderate and managed at home, or severe as to require hospital admission, the latter may also lead to death during admission. If they survive hospital admission the patient is effectively discharged and moves to the first month post-discharge state. Those who live without exacerbation, or experience only a moderate exacerbation (re)enter the stable health state. Figure A1 shows a pathway for a stable patient in GOLD stage 3; GOLD stage 4 pathway is identical except patients cannot move to GOLD stage 3.

### Post-discharge health state transitions

An example of the post-discharge health state pathway in the first month post-discharge for GOLD stage 3 in the stable population is shown in Fig A2.



**Figure A2 Pathway within a post-discharge health state for the stable population**

From the post-discharge health state patients could either continue their recovery, die at home, or be readmitted where they could die during admission. If they survived hospital admission, they (re)entered one of the first month post-admission health states. If recovery continued without being readmitted, they moved to the second and then third post-admission health states where they faced similar pathways. The additional costs and utility losses associated with a non-severe exacerbation during the recovery period were considered negligible as patients were already assumed to have incurred higher costs and utility loss. The pathways within the post-discharge health states were almost identical for months 1- 3 but in month 3 patients could transition to a stable health state, although GOLD stage 3 patients were allowed to transition to a parallel GOLD stage 4 state. As noted above, the post-discharge health states were identical for both the stable and post-hospital populations.



**APPENDIX 4****COPD-ADJUSTED ALL-CAUSE MORTALITY RATES, BY AGE AND SEX**

Table A2 lists COPD adjusted all-cause mortality rates applied in the economic model. These were derived from ONS 2017-2019 all-cause and 2017 COPD-related mortality rates by sex and age for England.

**Table A2****COPD-adjusted all-cause mortality rates, by age and sex**

Age (years)	All-cause mortality		Deaths caused by COPD		COPD-adjusted mortality	
	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
60	0.760	0.504	3.049	3.823	0.736	0.486
61	0.831	0.549			0.806	0.528
61	0.922	0.626			0.894	0.603
63	1.018	0.671			0.987	0.646
64	1.095	0.726			1.061	0.699
65	1.203	0.799	6.502	7.478	1.124	0.739
66	1.333	0.857			1.246	0.793
67	1.444	0.938			1.350	0.868
68	1.574	1.033			1.472	0.956
69	1.729	1.130			1.617	1.045
70	1.829	1.244			1.710	1.151
71	2.028	1.334			1.896	1.234
72	2.233	1.524			2.087	1.410
73	2.550	1.735			2.384	1.605
74	2.812	1.917			2.629	1.773
75	3.140	2.144	6.642	6.410	2.932	2.006
76	3.512	2.422			3.278	2.266
77	3.884	2.731			3.626	2.556
78	4.352	3.096			4.063	2.898
79	4.810	3.448			4.490	3.227
80	5.398	3.846			5.040	3.600
81	6.001	4.363			5.608	4.084
82	6.651	4.896			6.209	4.582
83	7.540	5.627			7.039	5.266
84	8.476	6.394			7.913	5.983
85	9.466	7.246	5.031	3.056	8.990	7.025
86	10.683	8.309			10.148	8.056
87	11.859	9.346			11.262	9.061
88	13.336	10.643			12.665	10.318
89	14.985	11.894			14.231	11.531
90	15.953	13.439			15.150	13.028
91	17.906	15.076			17.005	14.615
92	19.695	16.708			18.704	16.197
93	21.504	18.434			20.423	17.871
94	23.809	20.447			22.611	19.822
95	26.101	22.821			24.788	22.124
96	28.671	25.077			27.229	24.310
97	30.411	26.706			28.881	25.890
98	32.589	29.126			30.950	28.236
99	36.954	30.953			35.095	30.007
100	38.439	34.336			36.505	33.287

**APPENDIX 5****DISEASE PROGRESSION RATES APPLIED IN THE ECONOMIC MODEL**

Table A4 lists the annual disease progression rates, obtained from a published COPD Markov model [16]

**Table A5****Annual disease progression risks by age and smoking status**

Age (years)	GOLD stage 3 to GOLD stage 4	
	Ex-smoker (%)	Smoker (%)
60	5.120	7.823
61	5.229	7.989
61	5.338	8.155
63	5.386	8.229
64	5.434	8.304
65	5.482	8.379
66	5.530	8.454
67	5.579	8.529
68	5.618	8.589
69	5.658	8.650
70	5.698	8.710
71	5.737	8.770
72	5.777	8.831
73	5.789	8.849
74	5.801	8.868
75	5.814	8.887
76	5.826	8.905
77	5.838	8.924
78	5.857	8.953
79	5.876	8.982
80	5.895	9.011
81	5.914	9.040
82	5.933	9.069
83	5.993	9.161
84	6.054	9.254
85	6.114	9.347
86	6.175	9.439
87	6.236	9.532
88	6.296	9.624
89	6.357	9.717
90	6.417	9.810
91	6.478	9.902
92	6.538	9.995
93	6.599	10.088
94	6.659	10.180
95	6.720	10.273
96	6.781	10.365
97	6.841	10.458
98	6.902	10.551
99	7.891	10.643
100	7.891	10.643

## APPENDIX 6 DISTRIBUTIONS FOR PROBABILISTIC ANALYSES

As the standard error for the rate ratio on the natural scale isn't normally distributed for probabilistic sensitivity analysis to sample the parameter from a Normal distribution samples of the rate ratio were drawn from Ln(Rate Ratio), and then exponentiated for each draw.

**Table A6**

### Distributions for hospital admissions rate ratios used in the probabilistic analysis

<b>Definition All studies</b>		
<b>Post-hospital population</b>	<b>Ln (Rate Ratio)</b>	<b>SE of Ln (Rate Ratio)</b>
Pooled mean	-0.706	0.131
Best case NIV	-1.099	0.296
Worst case NIV	0.502	0.126
<b>Stable population</b>		
Pooled mean	-0.501	0.116
Best case NIV	-1.061	0.115
Worst case NIV	0.154	0.338
<b>Definition "UK-like" settings*</b>		
<b>Post-hospital population</b>		
Pooled mean	-0.317	0.630
Best case NIV	-0.944	0.096
Worst case NIV	0.316	0.128
<b>Stable population</b>		
Pooled mean	-0.331	0.077
Best case NIV	-0.442	0.203
Worst case NIV	0.154	0.338
*UK like studies included studies from Italy, Poland, The Netherlands, Germany, and the UK		
Abbreviations: SE (Standard Error)		

## APPENDIX 7 COSTING METHODS

Cost calculations were broken down into routine health-care visits, routine pharmacotherapy, moderate and severe exacerbations, and the cost of domiciliary NIV.

### Routine health-care visits

Resource use for routine care were based upon assumptions made in the COPD diagnosis and management economic model report accompanying the National Institute for Health and Care Excellence (NICE) guidance (2018). It was assumed that GOLD stage 3 and 4 patients would attend, respectively, one and two assessments per year in secondary care. Unit costs reflect a mean of respiratory outpatient procedures. The NICE model (2018) also had an average of one and a half, and two, GP visits for stage 3 and 4 respectively, using unit costs for a standard 9.22-minute consultation. The NICE model (2018) also had four respiratory team visits for a Gold Stage 4 patient, and two for a Gold Stage 3 patient. Each visit was assumed to last 40 minutes and comprise 75% of a band 6 nurse and 25% of a band 7 nurse. Nurse time was costed using the per-hour patient facing time for each nurse, derived from the Unit Cost of Health and Social Care 2019[22]. Cost of spirometry were obtained from NHS reference costs 2010/2011 (DH, 2010) and inflated using the NHS cost inflation index [22]. Both the cost, and usage of home oxygen therapy were taken from Hertel et al. (2012), costs inflated using both the hospital and community health services index and the NHS cost inflation index [22]. As in the previous model [7] 75% of patients in each severity group were assumed to receive the flu vaccination, the cost of the which was assumed to be the average of the two flu jabs currently available for reimbursement for over 65-year olds (NHS England, 2019). Costs of routine care for GOLD stage 3 and 4 are shown in Table A7. The annual cost of routine healthcare was £478.95 in gold stage 3, and £927.99 in gold stage 4.

Smoking cessation and pulmonary rehabilitation are also recommended by NICE (2010) as usual care for COPD patients, however these costs are omitted from this model on the basis they are assumed to be the same in both strategies.

Table A7

## Annual cost of routine healthcare by GOLD stage

Cost of routine healthcare			Gold Stage 3		Gold Stage 4	
Resource use type	Unit cost	Source	No. of visits	Weighted total cost*	No. of visits	Weighted total cost*
GP visit, 9.22 min standard consultation	£33.19	PSSRU [22]	1.5	£49.79	2	£66.38
Outpatient visit, mean of respiratory medicine outpatient procedures (NCL)	£157	NHS Reference costs, 2018/9 [35]	1	£157	2	£314
Respiratory team visit, 40 min visit from 75% band 6 nurse, 25% band 7 nurse	£70	PSSRU [22]	2	£140	4	£280
Spirometry test	£52	NHS Reference costs (2011)+	2	£104	3	£156
Home oxygen therapy	£17.17 per day	Hertel et al. (2012)+	1.22 days	£20.95	6.08 days	£104.40
Influenza vaccine, 73% of patients receive	£9.87	NHS England (2019)	0.73	£7.21	0.73	£7.21
<b>Annual cost of routine healthcare</b>				<b>£478.95</b>		<b>£927.99</b>
<b>Monthly cost of routine healthcare</b>				<b>£39.91</b>		<b>£77.33</b>

+Cost inflated to current value using HCHS inflation indices until 2015, and NHSCII from 2016 onwards, PSSRU [22]

### **Routine pharmacotherapy**

Drug reference costs listed on the NHS Drug Tariff database in 2020 were used to estimate unit costs and are shown in Table A8. As there does not appear to be consistent drug inflation costs during the period (2018-2020) unit costs were not deflated. As the NICE economic model (2018) used to estimate routine healthcare compared the cost of different pharmacological strategies, no typical routine pharmacological treatment strategy is provided. Therefore, annual and monthly costs were calculated by applying the 2020 unit cost to ratios of pack cost to annual cost reported by NICE (2011). Where there was more than one drug in each treatment class, an overall average cost was applied.

In order to obtain usage for each GOLD stage, the proportion of patients on each line of therapy by GOLD stage was obtained from data from a cohort of UK COPD patients in the Birmingham Lung Improvement (BLISS) study in the West Midlands [17]. As all patients were reported to be on an inhaled short-acting  $\beta$ 2-agonist (SABA), the assumptions of clinical experts on the previous model [7] regarding the number of delivery devices in each severity stage were used. Monthly costs for each GOLD stage are reported in Table A9.

Note, we acknowledge there is now a move to triple therapy inhalers (LAMA/LABA/ICS in one – Trelegy or Trimbow). However, at the time of conduct of most included RCTs these were not available. We accept it would reduce the costs of therapy; however model results were not sensitive to cost input parameters.

Table A8

## Unit costs of pharmacotherapy

Class	Drug, Dose	Price per pack+	Annual cost adjusted*	Monthly cost (£)
SABA	Salbutamol 100 µg dose dry powder inhaler (Easyhaler Salbutamol)	£3.31	£24.17	£2.01
	Terbutaline 500 µg/ dose dry powder inhaler (Bricanyl)	£8.30	£121.17	£10.10
	SABA average cost			£6.06
ICS	Beclometasone 250 µg / dose inhaler CFC free Clenil Modulite	£16.29	£29.73	£2.48
SAMA	Ipratropium 20 µg/ dose inhaler CFC free	£5.56	£30.56	£2.55
LABA	Salmeterol 25 µg /dose inhaler CFC free	£29.26	£356	£29.67
LAMA	Tiotropium 18 µg inhalation powder capsules (Spiriva)	£33.50	£407.58	£33.97
LABA	Budesonide 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler (Symbicort)	£28.00	£340.66	£28.39
And	Budesonide 400micrograms/dose / Formoterol 12micrograms/dose dry powder inhaler (Symbicort Turbohaler)	£28.00	£340.66	£28.39
ICS	Fluticasone propionate 500micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler (Seretide Accuhaler)	£32.74	£398.34	£33.19
	LABA and ICS average cost			£29.99
ICS, inhaled corticosteroids; LABA, long-acting β <sub>2</sub> -agonist; LAMA, long-acting muscarinic agonist; SAMA, short-acting muscarinic antagonist.				
*Annual costs weighted using the ratio of pack price to annual cost reported in NICE (2011).				
+NHS Drug Tariff database, 2020				

Table A9

**Pharmacotherapy by type, and monthly cost, by GOLD stage**

Gold Stage and cost	Assumed SABA's per month	Proportion on type of pharmacotherapy					
		SABA	ICS	LABA	LABA/ICS	LAMA	SAMA
Gold Stage 3	2	1.00	0.01	0.05	0.68	0.62	0.04
Gold Stage 4	2.5	1.00	0.05	0.02	0.77	0.65	0.05
Monthly cost GOLD stage 3		£50.42					
Monthly cost GOLD stage 4		£54.71					

**Cost of moderate exacerbation**

Resource use for moderate exacerbations were based upon assumptions made in the COPD diagnosis and management economic model report accompanying the National Institute for Health and Care Excellent guidance (2018). As such, moderate exacerbations were expected to be usually managed in primary care through GP appointment, with a small proportion expected to visit A&E without admission or receive a number of visits from a respiratory team. A respiratory team was expected to comprise 75% of a band 6 nurse, and 25% a band 7 nurse. Note that cost of nurse time relative to the previous model is higher, as it is now adjusted to reflect patient facing cost [22]. Prescribed additional medication for a moderate exacerbation was assumed to be a course of prednisolone and antibiotics. Overall cost of a moderate exacerbation is shown in Table A10.



Table A10

**Cost of a typical moderate exacerbation**

<b>Resource use type</b>	<b>% requiring resource</b>	<b>Unit cost</b>	<b>Source</b>	<b>Weighted total cost*</b>
GP visit, 9.22 min standard consultation	60%	£33.19	PSSRU [22]	£19.91
A&E visit without admission, weighted average of non-admitted	30%	£144.38	NHS reference costs (2019) [35]	£43.31
Respiratory team visit -cost per episode (6* 40 min visits *(75% band 6 nurse, 25% band 7).	10%	£420	PSSRU [22]	£42
Prednisolone 5mg tablets (six times a day for 5 days)	100% cohort, 1 per patient	£1.77	NHS Drug Tariff (2019)	£1.77
Amoxicillin 500mg capsules (3 times a day for 5 days)	100% of cohort, 2 per patient	£1.25	NHS Drug Tariff (2019)	£2.50
Prescription costs per consultation		£30.90	PSSRU [22]	£30.90
<b>Estimated cost of moderate exacerbation</b>				<b>£140.40</b>
*Weighted total cost, is the unit cost multiplied by % requiring the resource				

**Cost of severe exacerbation**

As per the COPD diagnosis and management economic model report accompanying the National Institute for Health and Care Excellent guidance (2018) severe exacerbations were assumed to be managed in hospital with 70% requiring an ambulance journey to hospital. The cost of an ambulance journey was most recently available in 2015/6 reference costs and inflated using the NHS cost inflation index [22]. For the

hospital stay, the weighted mean was taken of all unit costs for non-elective long-stay for COPD. Previous version of NICE modelling (2010) also suggested that all patients should be followed up after discharge, this is included here, as in the previous model, and was assumed to be 30% by a band 5 community nurse, 30% by a GP, and 40% attending a respiratory outpatient appointment. The estimated cost of a severe exacerbation is shown in Table A11.

Table A11

**Cost of a typical severe exacerbation**

<b>Resource use type</b>	<b>% requiring resource</b>	<b>Unit cost</b>	<b>Source</b>	<b>Weighted total cost*</b>
Ambulance journey to A&E	70%	£251.92	NHS Reference costs (2015/6)+	£176.34
Hospital stay, mean NEL long-stay, COPD.	100%	£2,026	NHS Reference costs (2018/9) [35]	£2,026
Prednisolone 5mg tablets (six times a day for 5 days)	100% cohort, 1 per patient	£1.77	NHS Drug Tariff (2019)	£1.77
Amoxicillin 500mg capsules (3 times a day for 5 days)	100% of cohort, 2 per patient	£1.25	NHS Drug Tariff (2019)	£2.50
GP visit, 9.22 mins standard consultation	30%	£33.19	PSSRU (2018/9) [22]	£9.96
Outpatient appointment, follow up, mean of respiratory outpatient procedures	40%	£157.16	NHS Reference costs (2018/9) [35]	£62.86
Community nurse follow, 12 mins appointment, band 5	30%	£12.50	PSSRU (2018/9) [22]	£3.75
<b>Estimated cost of severe exacerbation</b>				<b>£2283.18</b>

\*Weighted total cost, is the unit cost multiplied by % requiring the resource

+ Inflated using Health Service (HS) Index [22]

**Cost of non-invasive ventilation**

Table A11 shows the costs of providing the typical domiciliary NIV service. Both post-hospital and stable populations faced the same cost of providing NIV for an individual. In the base case, pricing information from suppliers of domestic NIV equipment was used to estimate the one-off equipment cost. Assumptions regarding machine type, and extent of the usage was identified by experts on the team. Four machines were identified as likely to be typical of the equipment to provide this service, Phillips Trilogy 100 and Dreamstation AVAPs, and ResMed Lumis 150 ST-A (iVAPS AE) and ResMed Stellar 100 (iVAPS AE). Each machine was assumed to be supplied 30% with humidification and 70% without, and all bundled with necessary modem and cloud-based remote monitoring facility. The Resmed Lumis 150 was assumed to represent 60% of the likely machine mix, 20% the Dreamstation AVAPs, and 10% each the Trilogy 100 and Stellar 100. It was assumed that each machine last five years and serves two patients on average during that time, the equipment cost is £2939.69 per patient. The cost of the machine was assigned monthly in the model and depreciated over 5 years at 3.5%. One-way sensitivity analysis was used to explore alternate costing assumptions supplied by the clinical expert, of machine cost £39.24 per month.

Table A11

**Cost of providing the domiciliary NIV service**

<b>Equipment</b>	<b>Cost</b>	<b>Unit Cost source</b>	<b>Resource use Source</b>
<b>Equipment costs</b>			
NIV equipment for domiciliary use	£2939.69	Supplier estimates	Clinician estimates of use of machines and cost estimate from firms
NIV equipment for domiciliary use monthly cost	£48.99		Depreciated over 5 years
<b>Set-up costs</b>			
NIV set-up and assessment month 1	£482.82	National Tariff Payment System 2019/20	Expert opinion
NIV Follow-up in m3: 1 x Consultant led outpatient app + 1 x Blood gas test	£157.16 + £194	NHS reference costs 2018/9	Expert opinion
<b>Annual costs therefore</b>			
2 x blood gas test conducted at routine follow up	2 * £194	NHS reference costs 2018/9	Expert opinion
1 x annual NIV assessment and consumable provision	£650	Estimate	Expert opinion
<b>Monthly costs</b>			
First 3 months	£294.32	Includes equipment and set-up costs	
>3 months	£90.58	Includes equipment and annual monitor and service costs	

Initial set up of the machine, respiratory testing of the patient, and starting on domiciliary NIV was assumed to take place in an NIV clinic and last four hours, and be led by a respiratory team covered by the tariff DZ37A: NIV Supporter Assessment, 19yrs and over, in the National Tariff Payment System workbook 2019/2020 (NHS Improvement, 2019). Between 8 and 12 months, patients on domiciliary NIV

were assumed to have attended a follow-up clinic, where blood gases were checked and NIV pressure settings and/or masks adjusted as required. This service was assumed to be covered by the NHS reference cost for a consultant-led outpatient appointment [35] and National Tariff Payment System [34] tariff for conducting blood gas tests. The set-up and follow-up costs were applied as monthly costs spread evenly over the first 3 months of starting NIV.

From 3 months onwards follow up care included a 6-monthly check of a patient's NIV usage and blood gases, as well annual NIV equipment check and consumable replacement. As all patients are assumed to attend two annual respiratory appointments, the only additional cost was for conducting a blood gas check. Whilst, expert opinion and consultation with suppliers, concluded that costs associated with an annual NIV equipment check, which would be assumed to include device verification, consumable replacement and technical support, were estimated to be £650.

The estimated costs of providing a domiciliary NIV service were £1698.18 in the first year and £1086 in subsequent years. The estimate lies in between estimates of Tuggey et al. (2003) who estimate domiciliary NIV cost £1060 per year in 2003 prices and Clini et al. (2009) who estimated €1920 in 2008 prices.

#### Additional References

Department of Health (2011). NHS 2010–11 Reference Costs. London: DH; 2011.

Department of Health and Social Care (2020). Electronic Drug Tariff. London: Department of Health; 2020 [online] available at <http://www.drugtariff.nhsbsa.nhs.uk/#/00787224-DD/DD00787219/Home>

Hertel N, Kotchie RW, Samyshkin Y, et al. Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis. *Int J Chron Obstruct Pulmon Dis* 2012;7:183–99. <http://dx.doi.org/10.2147/COPD.S29820>

NHS England (2019) Update on vaccines for 2019/20 seasonal flu vaccination programme , available online at <https://www.england.nhs.uk/wp-content/uploads/2019/01/vaccines-for-19-20-seasonal-flu-vaccination-programme.pdf> Accessed 29/06/20

NICE. Chronic Obstructive Pulmonary Disease: Costing report – Implementing NICE Guidance. NICE Clinical Guideline 101. NICE; 2011.

National Institute for Health and Care Excellence. (2018). *Chronic obstructive pulmonary disease in over 16s: diagnosis and management*. Nice guideline [NG115]. Retrieved from <https://www.nice.org.uk/guidance/ng115>

Tuggey JM, Plant PK, Elliott MW. Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: an economic analysis. *Thorax* 2003;58:867–71. <http://dx.doi.org/10.1136/thorax.58.10.867>

## APPENDIX 8 EXPECTED VALUE OF PERFECT INFORMATION

Value of information (VoI) analysis is essentially a quantitative method of assessing the marginal cost and value of further studies, and further translate it into information about the optimal design of additional research [25].

The EVPI uses the quantification of uncertainty from the PSA output, and calculates the net value of eliminating all uncertainty, such that the best treatment option could be selected in each model iteration.

In this case, two expected value of perfect information (EVPI) analyses were conducted for both stable and post-hospital COPD populations in the UK. In this study, per person EVPI was estimated using the TreeAge software. Information about the chosen willingness to pay threshold, and units of cost and effect measures, and population expected to benefit were used to obtain the population level EVPI.

### Population expected to benefit

In order to calculate the population expected to benefit, the original model used a population prevalence. Table A12 reports the sources used to update estimates of the stable and post-hospital populations. The UK COPD population was estimated using the 2.57% prevalence reported in Rayner et al. (2017). As reported in Haughney et al. (2013) the stable COPD population in either GOLD stage 3 or 4 was assumed to be 30.6% of the total COPD population. The authors did not report the proportion of patients in the 2007 GOLD stage admitted to hospital, but they did report on patients in each of the 2011 GOLD classifications (A-D) admitted to hospital at least once which was used to estimate the post-hospital population. However, because the decision relevance is thought to be ten-years, it is more appropriate to include new cases over that period also. NICE (2018) report that there are 80,443 incidence cases of COPD per year, unfortunately this incidence is not available by GOLD stage. Subsequently, estimates on the proportion of cases in GOLD stage from Haughney et al. were used to estimate the number of incidence cases in GOLD stage 3 and 4, as well as new post-hospitalisations. Accordingly, it was assumed that of the 80,443 incidence cases, 30.6% were stage 3 or 4, and 8.8% were post-hospitalisations.

For the population EVPI and EVPPI estimates, the SAVI software does not incorporate a discount rate, and therefore the estimated number of patients over 10-years was discounted at 3.5%. In order to perform this calculation, the number of incidence cases per year (24,615 and 7079) were summed over nine years and multiplied by a discount factor using the formula,  $\sum_{t=1}^T \frac{I_t}{(1+r)^t}$ . Having estimated the discounted

incidence cases, these were then added to the discounted initial populations to produce a discounted 10-year population of 661,199 for stable end stage COPD, and 190,049 for post-hospital end-stage COPD.

**Table A12**

**Population estimated applied in the Expected Value of Perfect Information (EVPI) analysis**

<b>Definition of Population</b>	<b>Prevalence</b>	<b>Population Estimate</b>	<b>Source of estimate</b>
UK		66,436,000	ONS mid-2018 projection
Diagnosed with COPD	2.57% of population	1,707,000	Rayner et al. 2017
COPD Annual Incidence cases	0.19% of adult population	80,443	NICE (2018)
Stable end-stage COPD (GOLD 3&4)	30.6% of COPD population	522,000	Haughney et al. 2013
Stable End-stage COPD annual incidence cases		24,615	
Ten-year discounted COPD population		661,199	
Post-hospital end-stage COPD	8.8% of COPD population	150,000	Haughney et al. 2013
Post-hospital end-stage COPD incidence cases		7,079	
Ten-year post-hospital end-stage COPD population		190,049	

**Additional References**

Haughney J, Gruffydd-Jones K, Roberts J, Lee AJ, Hardwell A, McGarvey L. The distribution of COPD in UK general practice using the new GOLD classification. *Eur Respir J* 2014;43:993–1002.

<http://dx.doi.org/10.1183/09031936.00065013>

L. Rayner, J. Sherlock, B. Creagh-Brown, J. et al. (2017) The prevalence of COPD in England: An ontological approach to case detection in primary care, *Respiratory Medicine*, 132 (217-225)

<https://doi.org/10.1016/j.rmed.2017.10.024>



## APPENDIX 9 SENSITIVITY ANALYSES: ALTERNATIVE MACHINE COST, LIFESPAN, AND ANNUAL MAINTENANCE COST OF NON-INVASIVE VENTILATION

### Post Hospital Population

#### *Varying NIV device cost*

In the base case it was assumed the machine would cost £2939. Table A13 shows the impact of differing assumptions. The ICER rises to £14,764/QALY gained even when the device is assumed to cost £5000, but the cost-effectiveness likelihood is still 94%.

**Table A13**

#### One-way sensitivity analysis in the post-hospital population varying NIV device cost

NIV device cost	Cost-difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective+
2000	£4,124	0.424	£9726	100%
2939 (base case)	£4,799	0.424	£11,318	99.9%
4000	£5185	0.424	£12,229	98%
5000	£6,260	0.424	£14,764	94.4%
+ Cost-effective at £20,000/QALY				
Abbreviations; ICER Incremental cost-effectiveness ratio; NIV Non-invasive ventilation; QALY (Quality-adjusted life-year)				

#### *Alternative machine lifespan*

In the base case it was assumed the machine would be used continuously for 5 years, Table A14 shows the impact of differing assumptions. The ICER rises to £14,551/QALY gained even when the device is assumed to last only 3 years, but the cost-effectiveness likelihood is still 95%.

Table A14

**One-way sensitivity analysis in the post-hospital population varying NIV device lifespan**

NIV device lifespan	Cost-difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective+
3 years	£6,170	0.424	£14,551	94.7%
4 years	£5325	0.424	£12559	98.5%
5 years (base case)	£4,799	0.424	£11,318	99.9%

+ Cost-effective at £20,000/QALY

Abbreviations; ICER Incremental cost-effectiveness ratio; NIV Non-invasive ventilation; QALY (Quality-adjusted life-year)

*Alternative costs of healthcare provision*

Varying the cost of NIV set-up and hospital admission for severe exacerbation had little impact upon cost-effectiveness and results are not reported here. The ICER was however more sensitive to changes in the cost of annual NIV service, rising to £14,007/QALY gained where the annual service cost was £1000, however the likely cost-effectiveness was relatively unaffected falling to only 96%, shown in Table A15

Table A15

**One-way sensitivity analysis in the post-hospital population varying cost of annual NIV maintenance**

NIV annual service cost	Cost-difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective+
550	£4,453	0.424	£10,502	100%
650 (base case)	£4,799	0.424	£11,318	99.9%
750	£5127	0.424	£12,091	98.9%
850	£5466	0.424	£12,891	98.2%
1000	£5939	0.424	£14,007	96.3%

+ Cost-effective at £20,000/QALY

Abbreviations; ICER Incremental cost-effectiveness ratio; NIV Non-invasive ventilation; QALY (Quality-adjusted life-year)

## Stable Population

### *Varying NIV device cost*

In the base case it was assumed the machine would cost £2939. Table A16 shows the impact of differing assumptions. The ICER falls to £23,738/QALY gained when the device is assumed to cost £2000, but the cost-effectiveness likelihood is still only 17%.

**Table A16**

### One-way sensitivity analysis in the stable population varying NIV device cost

NIV device cost	Cost-difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective+
2000	£7,359	0.310	£23,738	17.3%
2939 (base case)	£8,488	0.310	£27,380	4%
4000	£9,730	0.310	£31,387	0%

+ Cost-effective at £20,000/QALY

Abbreviations; ICER Incremental cost-effectiveness ratio; NIV Non-invasive ventilation; QALY (Quality-adjusted life-year)

### *Alternative machine lifespan*

In the base case it was assumed the machine would be used continuously for 5 years, Table A17 shows the impact of differing assumptions. The ICER rises to £30,161/QALY gained even when the device is assumed to last only 4 years, 0% likely to be cost-effective.

Table A17

**One-way sensitivity analysis in the stable population varying NIV device lifespan**

NIV device lifespan	Cost-difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective+
4 years	£9,350	0.310	£30,161	0%
5 years (base case)	£8,488	0.310	£27,380	4%
+ Cost-effective at £20,000/QALY				
Abbreviations; ICER Incremental cost-effectiveness ratio; NIV Non-invasive ventilation; QALY (Quality-adjusted life-year)				

*Alternative costs of healthcare provision*

Varying the cost of NIV set-up and hospital admission for severe exacerbation had little impact upon cost-effectiveness and results are not reported here. The ICER was however more sensitive to changes in the cost of annual NIV service, falling to £25,577/QALY gained where the annual service cost was £550, however the likely cost-effectiveness was relatively unaffected rising to only 8%, shown in Table A18

Table A18

**One-way sensitivity analysis in the stable population varying cost of annual NIV maintenance**

NIV annual service cost	Cost-difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective+
550	£7,929	0.310	£25,577	8%
650 (base case)	£8,488	0.310	£27,380	4%
750	£9,065	0.310	£29,241	1%
+ Cost-effective at £20,000/QALY				
Abbreviations; ICER Incremental cost-effectiveness ratio; NIV Non-invasive ventilation; QALY (Quality-adjusted life-year)				

**APPENDIX 10 SUBGROUP ANALYSES**

**Table A19** Disease severity, sex and age sub-groups post-hospital population

Subgroup	Cost-difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective+
Base case	+£4,799	0.424	£11,318	99.9%
All GOLD stage 3	+£4,719	0.433	£10,898	100%
All GOLD stage 4	+£4,857	0.416	£11,678	99%
All male	+£4,749	0.430	£11,044	99.5%
All female	+£4,827	0.417	£11,575	99.3%
55 start age	+£4,788	0.426	£11,239	99.5%
65 start age	+£4,784	0.426	£11,230	99.5%

+ Cost-effective at £20,000/QALY

Abbreviations; ICER Incremental cost-effectiveness ratio; NIV Non-invasive ventilation; QALY (Quality-adjusted life-year)

**Table A20** Disease severity, sex and age sub-groups stable population

Subgroup	Cost-difference (£)	QALY difference	ICER (£/QALY)	Probability cost-effective+
Base case	+£8,488	+0.310	£27,380	4%
All GOLD stage 3	+£9,311	+0.257	£36,230	0%
All GOLD stage 4	+£7,671	+0.363	£21,132	43%
All male	+£8,337	+0.305	£27,334	4%
All female	+£8,661	+0.312	£27,750	3%
55 start age	+£9,359	+0.328	£28,533	4%
75 start age	+£7,658	+0.269	£28,468	3%

+ Cost-effective at £20,000/QALY

Abbreviations; ICER Incremental cost-effectiveness ratio; NIV Non-invasive ventilation; QALY (Quality-adjusted life-year)