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Cost-effectiveness of home non-invasive ventilation in patients with persistent hypercapnia after an acute exacerbation of COPD in the UK

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ABSTRACT

Home non-invasive mechanical ventilation (HMV) with home oxygen therapy (HOT) in patients with persistent hypercapnia following an acute exacerbation of chronic obstructive pulmonary disease delays hospital readmission. The economic impact of this treatment is unknown. We evaluated the cost-effectiveness of HMV in the UK healthcare system using data from a previously published efficacy trial. Quality-adjusted life-years (QALYs) were computed from EQ-5D-5L. Accounting for all direct patient costs HOT-HMV was £512 (95%CI £36 to £990) more expensive per patient per year than HOT-alone. This small increase in cost was accompanied by increased quality of life leading to an incremental cost-effectiveness ratio of £10 259 per QALY. HOT-HMV was cost-effective in this clinical population. Trial registration number: NCT00990132.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) remains a common cause of hospital admission, with patients with persistent hypercapnic respiratory failure having worse outcomes.¹ A few studies have evaluated the cost of home non-invasive mechanical ventilation (HMV) with home oxygen therapy (HOT) for patients with COPD with persistent hypercapnia following hospitalisation.² HOT-HMV has been shown clinically efficacy in a previous UK randomised clinical trial.³ We hypothesised HOT-HMV would be cost-effective in the UK.

METHODS

A full description of the trial design can be found with the trial results.³ Patients with persistent hypercapnia ($\text{PaCO}_2 \geq 7$ kPa) between 2 weeks and 4 weeks after resolution of acidosis following an admission with an acute exacerbation of COPD were recruited. Patients were randomised to HOT-HMV or HOT. In addition to clinical data, healthcare utilisation, exacerbation frequency and quality-of-life data were collected at each follow-up visit (6 weeks then 3, 6 and 12 months). A detailed description of quality-adjusted life-year (QALY) calculations is provided in online supplemental eMethods. Medical resource utilisation was recorded throughout the trial at routine follow-up, which was reported by patients and verified by electronic health records, where possible. The economic analysis was conducted over 12 months, reflecting the clinical trial. Costs were calculated from 2017 tariff data from a National Health Service perspective (online supplemental eTable 1). Cost-effectiveness was a prespecified outcome of the efficacy trial using an intention-to-treat (ITT) approach. Details of the ITT and per-protocol approach are in online supplemental eMethods. Sensitivity analyses used realistic minimum and maximum costs.

RESULTS

A total of 116 patients were included in the base-case analysis: 57 in the intervention group (HOT-HMV) and 59 in the control group (HOT) (online supplemental eFigure e1). Baseline patient and retention data are provided in online supplemental



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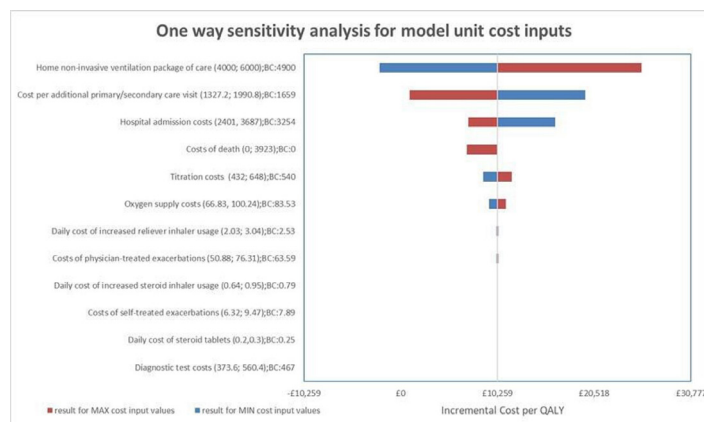


Figure 1 One-way sensitivity analysis results of home non-invasive ventilation with home oxygen therapy versus home oxygen therapy alone in the UK health systems (intention to treat).

Table 1 Cost-effectiveness results for home non-invasive mechanical ventilation (HMV) with home oxygen therapy (HOT) versus HOT alone (intention-to-treat analysis)

| Intervention | Total costs (£) (95% CI) | Total QALYs (95% CI) | ICER (Δ cost/ Δ QALYs) (95% CI) |
|--------------|------------------------------|----------------------|--|
| UK analysis | | | |
| HOT alone | £16 883 (£13 319 to £20 446) | 0.31 (0.23 to 0.39) | Ref |
| HOT-HMV | £17 395 (£14 309 to £20 482) | 0.36 (0.27 to 0.45) | £10 259 (£5438 to £16 449) |

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

eTable 2 and eTable 3. Diary card data were missing for 25 patients (HOT-HMV=8; HOT=17).

Base-case analyses for UK (ITT)

Average total 1-year device costs per patient for the intervention group were £6679 (95% CI £6447 to £6911) compared with £2684 (95% CI £2007 to £3360) in the control group. For all other cost categories, 1-year costs per patient were lower in the intervention group compared with the control group, including average 1-year total primary and secondary care physician visits (£5947 (95% CI £4394 to £7586) vs £8275 (95% CI £6428 to £10 122)); medication costs (£90 (95% CI £52 to £127) vs £104 (95% CI £61 to £146)) and costs for the treatment of exacerbations (£4679 (95% CI £2866 to £6493) vs £5821 (95% CI £4089 to £7552)). Total average annual direct costs per patient were £17395 (95% CI £14309 to £20 482) for the intervention group and £16883 (95% CI £13319 to £20 446) for the control group.

The average number of QALYs was 0.36 (95% CI 0.27 to 0.45) and 0.31 (95% CI 0.23 to 0.39) for the intervention group and control group, respectively. The incremental cost-effectiveness ratio (ICER) was £10 259/QALY (95% CI £5438 to £16 449) (table 1).

One-way sensitivity analyses and bootstrap sensitivity analysis for UK

One-way sensitivity analyses demonstrated parameters with the greatest influence on the ICER: HMV package of care costs for 12 months (ICER range -£2244 to £25 542), cost per additional primary and secondary care physician visit (£944 to £19,574) and hospital admission costs (£7152 to £19574) (figure 1). Bootstrap iterations indicated that at £20 000 and £30 000/QALY, the probability that HOT-HMV is cost-effective versus HOT alone is 56% and 61%, respectively (figure 2A). At £30 000/QALY, the probability that HOT-HMV is more costly and more effective than HOT is 45% (figure 2B). The probability that HOT-HMV is less costly and more effective than HOT alone is 34%.

DISCUSSION

HMV is increasingly used to treat chronic hypercapnic respiratory failure.⁴ A few publications have examined the cost-effectiveness of HMV, with existing economic evaluation largely confined to different HMV modes or setup strategies.⁵⁻⁷ HOT-HMV has previously demonstrated clinical effectiveness, increasing admission-free survival (time to hospital readmission or death) in patients with COPD following a life-threatening exacerbation requiring acute non-invasive ventilation.³ Our study demonstrates that HOT-HMV is cost-effective, with the upper limit of cost per QALY falling below £20 000. This result is consistent with previously conducted analyses using Markov models, which suggest a cost per QALY of £11 318 with a 99% chance of being cost-effective at the £20 000 threshold.^{8,9} The cost per QALY of HOT-HMV falls below that considered acceptable for interventions in the UK¹⁰ and compares favourably with other interventions commonly used in COPD (figure 3).

Limitations

The efficacy trial included a small population with a completion rate (64/116) limited principally by patient death (35/116), which was numerically but not statistically larger in the HOT-alone group. The cost-effectiveness analysis accounts for the lower completion rates as death significantly impacts QALY. Of the patients who withdrew, most (>70%) were in the HOT-alone group. The the most common withdrawal reason was disease progression, which is associated with worse quality of life and so would favour the control arm rather than the intervention.

All centres contributing data to the efficacy trial had established HMV services; therefore, it is possible that less established centres would take longer to set up HMV and would thus increase costs with HOT-HMV. Recent data have demonstrated outpatient setup of HMV in COPD not only is feasible but may be more cost-effective than inpatient titration,⁵ although this was not the case on a recent study of patients with obesity hypoventilation syndrome.¹¹

The trial design allowed patients initially allocated to HOT alone to have HMV if they breached safety criteria after reaching

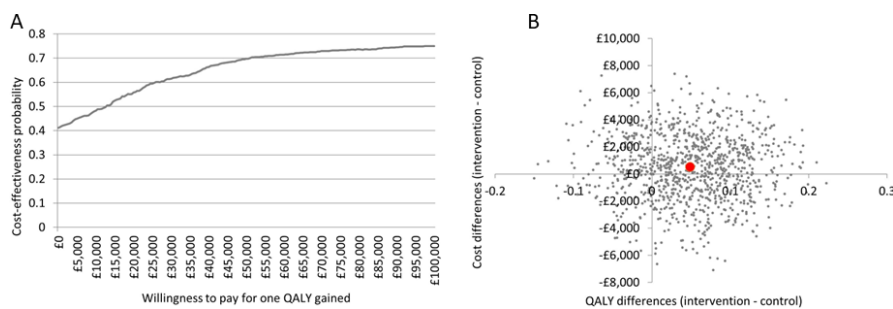


Figure 2 (A) Cost-effectiveness acceptability curve for home non-invasive ventilation with home oxygen therapy versus home oxygen therapy alone in the UK health systems (intention-to-treat analysis); (B) Cost-effectiveness plane for home non-invasive ventilation with home oxygen therapy versus home oxygen therapy alone in the UK health systems (intention-to-treat analysis).

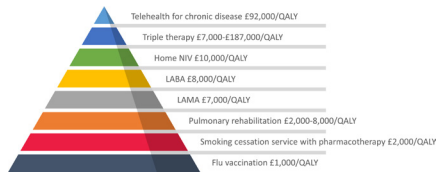


Figure 3 Value pyramid for interventions in the management of COPD. COPD, chronic obstructive pulmonary disease; LABA, long-acting inhaled beta agonist; LAMA, long-acting inhaled muscarinic antagonist; NIV, non-invasive ventilation; QALY, quality-adjusted life-year.

the primary outcome. As expected, the high number of cross-over patients diluted the impact on quality of life between intervention and control arm as these control arm patients were in poorer health than the HOT patients who did not cross-over. Importantly, an additional and modified per-protocol analysis showed increased ICERs compared with ITT (online supplemental eResults).

Finally, the health economic analysis required simplifications. The use of average costs of medical resources does not necessarily reflect actual individual healthcare expenditures but provides typical costs for the patient population. Furthermore, the use of QALYs as an effectiveness measure necessitates breaking the multidimensional construct of quality of life into one value. However, this approach is consistent with other research.¹²

CONCLUSION

HMV with HOT in patients with persistent hypercapnia following an acute life-threatening exacerbation of COPD is likely to be cost-effective in the UK.

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Online supplement: Cost-Effectiveness of Home Non-Invasive Ventilation in patients with persistent hypercapnia after an acute exacerbation of COPD

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This online-only supplement contains:

2 eMETHOD: 1) Calculation of QALY; 2) US specific analysis

2 eRESULTS: 1) US specific analysis; 2) Per protocol analysis for UK & US

1 eDISCUSSION: 1) review of alternative readmission avoidance in COPD

3 eTABLES: 1) Unit costs for treatments and medications; 2) Baseline clinical data for randomized patients; 3) Participant retention in clinical trial by assessment date; 4) Cost-effectiveness results for home non-invasive ventilation with home oxygen therapy vs. home oxygen therapy alone in US – intention to treat and per protocol analysis

2 eFIGURES: 1) Participant Flow Diagram – per protocol analysis; 2) One-way sensitivity analysis results of home non-invasive ventilation with home oxygen therapy vs home oxygen therapy alone in the US health systems (intention-to-treat); 3) Cost-effectiveness plane for home non-invasive ventilation with home oxygen therapy vs home oxygen therapy alone in the US health systems (intention-to-treat)

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eMETHOD**Trial design and patients**

A full description of the trial design of the base case can be found with the efficacy results of the clinical trial along with a copy of the trial protocol including a priori end points and statistical analysis plan.[1] In brief the trial was a UK based open-label, parallel-group randomised clinical trial with a 1:1 allocation of home oxygen therapy (HOT) alone or home mechanical ventilation (HMV) with HOT. Adult subjects hospitalised with a hypercapnic exacerbation of COPD requiring acute non-invasive ventilation were screened for eligibility at least 2 weeks after resolution of decompensated acidosis (arterial pH > 7.30) and within 4 weeks of attaining clinical stability. Patients with persistent hypercapnia ($\text{PaCO}_2 \geq 7\text{kPa}$) without evidence of clinically significant sleep apnoea were then randomised to HOT alone or HOT-HMV. Medical resource use was recorded as part of the original randomised clinical trial with the cost-effectiveness analysis conducted exclusively from these data. Study visits or other trial-related medical resource use subsequent to the initial randomisation visit were excluded from the medical resource use data.

Intervention

All patients had the medical management of their COPD optimised as per British Thoracic Society (BTS) guidelines.[2] Oxygen therapy was titrated to the lowest flow rate to achieve $\text{PaO}_2 > 8\text{kPa}$ in all patients. If achieving a $\text{PaO}_2 > 8\text{kPa}$ resulted in decompensation of respiratory acidosis (defined $\text{pH} < 7.30$) then the highest flow rate that did not lead to decompensation was delivered. Patients randomised to HMV had an additional night stay for overnight titration of NIV to ameliorate nocturnal hypoventilation. HMV was delivered using a bilevel ventilator designed for home non-invasive ventilation and was used with an appropriate interface to maximise patient comfort. Patients allocated to HOT alone could receive acute non-invasive ventilation (NIV) during hospital readmissions for decompensated respiratory failure.

Calculation of QALY

The EQ-5D-5L was used to estimate quality of life.[3] Quality-adjusted life years (QALYs) were used to estimate the time patients spent at specific levels of health status with a value of 1 representing 12 months of perfect health and 0 death.[4] To calculate QALYs an EQ-5D-5L index score was calculated for each of these time points based on the EQ-5D-5L index calculator.[5] UK-specific and US-specific index scores were used as appropriate and are based on general population valuation surveys that used time trade-off (TTO) methods.[6, 7] In the case of missing in-between EQ-5D-5L index scores, a linear change was assumed between the follow-up time points and a replacement by means of prior and post missing values was imputed. For patients who died during study follow-up with missing data a conservative approach was adopted with the final EQ-5D-5L score was imputed as 0. QALYs were calculated at the individual patient level by adopting the area under the curve method.[7, 8]

Medical resource use

Individual patient data recording exacerbation-related hospitalisations and outpatient contacts, as well as self-treated exacerbations were collected by study sites contemporaneously at pre-specified trial follow up. Additionally, patient-reported medication changes and the number of primary/secondary care visits were recorded using patient diaries, which were reviewed at each patient follow up. Patients continued to complete the diaries until trial completion or withdrawal, irrespective of whether they had met the primary outcome or not. All collected data were included in the analysis until the time of trial

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completion, withdrawal or death. To avoid over-counting physician visits, the patient-reported number of primary/secondary care visits was reduced by the documented number of physician-treated exacerbations for the same time period.

Economic outcomes and assessments

The economic analysis was conducted over a 12-month time horizon to reflect the data collection period of the clinical trial. All resource consumption units were multiplied by standardised 2017 UK unit costs (eTable 1a) from a National Health Service perspective. The associated tariff for the recorded contact was used with the cause of hospitalisation referenced to the appropriate organisation costing for that diagnosis; primary care visits were costed at a standard rate irrespective of cause of contact. Costs of medications associated with the management of acute exacerbations were included based on standard regimens. For patients with missing diaries, missing costs have been imputed by group averages. Total device costs were based on costs of the HMV device, diagnostic tests, titration and oxygen supply. Patients receiving HMV were assumed to require an additional inpatient day for titration in the UK analysis. Since the oxygen therapy flow rates were comparable in both treatment arms, monthly cost of HOT was considered to be equivalent between groups. In the UK, device costs (oxygen concentrators and HMV devices, including maintenance and support) were included as a one-time cost at the beginning of the treatment period based on a standardized cost of £4,900 for the first 12 months, with set-up included.

US economic analysis

All resource consumption units were multiplied by standardised 2017 US unit costs from a US Medicare payer (eTable 1b). Costs of medications associated with the management of acute exacerbations were included based on standard regimens. Total device costs were based on costs of the HMV device, diagnostic tests, titration and oxygen supply. Patients receiving HMV were assumed to have a split night study (diagnostic and titration) in the US analysis, in keeping with current practice (communicated by author GC). Device costs (oxygen concentrators and HMV devices, including maintenance and support) in the US were calculated monthly based on the actual period of device use.

Statistical analysis plan

The UK based cost-effectiveness analysis was an *a priori* secondary outcome contained within the original randomised clinical trial statistical analysis plan. The primary cost-effectiveness analysis was based on the intention-to-treat (ITT) approach, including all available data for patients randomised to initially allocated therapy irrespective of compliance or subsequent addition of HMV. The US cost-effectiveness analysis was not specified in the original trial protocol but was added following completion of the clinical trial but prior to the UK economic analysis being conducted. The final statistical analysis plan was completed to account for UK and US systems using an intention-to-treat and per protocol analysis strategy.

The trial protocol allowed the addition of HMV to patients in the control arm due to both ethical and clinical concerns. The pre-specified criteria are provided in the clinical publication.[1] In line with the clinical trial, a per protocol analysis was performed to account for this aspect of trial design. The per protocol design included all patients allocated to intervention from the point of receiving the trial intervention until either trial withdrawal (both groups) or addition of home non-invasive ventilation to clinical care (HOT alone group), at which point data were censored.

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All individual costs during the protocol-conforming treatment duration were extrapolated to the time period between crossover and the end of follow-up. To align with the conservative approach of this analysis, QALYs of crossover patients were taken as documented without data censoring.

All economic analyses reported were performed using MS Excel 2010 (Microsoft, Washington, USA).

The incremental cost-effectiveness ratio (ICER) was calculated as the incremental change in costs divided by the incremental change in QALYs (ICER = [Total cost of intervention - Total cost of control] / [QALYs with intervention - QALYs with control]). The willingness to pay thresholds were set at £30,000/QALY in the UK,[9] whereas no threshold was set for the US given the lack of consensus on a cost-effectiveness threshold in that country.

Sensitivity analyses

To account for uncertainty in the cost assumptions, a one-way sensitivity analysis was conducted by varying base-case unit costs within realistic minimum-maximum ranges (eTable 1). The resulting changes in the ICER compared to the base-case ICER were summarized in a tornado diagram.

Additionally, non-parametric bootstrapping was used to estimate the variability around the arithmetic mean of the base case results.[10] Bootstrapping was performed separately for each treatment allocation and in line with the recommendations from Drummond *et al.*[11] Bootstrapped samples were also used to generate cost-effectiveness acceptability curves, which show the probability of cost-effectiveness with regard to the willingness to pay for one extra QALY.

eResults

Clinical efficacy

The median time to readmission or death was 4.3 months in the intervention group versus 1.4 months in the control group. Risk of readmission or death was significantly reduced (adjusted HR 0.49, 95%CI 0.31 to 0.77, p=0.002; unadjusted HR 0.54, 95%CI 0.34 to 0.84, p=0.007). The hazard ratio was adjusted for the number of COPD admissions in previous year, prior use of long term oxygen therapy (LTOT), age and BMI. At 12 months, 16 patients had died in the intervention group versus 19 in the control group.[1]

Base-case analyses for US (ITT)

Total average annual device costs per patient were \$4,298 in the intervention group compared with \$1,582 in the control group. For the patients in the intervention group, average annual total primary/secondary physician visit costs per patient were \$10,805 compared with \$15,033 in the control group; similarly, average annual medication costs per patient were \$758 and \$1,087 for the intervention group and control group, respectively. The average annual total costs per patient for the treatment of exacerbations were \$8,598 in the intervention group compared with \$10,683 in the control group. The total direct costs per patient were \$24,458 (95%CI, \$18,824 to \$30,092) for the intervention group and \$28,386 (95%CI, \$22,149 to \$34,624) for the control group. The average number of QALYs was 0.49 (0.41 to 0.57) and 0.41 (0.33 to 0.49) for the intervention group and control group, respectively. These estimates resulted in an ICER of -\$50,856, suggesting HMV with HOT is dominant, being more effective and less costly compared with HOT alone (eTable 4).

One-way sensitivity analyses and bootstrap sensitivity analyses for US (ITT)

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One-way sensitivity analyses identified the input parameters with the largest impact on the ICER in the US: cost per additional primary/secondary physician visit (95%CI -\$61,804 to \$39,906), non-invasive device costs (95%CI -\$56,536 to -\$45,174) and hospital admission costs (95%CI -\$56,274 to -\$45,216) (eFigure 2).

The bootstrap sensitivity analysis indicated that at a threshold of \$50,000/QALY the probability that HMV with HOT is cost-effective compared to HOT alone is 94%. The probability that HMV with HOT is less costly and more effective is 76% and the probability that HMV with HOT is costlier and more effective than HOT is 14% (eFigure 3).

Per protocol analysis for UK

A total of 110 patients were included in the per protocol analysis: 56 in the HOT with HMV group and 54 in the HOT alone group. The total direct costs were £20,713 (95%CI, £14,602 to £26,823) per patient for the intervention group and £19,396 (95%CI, £14,162 to £24,630) per patient for the control group. The average quality-adjusted life years were 0.36 and 0.32 for the intervention group and control group, respectively. These estimates resulted in an incremental cost-effectiveness ratio of £34,004/QALY.

Per protocol analysis for US

The total direct costs were \$30,550 (95%CI, \$19,298 to \$41,803) for the intervention group and \$34,563 (95%CI, \$24,994 to \$44,133) for the control group. The average QALYs were 0.49 and 0.42 for the intervention group and control group, respectively. With these figures, the incremental cost-effectiveness ratio was -\$59,096/QALY, suggesting HMV with HOT was dominant (more effective and less costly) compared with HOT alone (eTable 4).

eDiscussion

Cost differences between UK and US models

In both the UK and US models, the HMV device cost was the major driver of the ICER. Thus, the difference in the ICER between the US and UK systems was accounted for largely by differences in charging for the HMV setup and package of care. The UK model used a single upfront charge for the device, consumables (mask, ventilator tubing), titration and 12 months of 24-hour-per-day medical, technical and nursing support. The UK upfront cost was not commuted if the patient discontinued non-invasive ventilation during the trial period, whereas the US system adopts a monthly charge for support with a lower upfront cost for device setup. Consequently, there were higher device costs in the UK compared with the US model within the ITT analysis in patients who withdrew or discontinued therapy after randomization. The UK base case analysis result is particularly sensitive to the cost of the HMV package of care. Varying the HMV package of care for 12 months by $\pm 20\%$ (£4,000, £6,000) has a large impact on the ICER (-£2,244 to £25,542). Consequently, in the UK improved cost-effectiveness could be achieved with a small change in initial setup costs, achieved by renting or recycling equipment and/or by using outpatient rather than inpatient titration. In addition, the trial design limited the cost estimates to a 12-month timeframe. Within the UK system a lower charge is levied for subsequent years of follow up as the device cost is not renewed and therefore the 3- or 5-year cost per QALY may be reduced with longer-term data.

In the UK, the average cost savings associated with reduced exacerbations was £1,141, which mainly arose from reduced hospitalizations (£1,166). The cost savings attributed to reductions in patient-

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reported medication and outpatient costs was £2,342, 99% of which is derived from reduced primary/secondary care visits. The one-way sensitivity analysis of the US model indicated a greater impact on ICER of variation in costs of primary/secondary care visits.

Limitation of US analysis

A major limitation of the US analysis is that the model is based on clinical data from a UK trial. To reflect medical resource use in the US, the data were further adjusted to reflect real-world clinical practice in several ways: (1) patients in the intervention group were assumed to have a separate outpatient visit for titration in US as opposed to one additional inpatient day in UK and (2) medication usage was verified by a US clinical expert (*Author GC*). In addition, quality-of-life values in the US were calculated by applying the US-specific index to the EQ-5D-5L values collected from the British patient population. Furthermore, the infrastructure in the US is less well adapted for HMV and as such the modelling is highly speculative and should be viewed with caution.

Other admission reduction strategies

Pulmonary rehabilitation is an evidence based intervention that improves quality of life, reduces exacerbations and is recommended following exacerbations in patients with COPD.[12] It can be delivered following an acute exacerbation with small and large trial data suggesting clinical benefits.[13, 14] The efficacy of pulmonary rehabilitation in patients with severe breathlessness is unclear. In the trial by Eaton *et al.*, the mean mMRC dyspnea score was 2.3 ± 1.2 compared to a median MRC score of 5 (range 4-5) in the patient population providing the data for the economic analysis.[14] The increased severity of dyspnea in the cohort of patients following life-threatening exacerbations questions the feasibility of pulmonary rehabilitation, reducing the applicability. Non-invasive ventilation (NIV) has been used to facilitate engagement and enhance long-term benefits of pulmonary rehabilitation in the subgroup of stable COPD patients with chronic respiratory failure.[15] It would not have been appropriate to utilize NIV to support pulmonary rehabilitation in these patients as this was the intervention under examination. In addition to the lack of data demonstrating efficacy in the more severe patient population studied, evidence shows that access to pulmonary rehabilitation can be limited by many factors (including patient engagement), leading to fewer than 10% of suitable patients completing therapy.[16] Despite these limitations and challenges, pulmonary rehabilitation has been incorporated into national and international guidelines for patients following acute exacerbations of COPD.[12]

In addition to the physiological burden of COPD, there is a clear psychological burden with high levels of anxiety and depression reported in patients with COPD.[17] These factors may influence readmission and interactions with health care providers. Cognitive behavioral therapy (CBT) is an evidence-based intervention for anxiety and has been used in patients with COPD in an attempt to reduce readmissions. Data show that the use of CBT in patients at high risk of exacerbations of COPD reduces admission rates and is cost-effective.[18] The study from Marshall *et al.* has many strengths and enrolled across the severity spectrum of COPD, including high levels of patients with severe dyspnea (47% MRC 5), but in comparison to the cohort of post life-threatening exacerbations included in our data, Marshall *et al.*'s study has fewer patients with severe airflow obstruction (22% GOLD IV compared with >50% in our cohort) and reports no measure of respiratory failure. Consequently, the applicability to those patients with established respiratory failure and a recent life-threatening exacerbation requires further

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investigation, as in this group readmission may be driven by more frail physiological factors less amenable to change with a psychological intervention.

Cost-effectiveness of other exacerbation reduction strategies in COPD

Exacerbations are an important event in the natural history of COPD and are associated with both short- and long-term harm. Exacerbations are associated with increased mortality,[19] more rapid progression of airflow obstruction,[20] decreased physical activity,[21] worse quality of life[22] and further exacerbations.[23] Exacerbations, therefore, represent an important time to intervene in patient care and improve outcomes. Additionally, they are recognized as important by patients themselves and so represent a target with relevance for the health system, clinicians and patients.

Patients with more severe exacerbations are at higher risk of readmission and clinical scoring,[24] and physiological scoring systems [25, 26] have been used to identify individuals at higher risk of readmission and therefore target readmission prevention. However, these systems are most effective at identifying patients at low risk of readmission who can access lower levels of support and are less sensitive at identifying those at high risk of readmission. Furthermore, there is evidence that some of the readmission risk is related to the structure of delivery of care,[27] with readmission rates across diseases correlating within hospitals but being unrelated to surgical readmission performance. Attempts have been made to standardise care using simple care bundles[28] as well as more complex interventions.[29] Whilst simple care bundles are cheap to implement (<£50 per patient) the reported clinical impact varies with much data being at risk of bias.[28, 30] The data are equivocal on the clinical outcome and cost-effectiveness of these interventions, with higher uncertainty in patients with more severe disease and with potential safety concerns following greater emphasis on self-management.[31-33] All patients recruited for the clinical trial that provided data for this economic analysis had severe disease, indicating the standard interventions above may not be applicable. The patients were all managed in line with the BTS guidance which incorporates self-management plans, optimization of pharmacotherapy and discharge bundles.

Incorporated into discharge bundles within UK practice is referral for pulmonary rehabilitation. Whilst rehabilitation is important, trials demonstrating efficacy of rehabilitation have included patients with lower levels of dyspnoea than in the population in this study.[34] Additionally strategies to improve acceptance of rehabilitation in patients with chronic respiratory failure have involved use of non-invasive mechanical ventilation, which would have been impossible in the trial design as this was the intervention under assessment.[15, 35] However, modelling of pulmonary rehabilitation after an acute exacerbation does indicate that this is a cost-effective strategy with a potential net saving (\$5721, 95%CI \$3307 to \$8388) to the health system.[36]

Readmission is a multifactorial process, and both physiological and psychological factors can influence the outcome. A cognitive behavioural therapy intervention may reduce hospital readmission in patients with COPD and co-morbid anxiety.[18] Similar to other post-exacerbation work described above, the patient cohort studied here was not selected immediately following an exacerbation and differs in terms of breathlessness and disease severity from the patients studied in the HOT-HMV trial; therefore the applicability of CBT as an intervention in this group with severe COPD and respiratory failure is unclear. Heslop-Marshall *et al.* also report readmission but not exacerbations, and it is not clear if admission avoidance occurred without a reduction of exacerbations.[18] However, the data still indicate that CBT would be a cost-effective strategy with 100% probability of being cost-effective compared to standard leaflets at a value of greater than £5000.

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Limitation of clinical trial

Although the use of an open label trial design is a potential criticism of the previously published study, this trial was similar in approach compared with other HMV trials.[37-40] Indeed, the use of a sham device is associated with a number of clinical and ethical considerations, which limit the use of a sham device in a clinical trial involving patients with chronic respiratory failure.[41-44]

Imputation was used due to the presence of missing values in the dataset. These values were imputed using a simple averaging method. Because of the small sample size involved, a more complex system of imputation was not felt appropriate as the validity of the model could not be guaranteed. Although there was a numerical difference in the missing data between interventions, this difference was not significant for either trial visits ($p=0.10$) or diary completion ($p=0.07$). Because of the lack of significant differences in baseline demographic and clinical values at randomisation, the final analysis was not further adjusted, with the exception of the change in patient-reported utility scores, which were adjusted as a change from baseline score.

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eFigures

eFigure e1: Patient flow diagram demonstrating recruitment and retention in original clinical trial

eFigure e2: One-way sensitivity analysis results of home non-invasive ventilation with home oxygen therapy vs home oxygen therapy alone in the US health systems (intention-to-treat)

eFigure e3: Cost-effectiveness plane for home non-invasive ventilation with home oxygen therapy vs home oxygen therapy alone in the US health systems (intention-to-treat)

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eTables*eTable 1a Unit costs for treatments and medications (UK)*

| Resource unit | Unit cost (DSA range) | Source |
|---|--|---|
| 2017 UK unit cost | | |
| Home non-invasive ventilation package of care for 12 months | £4,900.00 (£4,000.00-£6,000.00) ^a | NHS commissioned cost at Lane Fox Unit |
| Additional bed day for titrating non-invasive ventilation | £540.00 (£432.00-648.00) ^a | NHS tariff [45] |
| Oxygen supply per month | £83.53 (£66.82-£100.23) ^a | Trial data, and published cylinder costs [46, 47] |
| Hospitalization due to exacerbation | £3,254.00 (£2,401.00-£3,687.00) ^b | NHS tariff code DZ21J [48] |
| Physician contact due to exacerbation | £63.59 (£50.87-£76.31) ^a | Unit Costs of Health and Social Care 2016, PSSRU 2016 [49] |
| Self-treated exacerbation | £7.89 (£6.31 -£9.47) ^a | Assumption of 10 days increased steroid inhaler usage - Wedzicha 2017 Management of COPD exacerbations [50] |
| Increased steroid inhaler usage per day | £0.79 (£0.63-£0.95) ^a | Calculation based on AMENDMENTS TO THE DRUG TARIFF August 2017 [51] |
| Increased reliever inhaler usage per day | £2.53 (£2.02-£3.04) ^a | Calculation based on AMENDMENTS TO THE DRUG TARIFF August 2017 [51] |
| Steroid tablets per day | £0.25 (£0.20-£0.30) ^a | Calculation based on AMENDMENTS TO THE DRUG TARIFF August 2017 [51] |
| Antibiotic treatment per day: | | Calculation based on AMENDMENTS TO THE DRUG TARIFF August 2017 [51] |
| Amoxicillin | £1.66 | |
| Amoxiclav (clavulan acid) | £0.58 | |
| Azithromycin | £0.36 | |
| Benzylpenicillin | £5.46 | |
| Cefaclor | £1.07 | |
| Ciprofloxacin | £2.55 | |
| Clarithromycin | £1.92 | |
| Co-Amoxiclav | £5.18 | |
| Doxycycline | £0.20 | |
| Erythromycin | £1.54 | |
| Flucloxacillin | £1.14 | |

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| Resource unit | Unit cost (DSA range) | Source |
|--|---|--------|
| Metronidazole | £3.60 | |
| Tazocin | £52.20 | |
| Tetracycline | £0.26 | |
| Trimethoprim | £0.12 | |
| Additional primary/secondary care visits | £1,659.00 (£1,327.20-\$1,990.80) ^a | |

eTable 1b Unit costs for treatments and medications (US)

| 2017 US unit cost | | |
|---|--|--|
| Home non-invasive ventilation device cost per month | \$270.13 (\$253.29-\$286.96) ^c | CMS DMEPOS Fee Schedule 2017 HCPCS code E0471 [52] |
| Diagnostic test cost (excluding titration) | \$171.91 (\$137.53-\$206.29) ^a | CMS Physician Fee Schedule 2017 CPT code 95806 [53] |
| Titration cost | \$471.58 (\$377.26-\$565.89) ^a | CMS Physician Fee Schedule 2017 CPT code 95807 [53] |
| Oxygen supply per month | \$71.85 (\$66.53-\$77.16) ^c | CMS DMEPOS Fee Schedule 2017 HCPCS code E1390 [52] |
| Hospitalization due to exacerbation | \$5,977.69(\$4763.00-\$7145.00) ^a | DRG Summary for Medicare Inpatient Prospective Payment Hospitals DRG code 191 FY 2015 [54], inflated to 2017 USD using US CPI [55] |
| Physician fee due to exacerbation | \$44.14 (\$35.31-\$52.97) ^a | CMS Physician Fee Schedule 2017 CPT code 99212 [53] |
| Self-treated exacerbation | \$137.10 (\$109.68-\$164.52) ^a | Assumption of 10 days increased steroid inhaler usage - Wedzicha 2017 Management of COPD exacerbations [50] |
| Steroid inhaler usage per day | \$63.04 (\$50.43-\$75.64) ^a | Calculated based on WAC price [56] and Pulmicort Flexhaler inhalation powder dosing information [57] |
| Reliever inhaler usage per day | \$5.14 (\$4.12-\$6.17) ^a | Calculated based on WAC price [56] and Symbicort dosing information provided by clinical expert |
| Steroid tablets per day | \$13.71 (\$10.97-\$16.45) ^a | Calculated based on WAC price [56] and Prednisone dosing information [58] |
| Antibiotic treatment per day: | | |
| Amoxicillin | \$3.49 | WAC price [56], Gillisen 2007 [59] |

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|--|--|---|
| Amoxiclav (clavulan acid) | \$7.00 | WAC price [56], Augmentin dosing information [60] |
| Azithromycin | \$8.79 | WAC price [56], Gillisen 2007 [59] |
| Benzympenicillin | \$354.41 | WAC price [56], Benzympenicillin dosing information [61] |
| Cefaclor | \$45.68 | WAC price [56], Cefaclor dosing information [62] |
| Ciprofloxacin | \$2.97 | WAC price [56], Gillisen 2007 [59] |
| Clarithromycin | \$8.79 | WAC price [56], Clarithromycin dosing information [63] |
| Doxycycline | \$0.67 | WAC price [56], Gillisen 2007 [59] |
| Erythromycin | \$445.68 | WAC price [56], Erythromycin dosing information [64] |
| Flucloxacillin | \$67.13 | WAC price [56], Flucloxacillin dosing information [65] |
| Metronidazole | \$5.18 | WAC price [56], Metronidazole dosing information [66] |
| Tazocin | \$264.60 | WAC price [56], Tazocin dosing information [67] |
| Tetracycline | \$2.54 | WAC price [56], Tetracycline dosing information [68] |
| Trimethoprim | \$8.55 | WAC price [56], Trimethoprim dosing information [69] |
| Additional primary/secondary care visits | \$3014.00 (\$2411.20-\$3616.80) ^b | Calculated based on average of cost of hospitalization and physician fee due to exacerbation [53, 54] |

Abbreviation: DSA=deterministic sensitivity analysis; NHS= National Health Service; PSSRU=personal social services research unit; COPD=chronic obstructive pulmonary disease; CMS=Centers for Medicare and Medicaid services; DMEPOS= durable medical equipment, prosthetics, orthotics, and supplies; DRG= Diagnosis-related group; CPI=consumer price index; WAC=wholesale acquisition cost;

a. Varied by \pm 20%

b. Upper and lower bound obtained from NHS national tariff

c. Upper and lower bound obtained from CMS DMEPOS Fee Schedule 2017

eTable 2: Baseline patient data by treatment allocation

| Baseline characteristics | HOT HMV (N=57) | HOT (N=59) | Total (N=116) | P-value |
|--|---------------------|---------------------|---------------------|---------|
| *Age (years) ¹ | 66.4 (10.2) | 67.1 (9.0) | 66.7 (9.6) | 0.675 |
| *Median BMI (kg/m ²) ² | 21.5 (18.8 to 24.5) | 22.2 (17.9 to 26.9) | 21.6 (18.2 to 26.1) | 0.776 |
| *Prior use of LTOT (n (%)) ³ | 40 (70%) | 40 (68%) | 80 | 0.782 |
| * \geq 3 COPD related admissions in last year ³ | 30 (53%) | 31 (53%) | 61 | 0.992 |
| Gender (female) (n (%)) ³ | 29 (51%) | 32 (54%) | 61 | 0.717 |

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|---|----------------------|----------------------|----------------------|-------|
| Median smoking pack year history ² | 42.0 (30.5 to 60.0) | 45.0 (31.0 to 55.0) | 44.0 (31.0 to 60.0) | 0.691 |
| Median AHI (/hr) ² | 2.4 (0.9 to 6.2) | 2.0 (0.8 to 3.9) | 2.2 (0.8 to 5.1) | 0.509 |
| Median neck circumference (cm) ² | 36.3 (33.0 to 40.0) | 38.6 (35.3 to 41.0) | 37.0 (34.5 to 40.0) | 0.084 |
| Median waist circumference (cm) ² | 90.0 (78.0 to 100.5) | 87.5 (78.0 to 106.0) | 88.0 (78.0 to 102.0) | 0.706 |
| FEV ₁ ¹ | 0.6 (0.2) | 0.6 (0.2) | 0.6 (0.2) | 0.491 |
| FEV ₁ (%) ¹ | 24.0 (8.6) | 22.9 (8.6) | 23.4 (8.6) | 0.494 |
| FVC ¹ | 1.8 (0.8) | 1.5 (0.6) | 1.7 (0.7) | 0.091 |
| FVC (%) ¹ | 57.4 (19.7) | 49.3 (20.4) | 53.2 (20.4) | 0.034 |
| FEV ₁ /FVC ¹ | 0.3 (0.1) | 0.4 (0.1) | 0.4 (0.1) | 0.088 |
| Median LTOT prescription ² | 1.0 (0.5 to 1.5) | 1.0 (0.5 to 2.0) | 1.0 (0.5 to 2.0) | 0.113 |
| Median IPAP (cmH ₂ O) ² | 24.0 (22.0 to 26.0) | NA | 24.0 (22.0 to 26.0) | NA |
| Median EPAP (cmH ₂ O) ² | 4.0 (4.0 to 5.0) | NA | 4.0 (4.0 to 5.0) | NA |
| Median back up rate (bpm) ² | 14.0 (14.0 to 16.0) | NA | 14.0 (14.0 to 16.0) | NA |
| PaO ₂ on room air ¹ | 6.4 (1.2) | 6.4 (1.1) | 6.4 (1.1) | 0.823 |
| PaCO ₂ on room air ¹ | 7.9 (0.9) | 7.9 (0.9) | 7.9 (0.9) | 0.938 |
| [†] Median SGRQ summary ² | 74.7 (63.7 to 81.7) | 71.0 (62.6 to 78.6) | 73.8 (63.3 to 80.3) | 0.193 |
| ^{††} SRI summary ¹ | 45.8 (15.0) | 46.9 (15.6) | 46.4 (15.2) | 0.703 |
| ^{†††} EQ-5D-5L | 0.36 (0.35) | 0.42 (0.30) | 0.39 (0.33) | 0.338 |
| Median MRC dyspnoea score ² | 5.0 (4.0 to 5.0) | 5.0 (4.0 to 5.0) | 5.0 (4.0 to 5.0) | 0.340 |

Data summarised as mean (SD), median (IQR) or N (%) as appropriate.

*Minimisation factors. BMI=body mass index; LTOT=long term oxygen therapy; AHI=Apnoea Hypopnoea Index; FEV=forced expiratory volume in 1 second; FVC=forced vital capacity; IPAP=inspiratory positive airway pressure; EPAP=expiratory positive airway pressure; PaCO₂=Arterial partial pressure of carbon dioxide; PaO₂=Arterial partial pressure of oxygen; SGRQ=St George's Respiratory Questionnaire; SRI=Severe Respiratory Insufficiency Questionnaire.

[†] SGRQ on a 0 to 100 scale where 0 is the best QoL and 100 is the worst.

^{††} SRI on a 0 to 100 scale where 100 is the best QoL score and 0 is the worst.

^{†††} EQ-5D-5L measures health-related QoL. In the UK values range from a score of -0.594 (worse than death, as measured by the time trade-off method) to 1.000 (full health), with a score of 0.000 representing death.

¹ T-test for difference in means

² Mann-Whitney U test

³ Chi² test

eTable 3: Participant retention at follow up over 12-month follow-up period separated by treatment allocation

| Treatment | Visit | Number expected | Number attended (%) | Number withdrawn/ died |
|-------------------|-----------|-----------------|---------------------|------------------------|
| HOT HMV (N=57) | 6 weeks | 54 | 45 (83%) | 3 |
| | 3 months | 49 | 40 (82%) | 8 |
| | 6 months | 45 | 40 (89%) | 12 |
| | 12 months | 36 | 36 (100%) | 21 |

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|-------------------------------|-----------|----|-----------|----|
| <i>HOT</i> (<i>N</i> =59) | 6 weeks | 50 | 37 (74%) | 9 |
| | 3 months | 43 | 36 (84%) | 16 |
| | 6 months | 33 | 27 (82%) | 26 |
| | 12 months | 28 | 28 (100%) | 31 |

eTable 4: Cost-effectiveness results for home non-invasive mechanical ventilation (HMV) with home oxygen therapy (HOT) versus HOT alone intention-to-treat and per protocol analysis in US model

| Intervention | Total costs (£) (95%CI) | Total QALYs | ICER (Δ cost/ Δ QALYs) (95%CI) |
|--|------------------------------------|---------------------|---|
| United States ITT analysis | | | |
| Home oxygen therapy alone | \$28,368 (\$22,149 to \$34,624) | 0.41 (0.33 to 0.49) | Ref |
| Home non-invasive ventilation with home oxygen therapy | \$24,458 (\$18,824 to \$30,092) | 0.49 (0.41 to 0.57) | -\$56,195 (-£57,380 to -£54,831) |
| United States per protocol analysis | | | |
| Home oxygen therapy alone | \$34,563 (\$24,994 to \$44,133) | 0.42 | Ref |
| Home non-invasive ventilation with home oxygen therapy | \$30,550 (\$19,298 to \$41,803) | 0.49 | Dominant: - \$59,096 |

Abbreviations: ITT=intention-to-treat; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years

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