Airsonett® laminar flow device for treatment of uncontrolled asthma

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Summary

- Airsonett is a CE-marked medical device, intended for use by people with persistent allergic asthma that has not responded adequately to high-intensity pharmacotherapy. It is sizable, at up to 139 cm tall and weighing 25 kg. The device is installed at the patient’s bedside and directs a laminar flow of cooled, HEPA-filtered air around their head during sleep in order to reduce exposure to allergens during sleep.

- Although a number of trials have been conducted, the bulk of the clinical data relate to quality of life changes. The pivotal study (n=282) is a randomised double-blind trial with change in quality of life scores as the primary outcome. Patients used the Airsonett or an identical placebo (which did not filter or cool air) for one year. A significant improvement in quality of life, as measured by the mini asthma related quality of life questionnaire (AQLQ) or paediatric AQLQ, was more common with Airsonett than placebo (76% vs. 61%).

- The effect was more pronounced in the people with poorly controlled asthma at baseline. However, this pre-specified subgroup was small, and there is no evidence that pharmacotherapy was optimised prior to starting treatment with Airsonett. There was a high response rate in the placebo arm, suggesting a response bias may be present.

- Other published data show similar quality of life improvements. However, there is no good quality evidence that Airsonett improves rates of asthma exacerbations, hospitalisation, medication use, or objective measures of respiratory function other than fractional exhaled nitric oxide. A large UK-based trial is currently investigating the effect on exacerbations, but results are not likely to be available until 2017.

- No safety concerns were raised. While adverse events were reported commonly, none were considered to be related to study treatment. A small proportion of people discontinued treatment due to the draught or sound produced by the device causing a disturbance.

- The annual rental cost of Airsonett is £2,088, including routine servicing and filter replacement. Additional costs may be incurred if damage occurs due to misuse.

- A cost-effectiveness analysis estimates that due to decreased healthcare costs the net cost to the NHS will be approximately £535, with a corresponding ICER of £8,998 per QALY. However, this analysis is based on data from a small, uncontrolled, unpublished study conducted in Germany, whose applicability to the UK population can not be fully assessed.

- Airsonett is intended to be used alongside optimised pharmacotherapy at BTS/SIGN step 4 (high-dose inhaled corticosteroids plus regular bronchodilators, with or without additional drugs). The cost will therefore be additive.
Introduction and background

Asthma is a common chronic respiratory condition, characterised by airway inflammation and affecting approximately 6% of the population of England. Poorly controlled asthma is a major cause of hospital admissions, with over 54,000 recorded emergency admissions in England between June 2013 and May 2014. Asthma was recorded as the underlying cause of death of over 1,100 people in England and Wales in 2013. The direct cost of asthma to the NHS is estimated at £1 billion, and the indirect societal costs at £6 billion.

The airways of asthmatic people are hyper-responsive, and constrict easily in response to a range of stimuli, resulting in wheeze, cough, chest tightness and shortness of breath. Airway inflammation may reverse spontaneously, but regular medication to reduce and prevent symptoms is recommended for most people. In some people with chronic asthma the inflammation is not reversible. There is wide variation in severity, clinical course and response to treatment.

The British Guideline on the Management of Asthma (BTS/SIGN, 2014) is the major clinical guideline for asthma management in the UK. It defines disease control as:

- No daytime symptoms
- No night-time awakening due to asthma
- No need for rescue medicine
- No exacerbations
- No limitations on activity, including exercise
- Normal lung function (in practical terms – forced expiratory volume in 1 second (FEV₁) and/or peak expiratory flow rate (PEF), greater than 80% predicted (or the person's best value if unable to attain this)

Asthma management is primarily pharmacological, and aimed at achieving disease control while minimising adverse drug effects. BTS/SIGN recommend a step-wise introduction of short-acting beta 2 agonists (SABA), inhaled corticosteroids (ICS) and long-acting bronchodilators (LABA) according to individual need:

- Step 1: Occasional relief bronchodilator, e.g. a SABA.
- Step 2: Regular inhaled preventer therapy – consider starting an ICS at a standard dose most appropriate to the severity of symptoms (e.g. 200 to 800 micrograms/day for beclometasone CFC-free).
- Step 3: ICS + LABA – consider adding a LABA if symptoms are still uncontrolled with the ICS, irrespective of the dose used. Many patients derive greater benefit from add-on therapy than from increased ICS dose.
- Step 4: High-dose ICS + regular bronchodilators – if control is still inadequate, either increase ICS (up to 2,000 micrograms per day) or consider starting a fourth drug, such as a leukotriene receptor antagonist, modified-release theophylline, or an oral modified-release beta 2-agonist.
- Step 5: Continuous or frequent use of oral steroids – refer to a specialist in respiratory medicine. Maintain ICS at 2,000 micrograms/day while waiting, and consider other treatments to minimise oral steroid use.
Treatment should be stepped up where disease control remains inadequate. Before starting a new drug or stepping up treatment, clinicians should confirm with the patient their understanding of the role of treatment, adherence to treatment, inhaler technique, and steps taken for the appropriate elimination of triggers. Regular review is recommended, to facilitate stepping down of therapy where appropriate and avoid overtreatment.

People with asthma also commonly have allergic sensitisation to one or more substances, such as dust mites or pollen. Evidence on the benefits of avoiding these allergens is mixed. For example, there is no evidence of benefit in chemical or physical means of removing house dust mites, and mite allergen reduction should not be recommended. There is mixed evidence on the avoidance of pet allergens, but reduction of residual cat allergens in the home for allergic individuals may be of some benefit. An approach which reduces exposure to multiple airborne allergens, (e.g. mechanical ventilation) may be of more benefit, but evidence is limited.

Airsonett (Airsonett UK Ltd) is a medical device designed to reduce allergen exposure during sleep, and is an example of temperature-controlled laminar airflow (TLA) technology. The device was previously named Protexo, and is sometimes referred to as the Airsonett Airshower. It is positioned at the patient’s bedside such that filtered air is directed around the head during sleep. The circulated air is HEPA filtered to remove particles ≥0.5 μm, and cooled to 0.5-0.8°C below room temperature. The cooled air is denser than that in the surrounding room, and so settles around the patient’s head, providing filtered air without excessive breeze or draught. A recent technical study showed that the device reduces the number of airborne particles >0.5 μm in diameter in the breathing zone by >99% (p<0.001), with accompanying significant reduction in airborne allergens. The device does not affect allergen concentrations in the rest of the room.

Airsonett is rather large, standing 94-139 cm tall (depending on bed height), and with base measurements of 54 by 34 cm and a weight of 25 kg. It is intended to be installed at the bedside and then left in place. Airsonett consumes approximately the same energy as a 60-90 W lightbulb, and is relatively quiet in operation at ≤38 decibels. The device carries a CE mark, which is a mandatory requirement for medical devices in the EU. The mark shows that the manufacturer has declared that the device conforms to all relevant legislation, including safety requirements, and is fit for its intended purpose. Products with the CE mark can be freely marketed within the EU. Other air filtration devices are available in the UK, but none appear to be CE marked.

NICE considers the place in therapy for Airsonett to be as long-term add-on treatment for patients with severe, persistent allergic asthma with poor disease control despite high-intensity pharmacotherapy. Such patients are likely to be currently treated at SIGN/BTS stage 4, and to be candidates for long-term oral steroids, omalizumab or bronchial thermoplasty (BTS/SIGN stage 5). This document will review the evidence for the efficacy, safety and place in therapy of Airsonett in the management of asthma. It does not cover use for other allergic conditions such as rhinitis or eczema.
Clinical evidence

Two randomised controlled trials have been published. Boyle et al recruited participants aged 7-70 years with a diagnosis of asthma for at least one year. Patients had partly controlled asthma according to Global Initiative for Asthma (GINA) criteria (see appendix A). Quality of life scores were ≤5.5 at baseline, as measured by the Mini Asthma Quality of Life Questionnaire (mini AQLQ) or Paediatric Asthma Quality of Life Questionnaire (PAQLQ) (see appendix A). All participants had sensitisation to a pet allergen or house dust mite (as demonstrated by specific IgE ≥70 kU/litre or a positive skin prick test) and a daily ICS dose of ≥200 μg/day beclometasone or budesonide, or ≥100 μg/day fluticasone. Exclusion criteria included current cigarette smoke exposure (active or passive), participation in any drug trials or allergen avoidance programmes, treatment with allergen immunotherapy or omalizumab in the preceding 2 years (or 1 year for children), ICS dose >1200 micrograms/day beclometasone or budesonide (>1000 micrograms/day fluticasone).

Patients were randomised 2:1 to have either an Airsonett or placebo device installed in their bedroom within 4 weeks of study inclusion. The placebo devices were identical to the active machines except that the filters were bypassed and they did not cool the circulated air. The trial was double-blind, although the installation and maintenance technicians were necessarily unblinded. Patients and family members were absent from bedrooms during device installation and servicing in order to maintain blinding. Patients were asked to switch the device on each night when they went to bed and off again in the morning. Compliance was monitored by an electronic counter within the device which counted the total number of device uses.

Devices were used for 1 year, and asthma medications were not changed for the first 3 months of treatment. For the remainder of the trial medications were adjusted in line with GINA guidance, which is similar to the SIGN stepwise approach outlined above (see appendix B). The primary outcome was change in mini AQLQ or PAQLQ. Patients with an improvement of ≥0.5 were considered to be responders, which is in line with the publisher's guidance for the minimal clinically important difference in test scores. Secondary outcomes included changes in AQLQ scores, measures of airway inflammation, specific IgE levels, blood eosinophil count, and measures of airway obstruction including FEV₁, PEF, and forced expiratory flow at 50% of vital capacity (FEF₅₀). The primary analysis was performed in the intention-to-treat (ITT) population using a last observation carried forward (LOCF) method to impute missing values. The ITT population was more correctly a modified ITT population, since it consisted of all randomised patients with at least one day of treatment. The study had 80% power to detect a 20% difference in the number of responders between groups, based on recruitment of 234 patients aged ≥12 years.

A total of 312 patients were randomised, with a mean age of 25 years and asthma duration of 12-14 years. One quarter of participants were aged <12 years, and were therefore not included in the primary outcome analysis; the study is not powered to assess response in this population. The mean PEF at baseline was 93% of predicted and mean asthma control test (ACT) score was approximately 16, indicating poor asthma control (see appendix A). Most patients had some form of concomitant allergy, with more than half allergic to each of house dust mites, cats, and dogs. Over 40% were allergic to a seasonal allergen of some kind, and ≥95% had rhinitis. A significant proportion in each group also had eczema (17-24%) or a
food allergy (8-14%). Of the randomised patients, 282 (90%) had a device installed in their bedroom and were included in the ITT analysis.

There were significantly more responders in the active treatment group than with placebo in the ITT population (see table 1). A secondary analysis in the per-protocol (PP) population (defined as all patients with at least 80% compliance and without any major protocol violations) also showed a significant difference, as did most other secondary analyses. There was no difference between groups in rates of asthma exacerbation or medication use. Over 70% of patients in each group used the device on at least 80% of expected nights.

The proportion of patients in each group with a <1.0 improvement in AQLQ scores was also reported. The only subgroups with a significant improvement compared to placebo were patients with ACT score <18 (62% vs. 41%, OR 2.78, 95% CI 1.36 to 5.67, p=0.005) and those with ACT score <18 and treated at GINA stage 4 (65% vs. 37%, odds ratio 8.81, 95% CI 2.14 to 36.32, p=0.003). Although these subgroups were relatively small (see table 1), these data suggest that patients with poorly controlled asthma, with or without relatively intense pharmacotherapy, may derive the most benefit from Airsonett.

Active treatment was associated with a greater change in mean fractional exhaled nitric oxide (-5 parts per billion [ppb] vs. +3 ppb, p=0.03), but there was no significant difference in FEV₁, PEF or FEF₅₀.

Table 1: proportion of patients with ≥0.5 improvement in AQLQ score¹⁰

<table>
<thead>
<tr>
<th></th>
<th>Responders, % (n/N)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>ITT population</td>
<td>76% (143/189)</td>
<td>61% (56/92)</td>
<td>1.92 (1.09 to 3.38)</td>
</tr>
<tr>
<td>(primary outcome)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP population</td>
<td>77% (106/136)</td>
<td>61% (40/66)</td>
<td>2.22 (1.11 to 4.40)</td>
</tr>
<tr>
<td>&lt;12 years</td>
<td>80% (37/46)</td>
<td>64% (14/22)</td>
<td>5.57 (1.13 to 27.48)</td>
</tr>
<tr>
<td>≥12 years</td>
<td>74% (106/143)</td>
<td>60% (42/70)</td>
<td>1.89 (0.98 to 3.65)</td>
</tr>
<tr>
<td>GINA stage 4*</td>
<td>77% (63/82)</td>
<td>62% (29/47)</td>
<td>2.42 (1.05 to 5.60)</td>
</tr>
<tr>
<td>Poorly controlled (ACT &lt;18)**</td>
<td>74% (93/125)</td>
<td>52% (30/58)</td>
<td>3.45 (1.66 to 7.20)</td>
</tr>
<tr>
<td>GINA stage 4 + poorly controlled</td>
<td>75% (43/57)</td>
<td>50% (15/30)</td>
<td>4.74 (1.48 to 15.19)</td>
</tr>
</tbody>
</table>

*GINA stage 4 is approximately equivalent to BTS/SIGN step 3 or 4 (see appendix A)

**ACT scores <20 indicate poor asthma control (see appendix A)

Pedroletti et al published a much smaller double-blind crossover trial (n=22) which recruited people aged 12-33 years with asthma, taking a daily ICS dose of ≥400 micrograms/day budesonide or 200 micrograms per day fluticasone, plus SABA on no more than three days per week.¹² All participants were allergic to cat and/or dog allergens, and most were also sensitive to house dust mites, mould spores and birch pollen. Most patients (13, 59%) were taking low-dose ICS while 8 (36%) were using...
medium-dose and 1 was treated with high-dose ICS. The mean mini AQLQ score was 5.2 at baseline, and the mean FEV1 was 78% of predicted.

Each patient used either the active or placebo device for 10 weeks, then switched to the other treatment following a two week washout period. Medications were not changed during the study. The primary outcome measure was change in the mini AQLQ score, with a difference of 0.5 considered clinically significant. Six patients withdrew from the study, and a further two failed to complete the AQLQ questionnaire and could not be included.

There was a mean improvement in mini AQLQ score of 0.56 during active treatment, compared to no change with placebo (treatment difference 0.54, p<0.05, n=20). Eight episodes of asthma exacerbation were reported, with four during the active treatment period. No significant changes in PEF or FEV1 were recorded. Mean change in fractional exhaled nitric oxide was greater during active treatment (-7.0 ppb vs. -0.5 ppb, treatment difference -6.4, p<0.05, n=22).

The manufacturers also presented some unpublished data to NICE. One study was based in Germany, and prospectively recruited 30 patients aged 7 to 70 years. All were treated at GINA steps 3-5, and had inadequately controlled perennial allergic asthma according to German treatment guidelines. The outcome measures were rates of exacerbation and medication use before and during one year of treatment with Airsonett. The study found a significant reduction in exacerbations (3.57 vs. 1.30 per year, p=0.00013). The rate of unplanned clinic visits (76% vs. 33%, n=21, p=0.01) was also significantly reduced, while the hospitalisation rate was numerically lower (32% vs. 14%, n=22, p=0.1). There was also a reduction in patients exhibiting bronchial hyper-reactivity (70% vs. 30%, n=27, p=0.005). Asthma control was significantly improved when measured by both ACT scores and doctors' assessment.

A retrospective study of 70 Swedish patients with poorly controlled asthma found a significant reduction in the rate of emergency room visits (4.0 vs. 0.7, p<0.0001), hospital admissions (0.8 vs. 0.1, p=0.0004) and planned clinic visits (5.7 vs. 1.7, p<0.0001) when comparing the periods before and after Airsonett introduction). No other data are available on this study.

NICE found records for three additional studies which have been completed but not published. In addition, the randomised, double-blind placebo-controlled LASER trial is ongoing at sites throughout the UK. It aims to recruit 222 adults with severe uncontrolled asthma, and will assess the effect of Airsonett on frequency of asthma exacerbations. Recruitment is ongoing, and the study is not expected to be completed until the end of 2016.

**Limitations**

The pivotal study is a randomised, placebo-controlled trial, with adequate blinding and randomisation procedures.

A NICE Medtech Innovation Briefing published in August 2014 states that the likely place in therapy for Airsonett is as long-term add-on therapy for adults and children with severe, persistent allergic asthma with poorly controlled disease despite high-intensity pharmacotherapy (BTS/SIGN step 4, requiring escalation to step 5).
participants in the pivotal trial did not appear to fit these criteria, with a mean ICS
dose of approximately 600 micrograms (BDP equivalent) at baseline, although this
figure may be skewed by use of lower doses in children.\textsuperscript{10} A sub-group analysis of
people treated at GINA step 4 (approximately equivalent to BTS/SIGN step 3 or 4,
see appendix B) and with poor asthma control was included, but had relatively small
patient numbers (see table 1). There were no reported adjustments for multiple
comparisons.

The study had 80% power to detect a 20% difference in response rate between
treatment groups among individuals aged ≥12 years.\textsuperscript{10} In practice there was only a
14% difference between groups in this population, and no significant difference was
found. The response rate in the placebo arm was much larger than the 20% expected. The trial may have been underpowered to detect any true difference. The
group referred to as the ITT population included all participants under the age of 12
(77 children in total) and was more properly a modified ITT population, since only
patients with at least one day of device treatment were included. Confidence
intervals in several of the subgroups approached 1, indicating that the true treatment
effect may be small.

The primary outcome measure in both trials was change in quality of life scores.\textsuperscript{10,12}
While this is a patient-oriented outcome, it is also subjective and therefore
susceptible to bias. Response rate in the placebo arm was considerably higher than
the 20% expected, suggesting response bias may have been present. There were
no differences in objective measures such as asthma exacerbations, medication
use, peak expiratory flow or forced expiratory volume in 1 second in either trial.
Fractional exhaled nitric oxide was improved with active treatment in both trials,
although this measure is not routinely used in asthma management in the UK.
BTS/SIGN do recognise that the test is becoming increasingly available and may
have a place in identifying patients who may benefit from stepping up or down in
corticosteroid treatment.\textsuperscript{5}

The unpublished German study could not be fully appraised. However, the trial is too
small to draw reliable conclusions and it is not clear whether the enrolled patients
were similar to those likely to be seen in UK practice. All participants were treated at
GINA stages 3-5 (see appendix B), implying some had less severe asthma than
those who would be in the target population in the UK.

Safety

Boyle et al found no difference in the rate of adverse events or serious adverse
events reported (see table 2), and no adverse events were found to be treatment-
related.\textsuperscript{10} Twenty-three patients (12%) discontinued in the active treatment arm
following device installation, compared with 13 (14%) in the placebo arm. Five
patients (2.6%) were disturbed by the sound of the device in the active arm,
compared with six (6.5%) with placebo. Four people (2.1%) in the active treatment
arm were disturbed by the draught produced by the device. Pedroletti et al did report
any adverse effects.\textsuperscript{12}
Table 2: adverse events reported in the pivotal trial\textsuperscript{10}

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Active treatment</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>153 (74%)</td>
<td>79 (75%)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>32 (17%)</td>
<td>14 (15%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>117 (61.9%)</td>
<td>62 (66.7%)</td>
</tr>
<tr>
<td>Upper respiratory tract symptoms</td>
<td>54 (28.6%)</td>
<td>22 (23.7%)</td>
</tr>
<tr>
<td>General symptoms</td>
<td>43 (22.8%)</td>
<td>19 (20.4%)</td>
</tr>
</tbody>
</table>

Cost analysis

The NHS rental cost of Airsonett is £174 per month (excluding VAT), equivalent to £5.72 per day or £2,088 per year.\textsuperscript{7,18} This includes servicing, repairs and replacement filters every 6 months. Additional costs may be incurred in case of misuse or damage to the Airsonett device (excl VAT):

- Filter - £500
- Refurbishment followed by self-installation - £250
- Refurbishment on site by Airsonett - £500
- Refurbishment at Airsonett facility - £1000

Since Airsonett is intended to be added to optimised pharmacotherapy, these figures will be additive to existing asthma treatment costs. Currently omalizumab and bronchial thermoplasty are considered options for treatment in patients requiring continual or frequent oral steroids for asthma. Both are commissioned by NHS England.\textsuperscript{4}

Asthma prevalence is estimated at 5.9\% in England, and 6.22\% in the NTAG area.\textsuperscript{1} This equates to approximately 204,000 patients with asthma across the region, or 6,219 people per 100,000 population. It is not clear what proportion of people with asthma are treated at steps 4 and 5 of the BTS/SIGN treatment ladder, and would therefore be in the target population for Airsonett. Several sources state that 5\% of people with asthma have severe disease, which would equate to over 10,000 people in the NTAG region. However, the definition of “severe” is not clear in this context and may include patients who have poor control due to poor management.\textsuperscript{4,16}

Omalizumab is a treatment option for people with allergic asthma who require frequent or continuous oral steroids. Current use of omalizumab therefore provides another estimate of people who may benefit from Airsonett. The NICE costing statement for omalizumab (TA278, April 2013) estimated that 1,400 people in England were receiving omalizumab for severe allergic asthma at that time. An additional 150 children per year may now be treated, since NICE extended their recommendation to include children from the age of 6 years.\textsuperscript{17,18}
The manufacturers of Airsonett have conducted an economic analysis of its use in the UK. Data from the unpublished German study (n=30) was used to examine the impact of Airsonett on disease control and resource utilisation, and estimate cost-effectiveness.\textsuperscript{15} The analysis found that the £2,088 annual cost of Airsonett was partially offset by decreased healthcare costs of £1,535. The net cost to the NHS is therefore estimated at £553 per patient, with an incremental cost-effectiveness ratio (ICER) of £8,998 per quality-adjusted life year (QALY). NICE generally considers interventions costing less than £20,000 to be cost effective.

When split by treatment cost per episode, the analysis found that Airsonett was cost saving in the top quartile of patients, at -£151 per year (see table 3). The analysis assumed these patients had the most severe disease, and that they could be identified and targeted for treatment. The economic analysis is limited by the study it is based upon, as discussed above. The net cost in the bottom quartile was £973 per patient per year (£15,829 per QALY), but this group is unlikely to be in the target population for Airsonett in the UK.

Table 3: Cost-effectiveness of Airsonett in the NHS

<table>
<thead>
<tr>
<th>Severity of condition</th>
<th>Net cost (saving) per person per year</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>£553</td>
<td>£8,998</td>
</tr>
<tr>
<td>Top quartile</td>
<td>(£151)</td>
<td>Dominant</td>
</tr>
<tr>
<td>Second quartile</td>
<td>£524</td>
<td>£8,527</td>
</tr>
<tr>
<td>Third quartile</td>
<td>£822</td>
<td>£13,365</td>
</tr>
<tr>
<td>Bottom quartile</td>
<td>£973</td>
<td>£15,829</td>
</tr>
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</table>

A second cost-effectiveness report was conducted in Sweden, but only a summary is available.\textsuperscript{19} It reports that Airsonett costs approximately 33,000 Swedish krona (SEK) per year (£2,608). Compared to placebo, the ICER for Airsonett was 350,000 SEK (£27,757) per QALY when considering savings in both direct and indirect costs, and 460,000 SEK (£36,341) per QALY when considering direct savings only. In the absence of any direct comparisons between omalizumab and Airsonett an indirect comparison was made, which assumed comparable clinical effectiveness. Trials of omalizumab found that 61-77\% of patients had an improvement of ≥0.5 points on an appropriate AQLQ test after 28-52 weeks treatment.\textsuperscript{17} This improvement is similar to the outcome of the pivotal Airsonett trial and suggests the comparison is reasonable. Assuming a person weighing 41-90kg and with an IgE value of 101-200 IU/mL, omalizumab costs 96,000 SEK (£7,588) per person per year. Omalizumab therefore costs approximately three times as much for an assumed similar benefit in quality of life. However, there is also consistent evidence that omalizumab reduces the exacerbation rate in treated patients. Such evidence is lacking for Airsonett.

Omalizumab is currently recommended by NICE as an option for patients with confirmed allergic IgE-mediated asthma, as an add-on to optimised therapy at BTS/SIGN stage 5. Omalizumab should be used only when it is available with the discount agreed in the patient access scheme. The comparative cost-effectiveness
of omalizumab may therefore be substantially different in the UK than in the above analysis.

**Patient impact**

The Airsonett device is large, and is designed to be installed in a bedroom and left in situ. Patients are therefore unable to use it during trips away from home, making it potentially unsuitable for patients who travel frequently. The mean number of days the device was used in the pivotal trial was not reported, but the per protocol analysis (which excluded patients with <80% compliance) showed a similar treatment effect to the ITT population. It is therefore not clear how frequently the device must be used to achieve a good treatment effect.

No safety issues were identified in either trial. Current treatment options for patients with inadequate asthma control at BTS/SIGN step 4 include omalizumab, oral steroids, or bronchial thermoplasty. All have drawbacks such as adverse drug effects or need for invasive treatment, therefore use of a non-invasive non-pharmacological therapy may be appealing to some patients. Omalizumab is administered by a nurse or other health professional once every 2-4 weeks, which some patients may find inconvenient.

The cost of running the Airsonett device will likely be borne by the patient, but should be reasonably low. Assuming an electricity cost of 14p per kWh, power consumption of 60-90W and average of 8 hours use per night, estimated running costs are approximately £25-34 per year.²⁰

**Sleep quality**

The device is relatively quiet, reportedly producing approximately 38 decibels of sound while in use. For comparison, WHO guidelines state that sounds of 30 decibels and louder have a measurable effect on sleep. They recommend that background noise in a hospital ward should not exceed 30 decibels during the night, with peaks of no more than 40 decibels. Discontinuation due to noise was low in both arms (see safety section above), but the study did not report how many people were disturbed but did not discontinue. The relatively low dropout rate suggests that most people may be either undisturbed, or habituated to the sound of the device.

The manufacturers claim that there is no discernible draught associated with use of the device, since the cooled, filtered air is not propelled but is allowed to sink under gravity. There were 4 dropouts (2.1%) due to draught in the active arm, and none in the placebo arm. Since the placebo device was identical to the active one, but did not cool or filter the air, this suggests that Airsonett does produce a strong enough draught to be disturbing to a small proportion of people.

**Points to consider**

Airsonett is intended to be used by patients with allergic asthma and poor control despite optimised pharmacotherapy at BTS/SIGN step 4, and who would otherwise be considered for continuous or frequent oral steroids, omalizumab, or bronchial thermoplasty.
The largest trial to date found that after one year of use patients using Airsonett were more likely to have improved quality of life than those using a placebo device. The improvement in quality of life appears comparable to that observed in trials of omalizumab.\(^7\) However, there was also a high response rate in the placebo arm of the Airsonett trial, suggesting a response bias may be present. Additionally, omalizumab is also known to significantly reduce rates of exacerbations in people with severe allergic asthma, and to improve rates of severe exacerbations and hospitalisation.\(^7\) Other than a small (n=30), unpublished, uncontrolled study the clinical evidence for Airsonett is limited to quality of life data, with no evidence of improvements in any objective measure other than fractional exhaled nitric oxide. A large UK-based trial of Airsonett’s effect on asthma exacerbation rates is underway, but results are not expected until 2017.

There are no safety concerns regarding use of Airsonett. The device is quiet in operation and creates little draught, but a small proportion of people dropped out of the pivotal trial due to noise or breeze. The device is not portable, and may be unsuitable for patients who travel frequently.

The rental cost of Airsonett is £2,088 per year, including routine maintenance. A cost-effectiveness analysis based on unpublished data reported a net cost of £535 per patient per year, with a corresponding ICER of £8,998 per year. However, the study upon which this analysis is based is small, uncontrolled, unpublished, and it is not clear whether the enrolled patients were adequately representative of the UK population.

Airsonett may be a treatment option for patients with poorly controlled allergic asthma despite high-intensity pharmacotherapy. Current options for these patients include frequent or continuous oral steroids, omalizumab, or bronchial thermoplasty. Omalizumab and bronchial thermoplasty are specialist treatments currently commissioned by NHS England. Careful patient selection will be necessary to ensure that Airsonett is utilised in a cost-effective manner, but such selection is challenging with such a limited body of clinical evidence.

**Author’s declaration:** The author has no relevant interests to declare.

**References**

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17. NICE. TA278: Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201).
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Appendix A: Rating scales used to assess asthma severity and impact

Global Initiative for Asthma (GINA) criteria for asthma control
GINA assessment for asthma control asks whether the patient has experienced any of the following in the preceding 4 weeks:

1. daytime symptoms more than twice per week
2. any night waking due to asthma
3. reliever treatment needed more than twice per week
4. any activity limitation due to asthma

If all answers are no, asthma is considered well controlled. If one or two are answered yes, asthma is considered partly controlled. Answering yes to three or four indicates uncontrolled asthma.

Mini Asthma-Related Quality of Life Questionnaire (mini AQLQ)
The mini AQLQ consists of 15 questions covering 4 domains:

1. symptoms
2. activity limitations
3. emotional function
4. environmental stimuli

Each question is scored from 1-7, with higher scores representing better quality of life. The total score for the questionnaire is usually represented as the mean of the 15 responses. The mini AQLQ is validated in adults.

Paediatric Asthma-Related Quality of Life Questionnaire (PAQLQ)
The PAQLQ consists of 23 questions scored from 1-7, covering the same 4 domains as the mini AQLQ. Scores are again presented as a mean of the responses, with higher scores representing better quality of life. The PAQLQ is validated in children aged 7-17 years.

Asthma Control Test™ (ACT)
The ACT is a brief questionnaire that can be used to assess asthma control. Each of the following questions is ranked by the patient on a scale of 1 to 5, with higher scores representing better control:

1. During the past 4 weeks, how often did your asthma prevent you from getting as much done at work, school or home?
2. During the past 4 weeks, how often have you had shortness of breath?
3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, chest tightness, shortness of breath) wake you up at night or earlier than usual in the morning?
4. During the past 4 weeks, how often have you used your reliever inhaler (usually blue)?

5. How would you rate your asthma control during the past 4 weeks?

A score of less than 20 indicates poor asthma control which requires investigation. A change of 3 points can be considered clinically significant.\textsuperscript{21}
Appendix B: Step-wise asthma treatment approaches

BTS/SIGN asthma treatment steps
Step 1: Mild intermittent asthma – inhaled SABA, as required
Step 2: Regular preventer therapy – add ICS 200-800 micrograms/day BDP equivalent. Start at ICS dose appropriate to severity of disease
Step 3: Initial add-on therapy – add inhaled LABA. Assess control of asthma. Continue LABA if good response. If some benefit from LABA but control remains inadequate, increase ICS dose. If no response to LABA discontinue and increase ICS dose.
Step 4: Persistent poor control – consider trials of increased ICS (up to 2,000 micrograms/day BDP equivalent) or addition of a fourth drug, e.g. leukotriene receptor antagonist (montelukast), theophylline or oral beta 2 agonist.
Step 5: Continuous or frequent use of oral steroids – refer to a specialist in respiratory medicine.

Global Initiative for Asthma (GINA) treatment steps
Step 1: As-needed SABA with no controller
Step 2: Regular low-dose ICS plus as-needed SABA. A leukotriene receptor antagonist (LTRA) such as montelukast may be considered in place of ICS, for certain patients.
Step 3: Low-dose ICS/LABA plus SABA, OR low-dose ICS/formoterol as maintenance and reliever therapy. Other options include low-dose ICS plus LTRA, or low-dose theophylline SR.
Step 4: Low-dose ICS/formoterol maintenance and reliever therapy OR medium dose ICS/LABA plus SABA. Consider adding LTRA or theophylline SR if required. Consider a trial of high-dose ICS if other options do not give good control.
Step 5: Refer for expert investigation and add-on treatment. Add-on treatment may include omalizumab, bronchial thermoplasty or oral corticosteroids.

NB: GINA definition of high-dose ICS includes beclometasone HFA >400 mcg/day, budesonide >800 mcg/day, and fluticasone >500 mcg/day.
Appendix C: Abbreviations

ACT – asthma control test
AQLQ – asthma-related quality of life questionnaire
BDP – beclometasone dipropionate
BTS/SIGN – British Thoracic Society/Scottish Intercollegiate Guidelines Network
FEF$_{50}$ – forced expiratory flow at 50% of vital capacity
FEV$_1$ – forced expiratory volume in one second
GINA – Global Asthma Initiative
ICS – inhaled corticosteroid
LABA – long-acting beta 2 agonist
LAMA – long-acting muscarinic antagonist
LTRA – leukotriene receptor antagonist
PAQLQ – paediatric asthma-related quality of life questionnaire
PEF – peak expiratory flow