BMJ Open Respiratory Research

Economic analysis of temperature-controlled laminar airflow (TLA) for the treatment of patients with severe persistent allergic asthma

Peter Brazier,[1] Uwe Schauer,[2] Eckard Hamelmann,[2,3] Steve Holmes,[4] Clive Pritchard,[1] John O Warner[5]

To cite: Brazier P, Schauer U, Hamelmann E, *et al*. Economic analysis of temperature-controlled laminar airflow (TLA) for the treatment of patients with severe persistent allergic asthma. *BMJ Open Resp Res* 2016;**3**:e000117. doi:10.1136/bmjresp-2015-000117

Received 13 October 2015
Revised 12 February 2016
Accepted 14 February 2016

[1]Optimity Advisors, London, UK
[2]University Children's Hospital, Allergy-Center-Ruhr, Ruhr University Bochum, Bochum, Germany
[3]Children's Centre Bethel, Evangelisches Krankenhaus Bielefeld, Bielefeld, Germany
[4]The Park Medical Practice, Somerset, UK
[5]Department of Medicine (Paediatrics), Imperial College, London, UK

Correspondence to
Professor John O Warner;
j.o.warner@imperial.ac.uk

ABSTRACT

Introduction: Chronic asthma is a significant burden for individual sufferers, adversely impacting their quality of working and social life, as well as being a major cost to the National Health Service (NHS). Temperature-controlled laminar airflow (TLA) therapy provides asthma patients at BTS/SIGN step 4/5 an add-on treatment option that is non-invasive and has been shown in clinical studies to improve quality of life for patients with poorly controlled allergic asthma. The objective of this study was to quantify the cost-effectiveness of TLA (Airsonett AB) technology as an add-on to standard asthma management drug therapy in the UK.

Methods: The main performance measure of interest is the incremental cost per quality-adjusted life year (QALY) for patients using TLA in addition to usual care versus usual care alone. The incremental cost of TLA use is based on an observational clinical study monitoring the incidence of exacerbations with treatment valued using NHS cost data. The clinical effectiveness, used to derive the incremental QALY data, is based on a randomised double-blind placebo-controlled clinical trial comprising participants with an equivalent asthma condition.

Results: For a clinical cohort of asthma patients as a whole, the incremental cost-effectiveness ratio (ICER) is £8998 per QALY gained, that is, within the £20 000/QALY cost-effectiveness benchmark used by the National Institute for Health and Care Excellence (NICE). Sensitivity analysis indicates that ICER values range from £18 883/QALY for the least severe patients through to TLA being dominant, that is, cost saving as well as improving quality of life, for individuals with the most severe and poorly controlled asthma.

Conclusions: Based on our results, Airsonett TLA is a cost-effective addition to treatment options for stage 4/5 patients. For high-risk individuals with more severe and less well controlled asthma, the use of TLA therapy to reduce incidence of hospitalisation would be a cost saving to the NHS.

KEY MESSAGES

- Temperature-controlled laminar airflow (TLA) therapy provides asthma patients at BTS/SIGN stage 4/5 an add-on treatment option that is non-invasive, and has been shown in clinical studies to improve quality of life for patients with poorly controlled allergic asthma.
- This study demonstrates that the incremental cost-effectiveness ratio for TLA treatment with the target patient group (individuals with moderate to severe atopic asthma poorly controlled by standard medication), is £8998 per quality-adjusted life year (QALY) gained, that is, within the £20 000/QALY cost-effectiveness benchmark used by the National Institute for Health and Care Excellence.
- Based on our results, TLA is a cost-effective addition to treatment options for BTS/SIGN stage 4/5 patients. For high-risk individuals with more severe and less well-controlled asthma, the use of TLA therapy to reduce incidence of hospitalisation would be a cost saving to the NHS.

INTRODUCTION

The UK is considered to have one of the highest prevalence rates of asthma in the world, with an estimated 3–5.4 million people in the UK living with asthma,[1] of whom 20% are children.[2] Approximately 250 000 individuals continue to suffer severe asthma symptoms and frequent exacerbations inadequately controlled with available medications.[2] Emergency hospital admission rates for acute asthma attacks are high, with asthma in children constituting 20% of all paediatric emergency admissions.

Chronic asthma adversely impacts patients' quality of both working and social life, generating anxiety for family members and care providers as well as being a major cost to the nation. The National Health Service (NHS) spends approximately £1 billion[3] a year on managing people with asthma.

Patients with severe asthma account for a disproportionate share of the annual healthcare costs given more frequent exacerbations,

and an overall higher use of the medical system. In addition to the direct costs, indirect costs, those incurred by patients, family, friends and other care providers, amount to a significant economic impact for society as a whole. Asthma U.K. reports that 1.1 million working days were lost due to breathing problems in 2008/2009.[3] Asthma in children is a common cause of school absence and, consequently, compromised education, exam results, and therefore, lifetime career opportunities and earnings. There remains an unmet medical need for alternative and complementary approaches to managing asthma that reduce exacerbations, increase symptom control and provide patients with longer term effective therapy.

The Temperature-controlled Laminar Airflow (TLA: Airsonett AB) device is a non-pharmaceutical treatment that delivers filtered, allergen-free and particle-free air to the patient's breathing zone at night.[4 5] It has been shown in two placebo-controlled clinical trials and a pragmatic study to be safe and effective in reducing symptoms of asthma, including exacerbations and airway inflammation, and to improve quality of life.[6–8]

TLA is targeted at patients with moderate to severe perennial allergic asthma whose disease control is poor despite compliance with recommended drug therapy.[9] TLA is intended to complement or obviate the need for use of expensive and/or potent drug therapies that are associated with a greater risk of side effects. However, in order for a novel therapeutic approach to become accepted and recommended strategy, it is necessary to not only demonstrate efficacy but also cost effectiveness.

The objective of this study was to quantify the health economic value of TLA technology in the UK, based on published evidence.

METHODS

The economic analysis is based on the medical resources used by asthma patients participating in the clinical study described in detail in the paper by Schauer *et al*.[8] We evaluated the reported usage of health services for all 30 clinical study participants on an intention-to-treat basis for the 12 months pre-TLA and post-TLA adoption using English health service costs to determine the incremental cost of treatment.

For consistency with the Schauer study[8] the economic cost-effectiveness of TLA is initially calculated based on the reported clinical outcomes. Sensitivity analysis of the main economic drivers is then used to determine the potential underestimate or overestimate of the cost-effectiveness as initially calculated.

The incremental cost of treatment was then combined with quality-of-life data acquired from the 1-year randomised, double-blind, placebo-controlled, parallel-group trial,[7] to quantify the incremental cost-effectiveness ratio, that is, incremental cost per quality-adjusted life year (QALY) gained.

Clinical outcome observations

The Schauer study[8] conducted in Germany, was a pre-retrospective/post-retrospective observational study. Patients with moderate to severe allergic asthma, uncontrolled despite pharmacological treatment, were recruited. TLA was installed for 12 months, and data on medication use, asthma control, asthma symptoms, lung function, use of hospital resources and exacerbations (defined in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) definition[10]) were collected at 4 and 12 months. Data captured after installation of the TLA were analysed and compared with corresponding data collected retrospectively from medical records during the year prior to inclusion in the study.

In total, 30 patients (mean age 28 years; range 8–70 years) enrolled in the Schauer study.[8] All 30 participants completed 4 months, and 27 patients completed 12 months of TLA use (3 patients failing to attend the final visit). The clinical and economic analysis includes study participants on intention-to-treat basis, with the last observation being carried forward for those completing at least 4 months with TLA.

When comparing the last 12 months pre-TLA, with the consecutive 12 months of TLA use, the main clinical observations[8] were:

- The mean number of exacerbations was reduced from 3.6 to 1.3 ($p<0.0001$);
- The ratio of study participants with asthma-related emergency room visits or with hospitalisations diminished from 72.4% to 23.3% ($p=0.001$), and from 44.8% to 20.0% ($p<0.05$), respectively;
- No patient needed intensive care treatment after TLA was introduced as compared with 14% during the previous year, but this difference was not statistically significant.

Both the placebo-controlled[6 7] trials were powered to show an effect on quality of life and not on exacerbations. A post hoc analysis of the 1-year study results[7] from those patients with an Asthma Control Test (ACT) <18 in GINA stage 4 and >1 inhalant allergy was conducted. They had significantly fewer exacerbations on active treatment compared with placebo ($p=0.02$), (figure 1). These characteristics are similar to those in the observational study.[7]

In summary, these studies demonstrated that the addition of TLA to regular medication improved asthma control, reduced the number of exacerbations, and consequently, the usage of hospital resources declined. The reduced burden on the health service is the economic benefit quantified in the financial analysis.

Health service usage

Data collected prospectively from the 30 patients participating in the Schauer study[8] covered the 12 months of TLA use in terms of: emergency room (accident and emergency, A&E) attendances, intensive care unit (ICU) admissions or hospitalisations, that is,

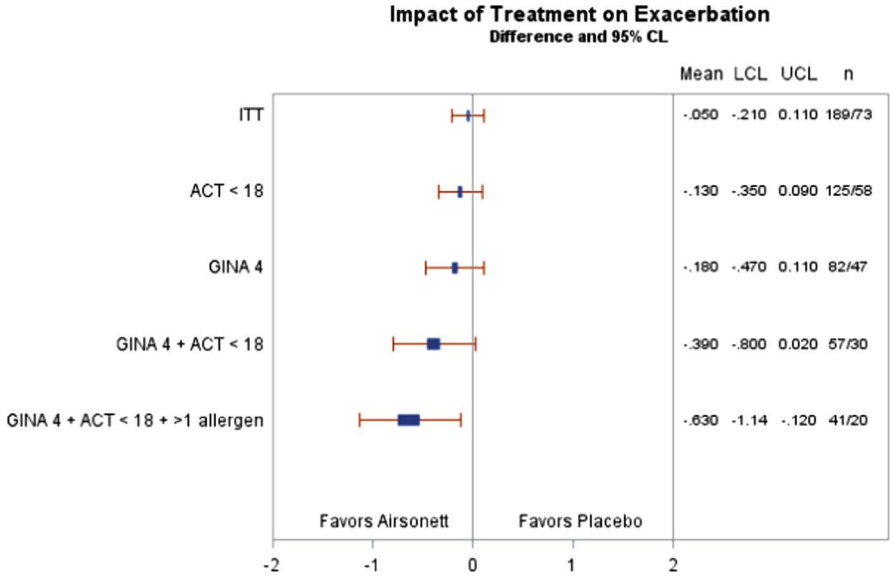

Figure 1 Airsonett temperature-controlled laminar airflow (TLA) impact on exacerbations, mean difference and 95% confidence limits.

general admission. These were compared with corresponding data (available for 29 patients) collected retrospectively for the study baseline from medical records at the hospitals or clinics where patients had been treated during the prestudy year. The close alignment between German and UK asthma management guidelines, and the consistent definition of exacerbations enables the usage of medical resources observed in the study to be valued in a UK context based on NHS costs.

For the purposes of the economic analysis, a record in the clinical study of a patient receiving inpatient treatment is interpreted as 'One hospital admission in 12 months'. This approach is conservative for quantifying the economic savings as, in reality, patients may have been admitted on more than one occasion.

The assumption is that all A&E, ICU and hospitalisation events occur as a result of asthma exacerbations. In the majority of cases, the number of exacerbations reported for a patient exceeds the aggregate number of A&E, ICU and hospital visits reported. The incremental exacerbations in these cases are presumed to have been treated by a General Practitioner (GP) dispensing medication for the patient to self-administer at home, or the patient increasing their medications following a self-management action plan.

Two patients in the year prior to using Airsonett reported three hospital episodes without exacerbations. Two patients reported one hospital episode without recording any exacerbation when using the TLA. In each case the cost of the hospital episode has been included in the economic analysis on the assumption that the inpatient visit was asthma related.

The overall reduction in inpatient episodes during the clinical study is presented in table 1.

The time a patient remains in hospital is a key driver of treatment cost. For the two modes of admission, A&E and general ward admission, the length of stay will vary according to the patient's needs, for example, A&E admission is followed by discharge within 4 h, or hospital admission, either for a short or long stay. Similarly, hospitalisation via general ward admission may be for either a short stay of up to 1 day or a long stay of more than 1 day.

Given that the target patient cohort of interest comprises individuals with more severe and less well-controlled asthma, the assumptions are that: the majority of patients (75%) admitted via A&E, and all patients admitted via the ICU, will be transferred to a general ward and remain in hospital for more than 1 day, that is, a long-stay episode; likewise, the majority (75%) of patients admitted directly to a general ward will remain for a long-stay episode. The remaining patients, 25% of A&E and 25% of general ward admissions are assumed to be discharged within 1 day, that is, they are classified as short stay.

Table 1 Number of exacerbations and inpatient episodes reported

	Exacerbations	Emergency room visits	Intensive care admissions	Hospital general admissions	Outpatient visits
12 Months prior to TLA	107	21	13	4	72
12 Months with TLA	39	7	6	0	28
Reduction	68	14	7	4	44

TLA, temperature-controlled laminar airflow.

Cost of health services

A summary of the medical costs used to calculate the total cost of treatment is presented in table 2.

Table 3 presents the total cost for each component of health services resource use assuming

- That 50% of A&E and ICU and 10% of direct hospital admission patients arrive by ambulance, at a cost of an ambulance call-out of £235, that is, an average cost per patient of £118 and £24, respectively.
- Patients admitted via ICU will remain in intensive care for 42 h on average at a cost of £1168 per day, that is, an average cost of £2044 per patient.
- Patients admitted via ICU are assumed to be discharged from ICU to a high dependency unit (HDU) for 24 h before being transferred to the general ward at a cost of £852.
- Patients admitted via ICU are assumed to remain in a general ward on average for 1.5 days (in addition to the ICU and HDU) at a cost of £694 (ie, £462 per day).
- Patients experiencing an asthma exacerbation visiting a GP or outpatient clinic are assumed to be prescribed standard rescue medication (£16), and the cost of medical professionals attending the patient is estimated at £54 given the need to monitor the patient experiencing the asthma exacerbation until the condition stabilises, that is, a total of £70 per visit.
- All patients are assumed to attend a follow-up GP appointment within two working days, the national standard of care,[11] at a cost of £36.

The longest inpatient episode duration including ICU, HDU and general ward of 4.25 days corresponds with the observed duration of stay of 2 (1–5) days.[12]

Table 2 Health service resource costs

Health resources	£	Source
Ambulance	235 per call out	1
A&E	115 per episode	2
Intensive care unit	1168 per day	3
High dependency unit	852 per day	2
Ward (admitted via A&E)		
Short stay	584 up to 1 day	4
Long stay	1387 over 1 day	4
Ward (direct admission)		
Short stay	523 up to 1 day	4
Long stay	1200 over 1 day	4
Ward average cost	462 per day	4
GP follow-up	36 per visit	1
GP/outpatient clinic	70 per visit	1

Sources:
1. PSSRU Unit costs of Health and Social Care 2013.
2. National schedule of reference costs 2012–13 for NHS Trusts and NHS Foundation Trusts.
3. Hansard answer to a written question 2 September 2014, 20 653.
4. Average treatment costs based on a Hospital Episode Statistic (HES data) sample of 426 episodes classified by HRG codes D15F and PA12Z Optimity Advisors research.
A&E, accident and emergency; GP, general practitioner.

The weighted average cost per patient admitted via A&E or general ward (table 4) is based on the costs (see table 3) and the assumed duration of stay mix (see above). Costs for the ICU and GP/outpatient clinic routes of admission are the sum of the costs for the individual items of resource use applicable to those routes.

The derived average medical costs by mode of admission (table 4) are; A&E £1455, general ward £1090 and ICU £3743 with a cost of £70 for treatment via outpatient GP.

TLA cost

The reference TLA (Airsonett AB) cost to the NHS in the UK is £2088 per patient for 12 months use. This cost includes all maintenance/servicing, filter replacements, and replacement with a new machine at the end of the deemed lifetime of the device.

Quality-adjusted life years gained

Health-related quality-of-life was not an endpoint measured within the scope of the Schauer study.[8] However, in the prior 1-year placebo-controlled clinical trial comprising 312 asthmatics,[7] the Mini Asthma Quality of Life questionnaire (mini-AQLQ) and Paediatric Asthma Quality of Life Questionnaire (PAQLQ) were completed.

The Swedish Institute for Health Economics (IHE) used the mini-AQLQ data to derive five-dimensional Asthma Quality of Life Questionnaire (AQLQ-5D) utilities and, thereby, QALY outcomes for the 235 (75%) adult patient population[13] using an algorithm developed by Yang *et al*.[14]

The remaining 77 (25%) paediatric patients (<12 years) completed the PAQLQ, which included items similar in meaning for four of the five dimensions of the AQLQ-5D. Data from patients who had completed both the mini-AQLQ and the PAQLQ were used by the IHE to infer the AQLQ-5D outcomes, including the outstanding fifth dimension relating to air pollution, for those who had completed only the PAQLQ. These data were used to determine utilities, and thereby, QALY outcomes for the paediatric population using the same algorithm by Yang *et al*.[14]

A subgroup of 82 participants in the 1-year placebo-controlled clinical trial[7] were characterised as ACT <18 and GINA 4, that is, equivalent to the asthmatic condition of the Schauer study[8] participants. The quality-of-life outcome, using the individuals' utility values of this subgroup, is a statistically significant 0.0615 utility improvement ($p<0.0001$),[13] that is, a 0.0615 QALY gain over a year. The 0.0615 utility gain is used for the cost-effectiveness calculation presented below.

RESULTS

Economic cost-effectiveness

Table 5 summarises the cost-effectiveness calculations where

Table 3 Total treatment costs by mode of hospital admission

Patient pathway	Ambulance (£)	A&E (£)	ICU (£)	HDU (£)	Ward short stay (£)	Ward long stay (£)	GP outpatient (£)	Total (£)
(A) A&E								
A1	118	115					36	269
A2	118	115			584		36	852
A3	118	115				1387	36	1656
(B) Hospitalisation								
B1	24				523		36	583
B2	24					1200	36	1259
(C) Intensive Care	118		2044	852		694	36	3743
(D) GP/outpatient clinic							70	70

A&E, accident and emergency; GP, general practitioner; HDU, high dependency unit; ICU, intensive care unit.

- Total savings=cost per episode × reduction in episodes=£46 039
- Savings per person=total savings/30 study participants=£1535
- Incremental cost/(savings)=TLA (Airsonett) cost (£2088—savings per person £1535)=£553
- Incremental cost-effective ratio (ICER)=incremental cost (£553)/incremental QALY gain (0.0615)=£8998/QALY.

Sensitivity analysis

The sensitivity analysis (table 6) evaluates the potential impact of the underlying assumptions supporting the economic model on the study's findings and conclusions.

The variables analysed are as follows:

1. *Treatment costs*: Substitution of inpatient A&E and rates of hospitalisation costs used above with the following reference costs; National Reference Costs by Service Description 2012/13, Reimbursement Tariff for DRG codes DZ15F and PA12Z, and National Reference Spell Cost Data 2012/13. Results indicate that TLA remains cost-effective with ICER values of £11 170, £15 108 and £6515 per QALY, respectively.
2. *Severity of condition*: The severity of the patient's condition on arrival at hospital determines the degree of medical attention a patient receives, and their rate of recovery determines their duration of hospital stay; both factors impact the healthcare resources required, and thus, treatment cost.

Table 4 Weighted average cost by treatment pathway

Patient pathway	Total cost (£)	Patient mix (%)	Weighted average (£)
(A) Emergency room			1455
A1	269	0	
A2	852	25	
A3	1656	75	
(B) Hospitalisation			1090
B1	583	25	
B2	1259	75	
(C) Intensive care	3743	100	3743
(D) General practitioner	70	100	70

TLA is targeted for patients with severe uncontrolled perennial allergic asthma, thus, the actual cost to the health service would be greater than the average cost of treatment of patients classified by DRG codes DZ15F and PA12Z.

To illustrate the variation in treatment costs, the analysis ranks the total actual episode cost per patient from highest to lowest, segregates into quartiles, and calculates the net cost and cost-effectiveness using the average cost by quartile.

The analyses indicate that valuing the cost of treatment based on the highest cost rates delivers the greatest savings, that is, largest cost reduction, and results in the use of TLA being dominant, that is, cost saving while improving the patient's utility. Treatment costs based on the lowest cost rates results in TLA being cost-effective at an ICER of £15 829/QALY.

3. *Inpatient events*: Participants in the Schauer study[8] recorded if they had 'At least one' A&E, ICU or hospital visit in the year prior to, or the year following, TLA use.

In the absence of more detailed information, the most conservative interpretation of 'At least once' is exactly one inpatient admission. Given that the patient cohort was specifically selected to comprise the more severe and less controlled asthma patients, it is likely that some patients would have experienced more than one A&E, ICU or hospital visit during each year in question, particularly for patients with multiple exacerbations.

Of the eight patients who reported just one exacerbation, these also reported inpatient admission on six of those occasions, that is, a 75% admission rate. Patients who reported three or fewer exacerbations were admitted as inpatients for 73% of their exacerbations. However, patients reporting four or more exacerbations were admitted for only 22% of their exacerbations. The low admission rate for patients with more frequent exacerbations is likely to be attributable to the under-reporting, there is no clinical reason why people with more frequent exacerbations should be admitted to hospital less often.

Table 5 Cost-effectiveness calculation

	A&E	ICU	Hospitalisation	Outpatient	
12 Months prior to TLA	21	4	13	72	
12 Months with TLA	7	0	6	28	
Reduction	14	4	7	44	
Cost per episode	£1455	£3743	£1090	£70	
					Total
Total savings	£20 367	£14 973	£7630	£3069	£46 039
Savings per person					£1535
Incremental cost/(savings)					£553
Incremental cost-effective ratio					£8998/QALY

A&E, accident and emergency; ICU, intensive care unit; QUALY, quality-adjusted life years; TLA, temperature-controlled laminar airflow.

The sensitivity analysis assumes that patients reporting four or more exacerbations in a year who were admitted to hospital did so for 50% (rather than 22%) of their exacerbations. This results in the use of TLA being dominant.

Table 6 Sensitivity analysis

Sensitivity variable	Net cost (saving) £ pp/pa	ICER £/QALY
Base case	553	8998
1. Treatment costs		
National reference costs by service description 2012/13	687	11 170
Reimbursement tariff 2014/15	929	15 108
National reference costs spell data 2012/13	401	6515
2. Severity of condition		
Top quartile by treatment cost per episode	(151)	Dominant
Second quartile by treatment cost per episode	524	8527
Third quartile by treatment cost per episode	822	13 365
Bottom quartile by treatment cost per episode	973	15 829
3. Inpatient events		
Increased inpatient visit frequency	(142)	Dominant
4. Length of inpatient stay		
Pathway mix long: short stay 50:50	687	11 163
Pathway mix include discharge from A&E	840	13 656
5. Intention to treat	640	10 400
6. Incidence of inpatient admissions without reported exacerbation	590	9588
7. QALY value		
55% increase in QALY	553	5800
55% decrease in QALY	553	20 000
8. 'Least cost-effective' scenario	1161	18 883

A&E, accident and emergency; ICER, incremental cost-effectiveness ratio; pp aa, per patient per annum; QUALY, quality-adjusted life year.

4. *Length of inpatient stay*: The shorter the length of stay the lower the treatment costs, and the lower are cost savings using TLA. Under the following two scenarios, first, only half the patients admitted via A&E or a general ward remained for a long stay, with half discharged the same day or, second, patients admitted via A&E are discharged within 4 h (one-third), hospitalised for a short stay (one-third), or hospitalised for a long stay (one-third); the resulting ICERs are £11 163/QALY and £13 656/QALY, respectively, that is, the use of TLA remains cost-effective.
5. *Intention to treat*: Of the 30 participants in the clinical study, all completed 4 months use of TLA, and 27 completed the full 12 months. To test the economic impact of using the last observation carried forward for the three individuals who did not complete the full 12 months with TLA, the 4-month exacerbation and frequency of inpatient admission for these participants were extrapolated at the observed rate over the full 12 months. The resulting ICER under this scenario was £10 400/QALY. While this ICER value is higher than the base case £8998/QALY the difference does not impact the overall conclusions drawn from the economic analysis.
6. *Incidence of inpatient admissions without reported exacerbations*: Elimination of inpatient admissions where no corresponding exacerbations had been reported results in an ICER of £9588/QALY, the increase being immaterial to the overall conclusion.
7. *QALY value*: A change in QALY gain results in an inversely proportional change to the ICER outcome. A 55% decrease in the QALY to 0.0277 is required to generate an ICER of £20 000/QALY, the cost-effectiveness threshold. A similar increase of 55% in the QALY to 0.0953 reduces the ICER to £5800. Uncertainties associated with the QALY value calculation are not anticipated to result in this order of magnitude variation, hence, are not anticipated to impact the overall conclusion regarding the cost-effectiveness of TLA.

8. *The 'Least cost-effective' scenario*: This is the combination of economic characteristics giving the highest cost-effectiveness ratio (assuming a QALY outcome of 0.0615) includes
   - The reimbursement Tariff 2014/15 with
   - One of 3 patients discharged from A&E, 1/3 short stay and 1/3 long stay
   - The extrapolation of the data for three patients from month 4 to month 12
   - No inpatient events reported in the absence of an exacerbation.

The resulting ICER is £18 833, within the £20 000/QALY threshold.

The sensitivity analysis indicates that the three most significant factors that impact the cost-effectiveness of TLA treatment are:

- ICU admissions. Patient admission via ICU followed by additional time in HDU is the most expensive clinical pathway, at £3738 per episode of 4.25 days in hospital.
- The cost base used for the valuation of health services. There is a notable difference between the HES data and National Reference cost for long-term inpatient treatment (ie, in excess of £1000 per patient episode) and the corresponding Reimbursement Tariff for reimbursement, that is, £630 per patient episode. The resulting ICER values using the three cost sources are £9998, £11 170, and £15 108, respectively (table 6).
- Actual costs incurred for the provision of care are best represented by the local NHS Trust cost, that is, HES data, or the National Reference Costs at an overall NHS level. From the perspective of commissioning health service, using the Reimbursement Tariff to value TLA therapy results in a less cost-effective outcome, but significantly remaining below the £20 000/QALY threshold.

DISCUSSION

TLA therapy is intended for use as an add-on therapy by patients with perennial allergic asthma whose disease control is poor despite compliance with recommended therapy, that is, corresponding to step 4 (GINA; BTS), as represented by the participants in the Schauer study.[8] The current study demonstrates the value of preventing exacerbations from the perspective of both the well-being of the patient and the economic advantage to the NHS arising from the reduced burden on health services.

Life-time cost-effectiveness cannot be accurately assessed for any asthma treatment given too many variables including, the natural history of the condition, treatment compliance, changes in allergen exposures, frequency of rhinovirus infections, and side effects of treatment. We believe that TLA, by reducing particulate allergen exposure over long periods, is more likely to alter the long-term outcomes beneficially. However, we consider it inappropriate in the absence of long-term trials to make such assumptions.

Given the significant burden of uncontrolled asthma, TLA as a treatment option that provides short-term clinical and economic benefits, is of interest to patients and society. The current economic analysis considers the cost-effectiveness of over 1 year of treatment deemed to be the minimum time needed to capture seasonal variations.

The Schauer study[8] is a precomparison and postcomparison of TLA use, with patients serving as their own control. The data quality of retrospective studies relies very much on the accuracy and completeness of the clinical records. Incomplete data may have been obtained from patient records during the pre-TLA period leading to an underestimation of usage of hospital resources, compared with the TLA period consequently an underestimate of savings.

As there was no control group, spontaneous improvements in medical morbidity would not be identified. While not quantifiable, this is considered a low risk.

Adherence to treatment may have improved during the observation period of TLA use; the risk of bias was considered minimal given that patients selected had a history of good compliance with treatment. Eligible patients had a considerable disease burden for several years, making previous non-adherence to treatment unlikely.

From an economic perspective, the valuation of usage of health resources pre-TLA and post-TLA adoption were based on a common set of health service resource costs to eliminate any introduction of economic bias, and to neutralise the possible impact of inflation.

A degree of uncertainty arises from the QALY calculation. In the absence of quality-of-life data directly available from the Schauer study,[8] QALYs were derived from participants in the clinical study[7] with common characteristics of asthma. The QALY calculations are derived from AQL-5D values, which in the majority of cases are obtained directly from answers to the mini-AQLQ and/or PAQLQ, with good reliability. However, the degree of uncertainty associated with the QALY calculation is not considered material to the overall conclusion regarding the cost-effectiveness of TLA.

From the Schauer study,[8] economic savings in direct NHS medical costs is estimated at £1535 per patient per annum (pp pa). This saving is offset by the TLA cost of £2088 pp pa resulting in a net cost of £553 pp pa to the NHS. The resulting ICER is £8998, that is, it is less than half the £20 000/QALY threshold considered as the acceptable cost-effectiveness benchmark used by the National Institute for Health and Care Excellence.

There is a positive correlation between severity of condition and poor asthma control, and the economic burden to the health service with the most severe cases accounting for a disproportionately large share of both

direct and indirect healthcare costs (ie, lost time at work and education).[15] For certain high-risk individuals, with more severe and less well-controlled asthma, avoidance of two hospital admissions (via A&E or general admission), or one ICU admission per year, would result in the TLA therapy being a cost saving to the NHS.

The economic value of TLA as presented, is likely to be understated due to the prudent interpretation of inpatient episodes from the clinical study, that is, a maximum of one inpatient episode by mode of hospital admission irrespective of the number of exacerbations reported. Increasing the assumed frequency of inpatient visits per exacerbation would result in TLA being more cost-effective and potentially cost saving.

Improved asthma control provides additional economic and clinical benefits, for example:

- The patient's rate of recovery, and hence, duration of hospital stay is a key cost driver of actual costs incurred by the NHS. Improved asthma control, through TLA use, may result in less intensive care or shorter inpatient stay when treating an exacerbation.
- Reduced use of rescue medication.
- Less absenteeism from work or education for the individual patient, family and care providers.
- Decreasing the incidence of asthma exacerbations improves lung function, thereby, particularly for children, reducing the risk of developing persistent severe asthma.[16]

The analysis in this study has shown that TLA provides asthma patients a treatment option that is non-invasive, with demonstrable health and economic benefits. These findings are consistent with previous studies demonstrating the economic and clinical value of TLA treatment for asthma sufferers.[13 17–19]

Our primary analysis of cost is based on one uncontrolled observational study, and a large placebo-controlled trial to derive the ICER. Our health economic evaluation also uses a number of assumptions, namely, that the pathways of care in Germany are similar to those in the UK, and extrapolates healthcare costs based on UK national averages.

Clearly, a placebo-controlled trial powered to detect an effect on exacerbations will provide the ultimate confirmation of cost-effectiveness, and such a study is now in progress: Laminar Airflow in Severe Asthma for Exacerbation Reduction (LASER).[20]

However, we believe, that based on our results, Airsonett TLA provides a cost-effective additional option for the treatment of BTS/SIGN stage 4/5 patients. Further studies into the long-term outcomes of TLA therapy would provide valuable clinical and economic insights.

Contributors US and EH led the clinical research study evaluating temperature-controlled laminar airflow (TLA) as an add-on treatment for patients with moderate to severe atopic asthma poorly controlled with standard medication. SH provided primary care clinical expertise from a UK perspective. CP and PB undertook the economic analysis. JOW, FMedSci provided overall guidance and direction plus medical expertise in the treatment of patients with moderate to severe asthma from an NHS perspective.

Disclaimers Airsonett AB funded Optimity Advisors to conduct an impartial and independent economic analysis of the TLA observational study[7] and the placebo-controlled clinical study.[7] The authors of this paper analysed and interpreted the results independent of any input from Airsonett AB, and have no financial interest in the outcome of the evaluation or future success of the product.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Department of Health/Medical Directorate/Respiratory Team. *An outcomes strategy for chronic obstructive pulmonary disease (COPD) and asthma in England*: Department of Health, 2011.
2. Asthma U.K. Strategy 2014–17. *Asthma U.K.*, 2014.
3. Asthma facts and FAQs. http://www.asthma.org.uk/asthma-facts-and-statistics (accessed Aug 2015).
4. Gore RB, Boyle RJ, Gore C, *et al*. Effect of a novel temperature-controlled laminar airflow device on personal breathing zone aeroallergen exposure. *Indoor Air* 2015;25:36–44.
5. Fisk WJ. Health benefits of particle filtration. *Indoor Air* 2013;23:357–68.
6. Pedroletti C, Millinger E, Dahlén B, *et al*. Clinical effects of purified air administered to the breathing zone in allergic asthma: a double-blind randomized cross-over trial. *Respir Med* 2009;103:1313–19.
7. Boyle RJ, Pedroletti C, Wickman M, *et al*. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax* 2012;67:215–21.
8. Schauer U, Bergmann KC, Gerstlauer M, *et al*. Improved asthma control in patients with severe, persistent allergic asthma after 12 months of nightly temperature-controlled laminar airflow: an observational study with retrospective comparisons. *Eur Clin Respir J* 2015;2. doi:10.3402/ecrj.v2.28531
9. The National Institute for Health and Care Excellence (NICE). The Airsonett temperature-controlled laminar airflow device for persistent allergic asthma. NICE Medtech Innovation Briefing 8, 2015.
10. Reddel HK, Taylor DR, Bateman ED, *et al*. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59–99.
11. British Guideline on the Management of Asthma, Emergency Asthma Care: Asthma UK, 2013.
12. Hanson AJ, Vali Y, Fisher-Black J, *et al*. P57 Factors influencing length of hospital stay in asthma exacerbations: results of a service improvement project. *Thorax* 2014;69:A99–100.
13. Persson U, Hofmarcher T. *Cost-effectiveness analysis of Protexo (Airsonett TLA)*. The Swedish Institute for Health Economics, 2012.
14. Yang Y, Brazier JE, Tsuchiya A, *et al*. Estimating a preference-based index for a 5-dimensional health state classification for asthma derived from the asthma quality of life questionnaire. *Med Decis Making* 2011;31:281–91.
15. Peters SP, Ferguson G, Deniz Y, *et al*. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med* 2006;100:1139–51.
16. Custovic A, Johnston SL, Pavord I, *et al*. EAACI position statement on asthma exacerbations and severe asthma. *Allergy* 2013;68:1520–31.
17. Brodtkorb TH, Zetterström O, Tinghög G. Cost-effectiveness of clean air administered to the breathing zone in allergic asthma. *Clin Respir J* 2010;4:104–10.

18. Cost-minimization analysis of Protexo and Xolair in asthma treatment: The Swedish Institute for Health Economics, February 2013.
19. Cost assessment issues for implementation of medical devices: a case example, ABA Business Associates, European Medical Device Technology web page accessed August 2015. Adams Business Associates. Economic assessment impact of Protexo device for atopic asthma treatment. 2013;1–34
20. Storrar W, Fogg C, Brown T, *et al*. Temperature-controlled laminar airflow in severe asthma for exacerbation reduction (The LASER Trial): study protocol for a randomised controlled trial. *Trials* 2016;17:15.