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

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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.

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.

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.[1] 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 designs have consistently shown better outcomes for NIV in the form of reduced inpatient mortality and length of stay.[2–6]

NIV may also be administered at home with or without oxygen therapy. Based on randomised controlled trials (RCTs), a previous systematic review[7] 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.[7] 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

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.[1] This paper reports an analysis of the cost-effectiveness of domiciliary NIV for end-stage COPD updating our previously published model[7] with estimates of clinical effectiveness including recent and previously missed evidence.[8] Other model parameters are updated using real-life COPD data from the UK, including the National COPD audit[9] and Clinical Practice Research datalink,[10] 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).[7]
- 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[11] 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.[8] 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_1) ≥30%, <50% and GOLD stage 4 a predicted FEV_1 ≤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,[9] 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*,[7] 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.

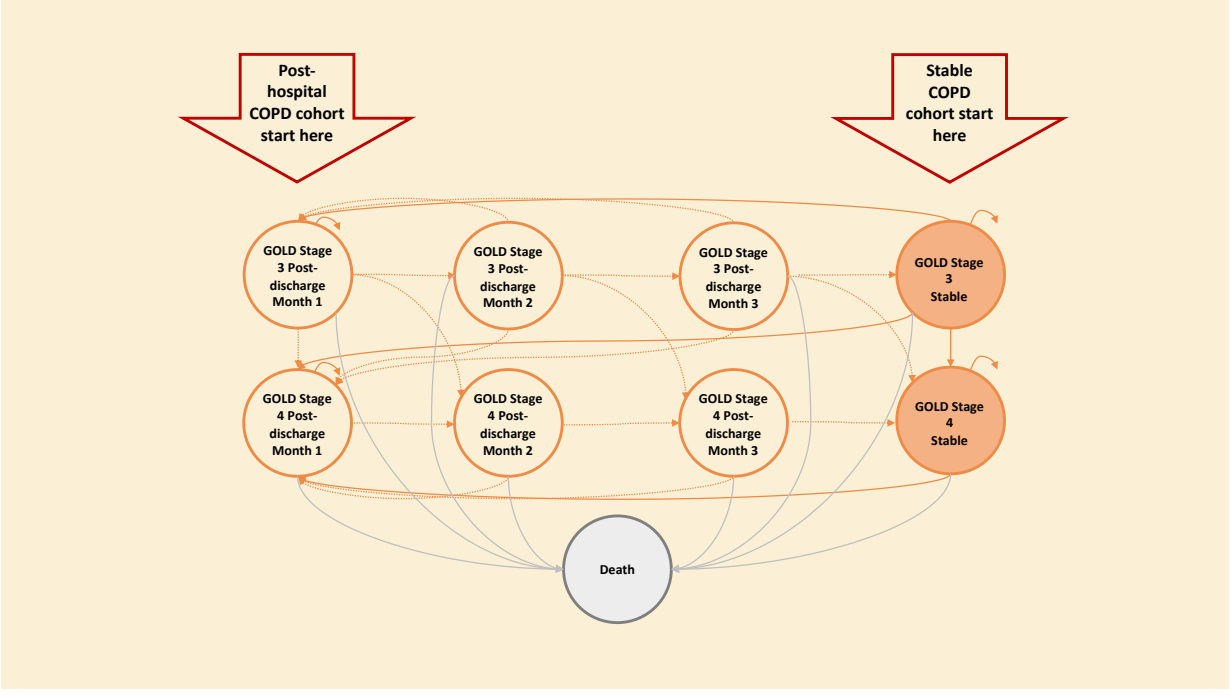

Figure 1 State-transition schematic. GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 1 Hospitalisation, mortality and discontinuation parameters

Mortality and hospitalisation in postadmission states			
Definition	**Probability**	**Beta distribution, α, β**	**Source**
COPD-related death during admission			2017 National UK COPD audit[9]
Men	0.046	654, 13 552	
Women	0.035	570, 15 514	
COPD-related 90-day death post admission			2017 National UK COPD audit[9]
Men	0.073	1043, 13 163	
Women	0.066	1058, 15 027	
90-day COPD-related readmission			2017 National UK COPD audit[9]
Men	0.171	2423, 11 784	
Women	0.162	2609, 13 476	
All-cause COPD mortality post admission			2017 National UK COPD audit[9]
90-day men	0.046	650, 13 556	
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			Garcia-Aymerich *et al*[12]
COPD admissions per year	1.6	340	
Non-COPD-related mortality	0.071	340	
Lowest rates			Bucknall *et al*[14]
COPD admissions per year	0.47	464	
Non-COPD-related mortality	0.194	464	
Highest rates			Budweiser *et al*[13] and Heinemann *et al*[15]
Base case risks multiplied by 2			

Treatment and exacerbation rates for stable population				
		Proportion of exacerbations hospitalised		Source
Severity stage	**Annual exacerbation rate**	**%**	**Beta distribution, α, β**	
GOLD 3	2.356	10.2	2267, 22 062	Rothnie *et al*[10]
GOLD 4	2.914	13.4	862, 6429	Rothnie *et al*[10]

Base case rate ratios for admission to domiciliary NIV relative to usual care		
	Rate Ratio (95% CI)*	**Source**
All studies estimates		
Posthospital population		
Pooled mean	0.494 (0.382 to 0.638)	Pooled result of 11 RCTs[8]
Best-case NIV	0.333 (0.187 to 0.596)	Li *et al*[30]
Worst-case NIV	1.372 (1.067 to 1.763)	Struik *et al*[31]
Stable population		
Pooled mean	0.606 (0.482 to 0.760)	Pooled result of 10 RCTs[8]
Best-case NIV	0.346 (0.276 to 0.433)	Luyang *et al*[32]
Worst-case NIV	1.166 (0.601 to 2.264)	Kamiński *et al*[33]
Western setting estimates†		
Posthospital population		
Pooled mean	0.728 (0.212 to 2.504)	Pooled result of 2 RCTs[8]
Best-case NIV	0.389 (0.321 to 0.470)	Murphy *et al*[1]
Worst-case NIV	1.372 (1.067 to 1.763)	Struik *et al*[31]
Stable population		
Pooled mean	0.718 (0.617 to 0.836)	Pooled result of 4 RCTs[8]
Best-case NIV	0.643 (0.432 to 0.956)	Clini *et al*[34]
Worst-case NIV	1.166 (0.601 to 2.264)	Kaminski *et al*[33]

Continued

Table 1 Continued

Discontinuation			
Health state	**Discontinuation Rate**	**Normal distribution, 95% CI**	**Source**
All patients	15%	10% to 20%	Assumption and Dretzke *et al*[8]

*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 Iniative 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.[9] 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.[7]

Hospitalisation and mortality risks for the posthospital population

Beyond the postdischarge period for the posthospitalised population, there was greater uncertainty regarding admission rates and mortality. Four studies[12–15] 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.[9] These risks in combination with the all-cause mortality risk reported in Garcia-Aymerich *et al*[12] 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=12 830) with long-term follow-up of a COPD general practice population.[9]

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,[8] 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 posthospital 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[16] 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[8] 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.[8]

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,[17] 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,[18–20] disutility values associated with moderate or severe exacerbation were taken from Rutten-van Mölken *et al*.[21] 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.[22] 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)
Type of healthcare	**Cost GOLD stage 3**	**Cost GOLD stage 4**
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	

Estimation of the cost of providing a domiciliary NIV service			
Cost type	**Cost**	**Unit cost source**	**Resource use source**
Equipment costs			
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	
Set-up costs			
NIV set-up and assessment month 1	£482.82	National Tariff Payment System 2019/20[35]	Expert opinion
NIV Follow-up in m3: 1 × Consultant led outpatient app+1 × Blood gas test	£157.16 + £194	NHS reference costs 2018/2019[36]	Expert opinion
Annual costs therefore			
2 × blood gas test conducted at routine follow-up	2 × £194	NHS reference costs 2018/2019[36]	Expert opinion
1 x annual NIV assessment and consumable provision	£650	Estimate	Expert opinion
Monthly costs			
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 Iniative 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.[23] 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.[24] 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.[24] 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.[25] 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

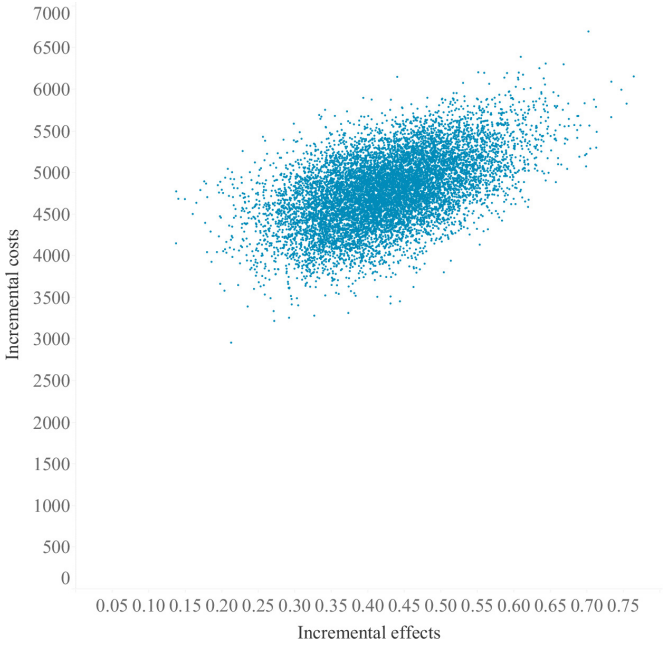

Figure 2 Base case cost-effectiveness plane for domiciliary NIV for posthospitalised patients. Incremental costs and effectiveness reflect the sum of mean costs and quality-adjusted life years (QALYs) of domiciliary non-invasive ventilation (NIV) minus those of usual care. Results are generated from 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.

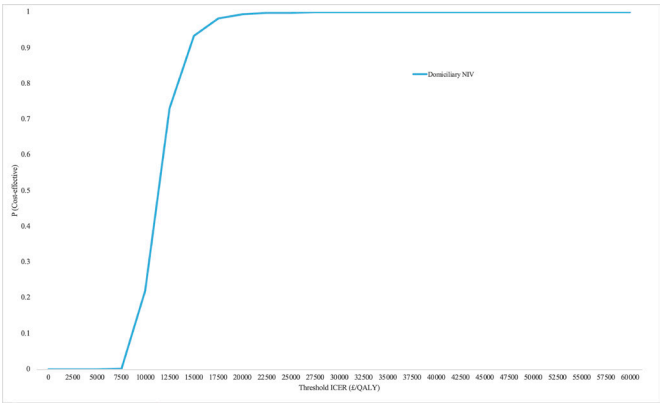

Figure 3 Base case cost-effectiveness acceptability curve. The graph plots the probability that domiciliary NIV is cost-effective at various UK thresholds for willingness to pay for 1 QALY (£/QALY). Between the commonly used UK thresholds of £20 000 to £30 000 per QALY, it can be seen NIV is consistently 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[14] 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.[26] 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).[8]

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*
Varying the rate ratio				
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%
Change in utility on NIV				
+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%
Varying duration of effect				
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%
Alternate model time horizon				
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%
Alternate Mortality and readmission risk				
Lower risks from Bucknall *et al*[14]	+£3715	+0.173	£21 473	39.34%
Doubling all mortality risks[13 15]	+£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[12] 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).

Table 5 Base case analyses stable population

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

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.

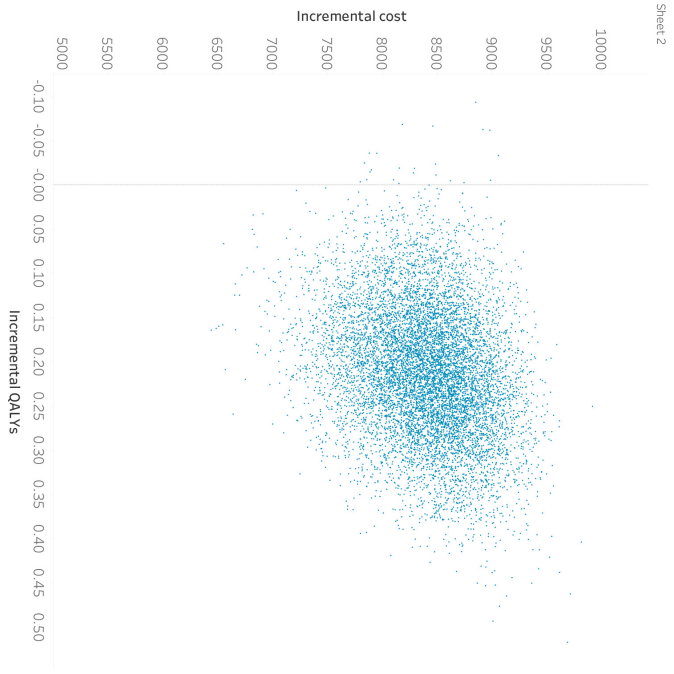

Figure 4 Base case cost-effectiveness plane for domiciliary NIV for stable patients. Incremental costs and effectiveness reflect mean the sum of mean costs and quality-adjusted life years (QALYs) of domiciliary non-invasive ventilation (NIV) minus those of usual care. Results are generated from probabilistic 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.

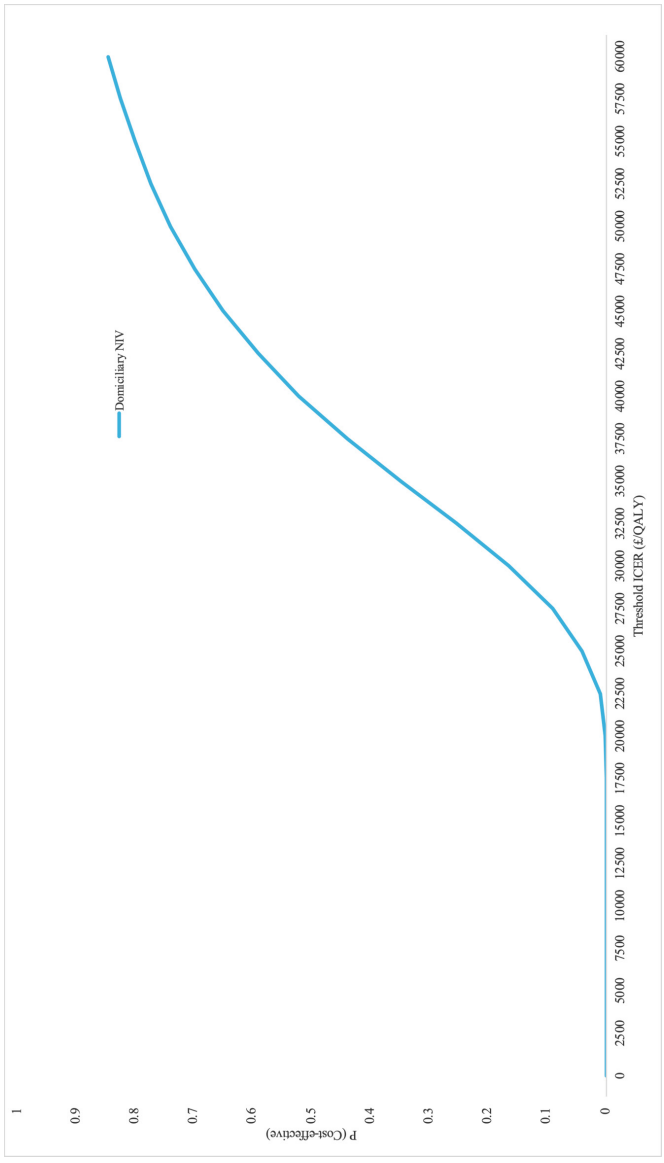

Figure 5 Base case cost-effectiveness acceptability curve. The graph plots the probability that domiciliary NIV is cost-effective at various UK thresholds for willingness to pay for 1 QALY (£/QALY). Above thresholds of £40 000 per QALY, it can be seen NIV emerges as likely to be cost-effective. ICER,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

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 post-hospitalised 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.[8] 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 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_2 level[27] 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*
Varying the rate ratio				
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%
Change in utility on NIV				
+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%
Varying duration of effect				
2 years	+£8488	+0.150	£56 153	0%
10 years (model horizon)	+£7896	+0.413	£19 119	58%
Alternate model time horizon				
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%
Alternate mortality and readmission risk				
Higher risks from Garcia-Aymerich *et al*[12]	+£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 heterogenous 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, pCO_2>7.5 kPa), and studies using higher pressure settings[28] 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.[29] 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.

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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.

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APPENDIX 1 MODEL POPULATION

Table A1

Model population

Population	Stable	Post-hospital
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.

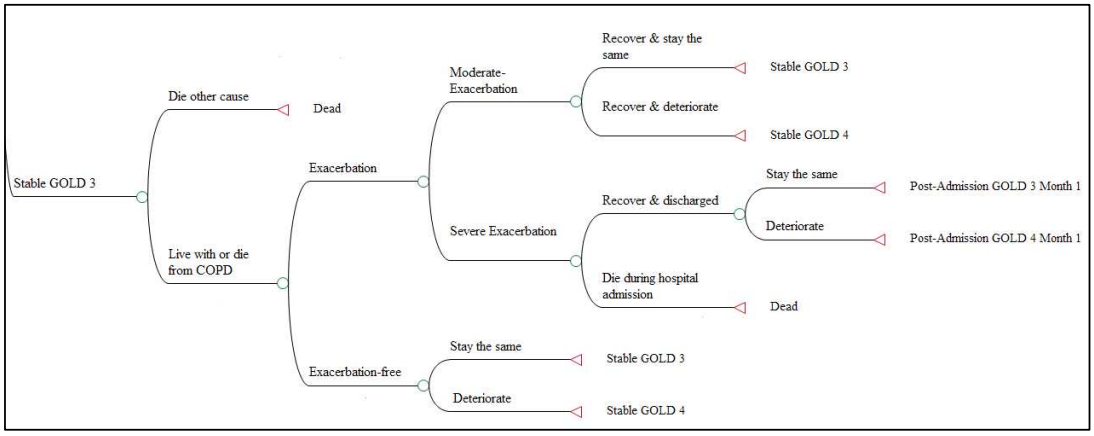

Figure A1 Stable health state transitions

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.

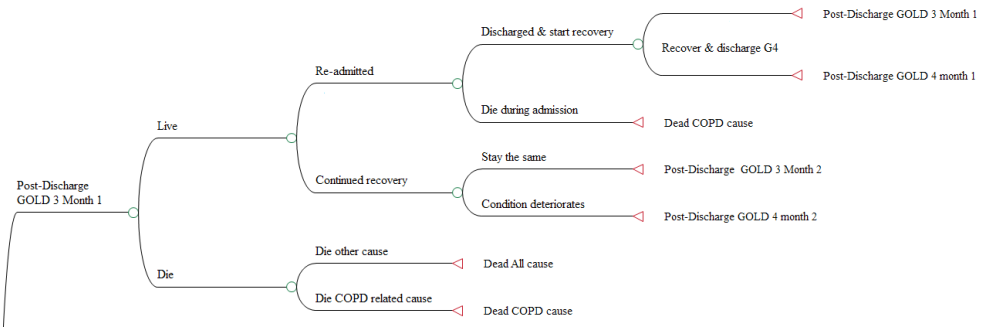

Figure A2 Pathway within a post-discharge health state for the stable population

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

	All-cause mortality		Deaths caused by COPD		COPD-adjusted mortality	
Age (years)	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			17.229	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

	GOLD stage 3 to GOLD stage 4	
Age (years)	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 form Ln(Rate Ratio), and then exponentiated for each draw.

Table A6

Distributions for hospital admissions rate ratios used in the probabilistic analysis

Definition All studies		
Post-hospital population	**Ln (Rate Ratio)**	**SE of Ln (Rate Ratio)**
Pooled mean	-0.706	0.131
Best case NIV	-1.099	0.296
Worst case NIV	0.502	0.126
Stable population		
Pooled mean	-0.501	0.116
Best case NIV	-1.061	0.115
Worst case NIV	0.154	0.338
Definition "UK-like" settings*		
Post-hospital population		
Pooled mean	-0.317	0.630
Best case NIV	-0.944	0.096
Worst case NIV	0.316	0.128
Stable population		
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
Annual cost of routine healthcare			£478.95		£927.99	
Monthly cost of routine healthcare			£39.91		£77.33	

+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 β_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 β2-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

		Proportion on type of pharmacotherapy					
Gold Stage and cost	**Assumed SABA's per month**	**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

Resource use type	% requiring resource	Unit cost	Source	Weighted total cost*
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
Estimated cost of moderate exacerbation				**£140.40**

*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

Resource use type	% requiring resource	Unit cost	Source	Weighted total cost*
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
Estimated cost of severe exacerbation				**£2283.18**

*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

Equipment	Cost	Unit Cost source	Resource use Source
Equipment costs			
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
Set-up costs			
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
Annual costs therefore			
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
Monthly costs			
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 Refernces

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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

Definition of Population	**Prevalence**	**Population Estimate**	**Source of estimate**
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

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APPENDIX 9 SENSITIVTY 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 costs £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)