NICE advice

Alair bronchial thermoplasty system for adults with severe difficult to control asthma

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Summary

The Alair bronchial thermoplasty system is designed to reduce the amount of smooth muscle in the airway walls, with the aim of improving symptoms in people with severe, difficult to control asthma. Evidence from 3 systematic reviews (reporting on 3 randomised controlled trials of mixed quality) suggests that use of the Alair system is associated with some patient benefits (such as improved quality of life, and morning peak expiratory flow), but not all benefits were considered to be clinically significant. There is mixed evidence in relation to other outcomes (including asthma exacerbations, hospitalisations and emergency department visits).

The procedure must be done 3 times, once every 3 weeks. The device cost for 3 procedures is up to £6,930 (for 3 single-use catheters), with a capital cost of up to £31,500 for the radiofrequency controller. Additional costs include more detailed pre-bronchoscopy assessments, increased patient monitoring and treating short-term adverse events.

Product summary and likely place in therapy	Effectiveness and safety
• The Alair system uses radiofrequency energy (delivered during bronchoscopy procedures) to reduce the amount of smooth muscle in the airway walls. Excessive smooth muscle mass can contract causing breathlessness during asthma attacks. • It is intended for use in adults with severe difficult to control asthma, despite optimal therapy at step 4/5 of the British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines, as an add-on to standard therapy. • NICE interventional procedures guidance on bronchial thermoplasty for severe asthma recommends submitting details of all patients having the procedure to the 'difficult asthma' registry because more evidence is needed on long-term safety.	• The evidence in this briefing is taken from 3 systematic reviews, 2 of which have been published since the development of NICE interventional procedures guidance bronchial thermoplasty for severe asthma in January 2012. The systematic reviews reported on results from 3 randomised controlled trials (N=112, 34 and 288), all 3 of which were available when the NICE guidance was developed. • Pooled results from the 3 trials (N=429) showed patient benefits associated with using bronchial thermoplasty, such as improved quality of life and morning peak expiratory flow, but there is uncertainty about the clinical significance of the benefits. • Pooled results also showed that the risk of hospitalisation for adverse events increased in the first 6 weeks after treatment but not from 6 weeks to 1 year. There was no statistically significant differences in use of rescue medication or asthma control at 1 year. • Pooled results from the 3 trials (N=216) found that people having bronchial thermoplasty experienced had no significant decline in pre- or post-bronchodilator FEV1 over 5 years. The number of ER visits for adverse respiratory events remained unchanged and there was no significant increase in the incidence of hospitalisation for respiratory adverse events.

Technical and patient factors	Cost and resource use
• The Alair system consists of a sterile, single-use catheter and a reusable radiofrequency controller. The catheter is positioned using a bronchoscope. The catheter includes an expandable electrode array which delivers controlled thermal energy from the radiofrequency source to a patient's airways. • Bronchial thermoplasty is delivered in 3 separate procedures, a minimum of 3 weeks apart, to different sections of the lungs. Each session takes between 45 and 60 minutes to complete and typically involves 40 device activations. • The Alair system is the only bronchial thermoplasty system currently available and is indicated for patients aged 18 years and older. The system should be used by respiratory clinicians familiar with bronchoscopy procedures and trained in its use.	• The cost of 3 procedures, each requiring a single-use catheter at £2,310 and a patient return electrode at £4.04, is £6,942.12. There is also a capital cost for the reusable radiofrequency controller of up to £31,500. Assuming a 10-year life for the controller, the associated cost per patient ranges from £157.50 to £315.00, giving a total cost per patient of £7,099.62 to £7,257.12. • In addition to the device costs, patients having bronchial thermoplasty with the Alair system need 3 complex bronchoscopies, follow-up monitoring at a tertiary centre, and treatment of adverse events, if any.

Introduction

Asthma affects 3.4 million people in England (Health and Social Care Information Centre Quality and Outcomes Framework 2015). As observed in NICE technology appraisal guidance on omalizumab for treating severe persistent allergic asthma, prevalence is

highest in children aged 5 to 15 years, and decreases in adulthood until age 55 to 64 years when it rises again. In adults, asthma is more common in women than men (Simpson 2010). Asthma exacerbations lead to costs of £800 million on pharmaceuticals, a direct cost to the NHS of £1 billion and indirect societal costs (time off work and lost productivity) of £6 billion per year (NHS England standard contract 2013). The British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network have produced a joint guideline recommending a stepwise approach in the management of asthma (BTS/SIGN 2014).

Severe, difficult to control asthma affects up to 5% of people with asthma (around 140 people per million population; NHS England standard contract 2013). Patients with severe, difficult to control asthma have ongoing daily symptoms, despite therapy at step 4/5 of the BTS/SIGN guideline, that reduce quality of life and cause fatigue and absence from work (BTS/SIGN 2014). Psychological problems, including stress, anxiety and depression, are up to 6 times more common in people with this condition than in the general population. People with severe, difficult to control asthma are more likely to be admitted to hospital and to need unscheduled care than those with mild or moderate asthma (NHS England standard contract 2013).

Increased airway smooth muscle is a characteristic of asthma, particularly when severe and difficult to control. The contraction of airway smooth muscle during an asthma attack decreases the internal diameter of the airways, making it difficult to breathe (Cox et al. 2007).

There is no cure for asthma. Treatment aims to control symptoms with minimal side effects.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

Bronchial thermoplasty (BT) is a catheter-based bronchoscopy treatment for severe,

difficult to control asthma in adult patients. The Alair system is designed to help control asthma symptoms by delivering thermal energy from a radiofrequency source to reduce the amount of excess airway smooth muscle.

CE marking

The Alair BT catheter (class IIb), radiofrequency controller (class IIb) and accessory kit (class I) were first CE marked to Asthmatx, the original developer of the Alair system, in November 2002. Boston Scientific acquired Asthmatx in October 2010. The current certification, issued to Boston Scientific in July 2014, is valid until December 2018.

Description

The Alair system consists of 2 main components:

- A sterile, single-use Alair catheter designed to be deployed through a standard bronchoscope. The catheter delivers radiofrequency energy through an electrode array, which expands against the airway wall to deliver energy and contracts to enable repositioning. The catheter has 4 marker bands, spaced 5 mm apart, to aid positioning for energy delivery at adjacent sites across the target airway.
- A reusable Alair radiofrequency controller designed to connect all system components and to provide temperature-controlled delivery of the thermal energy. The controller front panel includes 3 separate connectors for the Alair catheter, a gel-type patient return electrode (supplied by third-party manufacturer) used to complete the radiofrequency circuit, and a footswitch allowing the operator to start and stop thermal energy delivery. The controller incorporates a temperature control algorithm, which uses temperatures measured every 0.02 seconds by a thermocouple attached to one of the catheter electrodes. The algorithm automatically adjusts and delivers low power (up to 18 Watts), temperature-controlled radiofrequency energy to the airway at 65°C for 10 seconds. There are no user controls for these parameters. A small display counter indicates the number of complete activations during the procedure.

The Alair system delivers BT in 3 separate treatment sessions to different sections of the lungs. The first procedure treats the airways in the right lower lobe, the second treats the airways in the left lower lobe, and the final procedure treats the airways in both upper lobes. Each session is routinely done under moderate sedation and typically takes 45 to 60 minutes.

Patients are given 40 mg to 50 mg corticosteroids daily for 3 days before the procedure, on the day of the procedure and on the day after the procedure to minimise post-procedure inflammation.

During the BT procedure, a flexible bronchoscope is introduced into the patient's airways through the nose (or mouth if nasal access is difficult). The bronchoscope is then positioned at the first target treatment site, typically the most distal airway in the targeted lobe. The Alair catheter is introduced under direct visualisation through the bronchoscope working channel. Once in position, the electrode array is expanded until all electrodes are seen to be in contact with the airway wall. The operator presses the footswitch once to start automatic delivery of thermal energy and again to manually stop treatment, if necessary. The controller will automatically cease energy delivery if it detects atypical delivery or temperature response. The controller provides audio and visual user alerts to indicate correct energy delivery or if electrodes need to be redeployed. Following energy delivery, the electrode array is retracted and the catheter is repositioned (using the 5 mm marker bands as a guide) before the array is expanded again ready for the next activation. This process is repeated until the target lobe is fully treated, which typically involves 40 device activations.

Setting and intended use

BT is usually done as a day case at tertiary respiratory centres. Three treatments are needed, scheduled a minimum of 3 weeks apart. The Alair system is indicated as an add-on therapy for treating severe difficult to control asthma in patients aged 18 years and older, whose asthma is not well controlled despite management at step 4/5 of the BTS/SIGN guidelines.

The system is intended to be used by qualified respiratory clinicians with experience in bronchoscopy procedures and who are specifically trained to use the Alair system. The manufacturer advises that in the NHS, most procedures are done by 2 respiratory consultants plus a nurse. There may also be an additional nurse, operating department practitioner or a specialist registrar present.

The manufacturer has listed 6 contraindications to the BT procedure using the Alair system:

- presence of a pacemaker, internal defibrillator, or other implantable electronic devices

- known sensitivity to medications needed for bronchoscopy, including lidocaine, atropine and benzodiazepines
- repeat treatment (areas previously treated with the Alair system should not be treated again because of a lack of clinical data on safety and effectiveness of repeat treatments)
- active respiratory infection
- asthma exacerbation or changing dose (up or down) of systemic corticosteroids for asthma in the past 14 days
- known coagulopathy.

Current NHS options

Current NHS standard therapy for asthma follows the stepwise approach in the BTS/SIGN guidelines (BTS/SIGN guideline 2014). Severe, difficult to control asthma is recognised as an area of unmet therapeutic need (NHS England standard contract 2013). Current NHS standard therapy for severe asthma is inhaled high-dose corticosteroids, long-acting beta 2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids and smoking cessation if clinically appropriate (NICE asthma pathway 2016). NICE's technology appraisal guidance on omalizumab for treating severe persistent allergic asthma recommends the drug as an option when given as an add-on to optimised standard therapy in people 6 years and older, with confirmed presence of a perennial allergy, who need frequent treatment with oral corticosteroids.

Currently BT is available in around 9 tertiary respiratory centres in England, with over 215 procedures done (Burn et al. 2015).

NICE has issued interventional procedures guidance on bronchial thermoplasty for severe asthma that states the procedure should only be used with special arrangements for clinical governance, consent and audit or research. Actions required include submitting details of all patients having the procedure to the 'difficult asthma' registry.

NICE is not aware of any other CE-marked devices that have a similar function to the Alair system.

Costs and use of the technology

The cost of 3 procedures requiring single-use catheters at £2,310 each and a patient return electrode at £4.04 each is £6,942.12. Use of the Alair system also requires an initial capital cost (a one-time payment) of up to £31,500 for the radiofrequency controller. Assuming a 10-year lifespan for the radiofrequency controller and that each centre does 30 to 60 procedures each year (10 to 20 patients), the cost ranges from £157.50 to £315.00 per patient. The estimated total cost per patient thus ranges from £7,099.62 to £7,257.12.

Hospitals may choose to buy a service agreement at a cost of £1,663 to £1,950 per year depending on its length. This covers the cost of replacing a controller or parts of the controller if anything goes wrong. No servicing or maintenance is needed. The manufacturer provides initial set-up and training, education and ongoing clinical support at no extra cost.

Each BT procedure requires a pre-assessment review and up to 4 follow-up visits in the first year, as well as the procedure itself. This assumes the assessment is informed by standard investigations and no additional investigations are needed at follow-up. In 2014/15, the mean cost for a therapeutic bronchoscopy was £746 and the mean cost for a respiratory medicine outpatient appointment was £156 (Department of Health, 2015). If all appointments are assumed to be in addition to the current care pathway, the cost consequences are about £1,525 per patient, falling to about £900 if only the pre-assessment visit and procedure are considered additional to the current pathway. In practice, most patients are under regular follow-up so the 4 visits would not be additional.

Further resources and costs should be considered to manage respiratory adverse events during treatment.

Additional costs include the staffing and resource requirements associated with complex bronchoscopy procedures, particularly more detailed pre-bronchoscopy assessments and increased monitoring of patients (NIHR 2011). An estimate based on clinical trial data suggests that around 3.4% of bronchoscopies may result in a hospitalisation (NIHR 2011).

Potential savings arise from fewer subsequent attendances at primary care and unscheduled care through reduced symptoms and possibly fewer hospital admissions for severe asthma exacerbations (NIHR 2012).

Likely place in therapy

BT (and therefore the Alair system) is used in specialist centres that manage severe difficult to control asthma, as an add-on treatment at step 4/5 of the BTS/SIGN guidelines. This may include frequent courses of oral corticosteroid or maintenance oral corticosteroid with documented evidence of medication adherence, following systematic specialist review of symptoms. Patient selection and treatment is done by a specialist respiratory team.

Specialist commentator comments

One specialist commentator noted that the estimate of 3.4% of bronchoscopies resulting in hospitalisation assumes that patients have the same severity as those from the clinical trials that informed the estimate. The commentator advised that currently, most cases treated are materially more severe than those included in clinical trials, having higher baseline exacerbation and hospitalisation rates than patients in the trials. The cost calculation using clinical trial data may thus underestimate the potential reduction in emergency room and hospital admissions given that the baseline is substantially higher. The specialist added that competing treatments may need more intensive management than BT; for example, omalizumab requires around 16 visits for 2- to 4-weekly subcutaneous injections.

Two specialist commentators advised that a UK cost analysis using patients in the BTS difficult asthma registry is underway, with one adding that the current cost estimate for the BT package in their centre is about £13,000 per patient for all treatments and clinic visits.

Three commentators noted there are no phenotypes or biomarkers to direct clinicians as to which patients are most suitable for BT. One specialist commentator suggested that BT should be indicated when asthma is not well controlled despite treatment with inhaled corticosteroids and when other standard add-on therapies (such as leukotriene-antagonists, anti-muscarinic inhalers and theophyllines) have been tried.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In

producing guidance and advice, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

The device is indicated for treating severe asthma only in people aged 18 years and older. Age is a protected characteristic under the Equality Act (2010).

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device.

A search for 'Alair' in the 'brand name' field of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE) identified 237 records between 1 January 2008 and 31 October 2015.

Reported event types included:

- Injury (232 records): including asthma exacerbation, atelectasis, pneumonia upper respiratory tract infection, bronchitis, haemoptysis and chest pain.
- Malfunction (3 records): 5 mm black marker bands wearing off the catheter (with no manufacturer response).
- Death (2 records): 1 cardiac-related death (unrelated to the procedure) and 1 death in a patient with end-stage renal failure (a patient subgroup in whom safety had not been determined in the existing trials).

The manufacturer's responses and conclusions to the adverse event reports were as follows:

- product not returned; no device failure analysis conducted (132 records)
- known risk (86 records)
- not reported (7 records)
- operational context (3 records)
- inconclusive (2 records)
- patients with condition not studied; safety not determined in patient group (2 records)
- no longer a reportable event (1 record)
- product returned; analysis ongoing (1 record)
- report withdrawn by user (1 record)
- user did not follow procedure medication guidelines (1 record)
- device passed testing; event reported is a known risk (1 record).

Of the total 237 records, 77 (33%) were reported for a first BT procedure, 61 (26%) for a second, 77 (33%) for a third and 1 (0.4%) for a fourth. The frequency of BT procedure was not reported in the other 22 records.

It should be noted that the MAUDE database is a passive surveillance system and potentially includes incomplete, inaccurate, untimely, unverified or biased data. The incidence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device used.

Clinical evidence

Of the papers reviewed, 12 met the criteria for inclusion in this briefing. Three were systematic reviews: 2 (Torrego et al. 2014, Wu et al. 2011) presented meta-analyses of data from 3 randomised controlled trials (Cox et al. 2007, Pavord et al. 2007, Castro et al. 2010) and 1 compared data at 1- and 5-year follow-up after BT for intervention group patients (but not for controls) from the same 3 randomised controlled trials (Zhou et al.

2015). Three were randomised controlled trials (Cox et al. 2007, Pavord et al. 2007, Castro et al. 2010) and 4 reported on follow-up studies (Thomson et al. 2011, Pavord et al. 2013, Castro et al. 2011, Wechsler et al. 2013) from the same 3 trials. The remaining 2 papers were economic analyses (Zein et al. 2015, Zafari et al. 2016).

The randomised controlled trials and follow-up studies are not discussed separately in this briefing because they were included in the systematic reviews.

A Cochrane review (Torrego et al. 2014) of randomised controlled trials comparing BT to any active control in adults with moderate or severe difficult to treat asthma included the 3 randomised controlled trials described above (n=429). Results were pooled and it was found that quality of life scores (Asthma Quality of Life Questionnaire [AQLQ]) were significantly better after BT (weighted mean difference [WMD] 0.28, p=0.01) but the size of the difference was not clinically significant. BT increased the risk of hospitalisation for adverse events during the treatment period (BT: 9.2% [24/260], control: 2.4% [4/169]; relative risk 3.50, p=0.016). Most adverse events resolved within 1 week. The risk of hospitalisation after the treatment period was similar in the 2 groups (BT: 4.2% [11/260], control: 4.1% [7/169]), as was use of rescue medication at 1 year (WMD −0.68, p=0.65). There was no significant difference in Asthma Control Questionnaire (ACQ) scores over 1 year (pooled WMD from the 3 trials −0.15, p=0.23).

For some outcomes in the Torrego et al. (2014) review, results from the 3 trials could not be pooled and so the studies were presented individually. The largest study (Castro et al. 2010) found that BT was associated with a reduction in the proportion of people experiencing severe exacerbations at 1 year (26% of patients in the BT arm compared with 40% in the control arm). The follow-up study from this trial (Wechsler, 2013) reported that this reduction in severe exacerbations was maintained after 5 years (30.9% of patients in the BT arm compared with 51.6% in the BT group in the year before to BT therapy). In the Cox et al. (2007) study, there was no statistically significant differences between groups in terms of number of severe exacerbations per patient, with patients in both groups having fewer severe exacerbations at 12 months. Castro et al. (2010) showed a significant reduction in proportion of patients visiting the emergency department for respiratory symptoms over 12 months following BT (BT: 8.4%, sham treatment: 15.3%).

An earlier systematic review by Wu et al. (2011) included randomised controlled trials that compared BT with any active control in adults with moderate or severe persistent asthma, and included the same 3 randomised controlled trials. Results were reported for AQLQ and hospitalisations for respiratory adverse events, which were similar to those reported in the

Cochrane review by Torrego et al. (2014). The authors calculated the number needed to harm and reported that there would be 1 extra hospitalisation per year for respiratory adverse events during treatment for every 15 patients having BT. The pooled results from the 3 randomised controlled trials showed that BT had a significant benefit on morning peak expiratory flow at 1 year (WMD 21.78 l/min; p=0.002).

A third systematic review (Zhou et al. 2015) included randomised controlled trials of adults with moderate to severe persistent asthma who had BT at least once using Alair system, and included and pooled data from the 3 randomised controlled trials from patients having BT (n=249) who had data at 5-year follow-up (n=216) compared with data at 1 year (not compared with the original the control group). There was no significant decline over time in pre-bronchodilator forced expiratory volume in 1 second ($FEV_{1;}$ WMD −0.75, p=0.57) or post-bronchodilator FEV_1 (WMD −0.62, p=0.65). The number of emergency room visits for adverse respiratory events remained unchanged (relative risk 1.06, p=0.71) and there was no significant increase in the incidence of hospitalisation for respiratory adverse events (relative risk 1.47, p=0.32).

These 3 systematic reviews are summarised in the appendix.

A specialist commentator identified a recent audit (published in December 2015, after the search cut-off date) comparing safety and efficacy outcomes, 12 months after BT, in 10 clinic patients and 15 patients recruited to clinical trials at the same UK centre. Baseline asthma severity was greater in the clinic group. Clinical improvements occurred in 50% of the clinic patients compared with 73% of the research patients (Bicknell et al. 2015).

Recent and ongoing studies

Eleven ongoing or in-development trials on BT using the Alair system for severe asthma were identified in the preparation of this briefing (see table 1).

Table 1 Recent and ongoing studies of the Alair system

Study name	Design	Inclusion criteria	Outcomes	Estimated completion

Bronchial thermoplasty for severe asthma (BTS difficult asthma registry)	Prospective, open-label, single-arm using patients from British Thoracic Society difficult asthma registry	Adults scheduled to have BT at a UK centre	Respiratory adverse events, lung function, AQLQ scores, unscheduled healthcare use, hospital admissions for respiratory cause, rescue medication use and days lost from normal activities	March 2017
Bronchial Thermoplasty Global Registry	Prospective, open-label, single-arm, observational registry. to collect outcome data and clinical and demographic characteristics of patients having BT	Adults scheduled to have BT at a UK centre	Primary: proportion of patients with severe exacerbations at 1 and 2 years after BT. Secondary: AQLQ and ACT scores, emergency department visits, unscheduled office visits and hospitalisations for asthma symptoms and pre- and post-bronchodilator FEV_1 at 2 years	December 2018

Bronchial Thermoplasty in Severe Persistent Asthma (PAS2)	Phase IV open-label, single-arm study, 284 patients, 27 centres in the US with 5-year follow-up	Adults with severe persistent asthma having BT	Severe exacerbations. Secondary: respiratory adverse events, emergency room visits, hospitalisations and FEV_1	December 2019
Bronchial Thermoplasty: Effect on Neuronal and Chemosensitive Component of the Bronchial Mucosa	Open-label, single-arm study, 12 patients in Italy	Patients with severe persistent uncontrolled asthma	Analysis of the risk and benefit profile with ACT and AQLQ questionnaires at 1 year	December 2015. (See Facciolongo et al. [2015])
Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma	Randomised controlled trial, comparing immediate BT treatment with BT treatment delayed to week 25. 40 patients, 3 European centres	Adults with asthma having maintenance medication including systemic corticosteroids	Primary: change in ASM mass. Secondary: $FEV_{1,}$ ACQ and AQLQ; healthcare utilisation and rescue medication use	April 2018

Study of Physiopathological Mechanisms and Results of Treatment With Bronchial Thermoplasty in Severe Asthma	Open-label, single-group biological study, 15 patients, 1 Spanish centre	Adults with severe persistent asthma	Primary: change from baseline in bronchial smooth muscle at 6 months post-treatment. Secondary: AQLQ, ACT, number of exacerbations, number of hospitalisations, respiratory function, radiological findings (thorax HRCT scan) and biological inflammatory markers at 6 months	September 2016
Bicentric Prospective Study, Evaluating Bronchial Thermoplasty in a Patient Presenting Severe Uncontrolled Asthma	Prospective, 80 patients in 2 centres in France	Adults with severe difficult to control asthma	Primary: reduction in smooth muscle surface area. Secondary: AQLQ and ACQ, severe exacerbations, respiratory function, use of rescue medication, emergency room visits and hospitalisations	November 2015 (see Pretolani et al. [2014])

A Prospective Observational Study of Biopredictors of Bronchial Thermoplasty Response in Patients With Severe Refractory Asthma (BTR Study)	Prospective, 1-year, observational study. 70 patients, 7 US centres	Adults with severe difficult to control asthma	Primary: relationship between baseline clinical, physiologic, biologic and imaging markers and response to BT, defined as improvement in asthma quality of life. Secondary: baseline predictors of severe exacerbations, healthcare utilisation, safety, and predictive models of response to BT	August 2018
Efficacy of Bronchial Thermoplasty in Korean	Open-label single-group treatment study. 9 patients at 1 Korean centre	Patients with severe difficult to control asthma	Primary: Quality of Life Questionnaire for Adult Korean Asthmatics at 3 months. Secondary: the same measure at 6 months and acute exacerbations at 3 and 6 months	February 2015

Bronchial Thermoplasty for Severe Asthma With Dynamic Hyperinflation	Open-label single-group study. 15 patients in 1 French centre	Adults with severe difficult to control asthma	Primary: evolution of dynamic hyperinflation at 3 months. Secondary: description of the structural modification of the bronchial wall induced by BT, ACQ and AQLQ	December 2018
Bronchial Thermoplasty in Severe Asthma With Frequent Exacerbations	Randomised controlled trial. 34 patients with severe difficult to control asthma in 1 French centre	–	Primary: severe exacerbation rate. Secondary: FEV_1, ACQ and AQLQ, structural airway remodelling and inflammatory cells and markers in induced sputum	The estimated study completion date is November 2018
Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Qu Questionnaire; BT, bronchial thermoplasty; FEV_1, forced expiratory volume in 1 second; GRCT, hi computed tomography.				

Costs and resource consequences

Two economic analyses were identified, both set in the US. Zein et al. (2015) assessed the 10-year cost effectiveness of BT compared with usual care for a hypothetical cohort of 41-year old patients with severe, uncontrolled asthma. The authors used: efficacy and safety data from the trial by Castro et al. (2010), which was done in multiple countries; a US healthcare payer perspective; average Medicare reimbursement rates; and 2013 price levels. Compared with usual care, BT resulted in more quality-adjusted life years (6.40 compared with 6.21) and a higher cost ($7,512 [£5,067] compared with $2,054 [£1,385]) per patient. The incremental cost-effectiveness ratio (ICER) for BT at 10 years was $29,821 (£20,114) per quality-adjusted life year gained. The authors concluded that in the US, BT is

a cost-effective treatment for severe asthma in people at high risk of exacerbations (at least 0.63 per year), if the 3 BT procedures in total cost no more than $10,384 (around £7,000). The study was funded by Federal grants and no conflicts of interest were declared.

Zafari et al. (2016) evaluated the 5-year cost effectiveness of standard therapy, BT and omalizumab for moderate to severe uncontrolled asthma. The perspective was the healthcare system and costs were 2013 US dollars. The ICER for BT compared with standard therapy was US $78,700 (£53,083) per quality-adjusted life year. The ICER for omalizumab compared with BT was US $3.86 million (£2.60 million) per quality-adjusted life year.

Strengths and limitations of the evidence

One high-quality Cochrane systematic review (Torrego et al. 2014) and another moderate quality systematic review (Wu et al. 2011) compared BT and control group data from the same 3 randomised controlled trials (Cox et al. 2007, Pavord et al. 2007 and Castro et al. 2010). The 3 trials included patients with different severities of asthma, were limited in size, underpowered to examine important outcomes and 2 (Cox et al. 2007 and Pavord et al. 2007) had no sham intervention. Unpublished studies were not included. A third systematic review of moderate quality (Zhou et al. 2015) compared data for thermoplasty patients at 1 and 5 years after the procedure, with no data from the control patients. In this review, the authors used a denominator of '1,715' to compare the number of adverse events, but it is unclear what this denominator represents. We did not find any high-quality long-term comparative evidence.

Relevance to NICE guidance programmes

NICE is developing a clinical guideline on asthma management, with an anticipated publication date of 2017.

NICE has issued the following guidance:

- Bronchial thermoplasty for severe asthma (2012) NICE interventional procedure guidance 419
- Asthma management (2016) NICE pathway

- Omalizumab for treating severe persistent allergic asthma (2013) NICE technology appraisal guidance 278

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Appendix

Contents

Data tables

Table 2 Summary of the Torrego et al. (2014) systematic review and meta-analysis

Study component	Description
Objectives/ hypotheses	To determine the efficacy and safety of BT in adults with bronchial asthma.
Study design	Systematic review and meta-analysis.
Inclusion/ exclusion criteria	RCTs that compared BT versus any active control in adults with moderate or severe persistent asthma were included.
Primary outcomes	Quality of life (AQLQ), asthma control (ACQ), asthma exacerbations and adverse events.
Statistical methods	Meta-analyses using a random-effects model using the inverse variance method.
Participants	3 RCTs (429 participants) with differences in design (2 RCTs compared BT vs. medical management and the other vs. a sham intervention) and participant characteristics (1 RCT included only participants with severe difficult to control asthma; the other 2 included patients with less severe asthma).

Results: Quality of life (AQLQ final scores) at 12 months	WMD score +0.28 points, 95% CI 0.07 to 0.50; p<0.01 but not clinically significant.
Results: Symptom control (ACQ scores)	WMD -0.15, 95% CI -0.40 to 0.10; p= 0.23.
Results: Exacerbations at 12 months (data not pooled)	AIR trial (Cox et al. 2007): Mild exacerbations during a 2-week period in which LABA was withdrawn: BT: -0.16 ± 0.37 vs. control: 0.04 ± 0.29, p<0.05. Severe exacerbations: BT: 0.01 ± 0.08 vs. control: 0.06 ± 0.24, NS. AIR2 trial (Castro et al. 2010): Patients with severe exacerbations: BT 50/190 (26.3%) vs. control: 39/98 (39.8%). Rate of severe exacerbations per patient per year: 0.48 ± 0.067 vs. 0.70 ± 0.122, p<0.05.
Results: Hospitalised for an adverse event during treatment period	BT: 24/260,[a] control: 4/169;[a] RR 3.50 (95% CI 1.26 to 9.68), p=0.016.
Results: Hospitalised for an adverse event during post-treatment period	BT: 11/260;[a] control: 7/169;[a] RR 1.12 (95% CI 0.44 to 2.85), p=0.82.

Results: Visits to the emergency department during post-treatment period (data from 1 trial only)	AIR2 trial (Castro et al. 2010): BT: 0.07 visits/year (8.4% of patients), sham treatment: 0.43 visits/year (15.3% of patients).
Results: Use of rescue medication at 12 months of follow-up (short-acting bronchodilator puffs per week)	WMD: -0.68 (95% CI -3.63 to +2.28), p=0.65.
Results: Hospitalised for an adverse event during 5 year follow-up period (data from 1 trial only)	(Pavord et al. 2007): overall rate of 0.23 hospitalisations per patient per year during 5 years following BT compared with 0.71 hospitalisations per patient per year before BT (BT patients only).
Results: Severe exacerbations during 5 year follow-up period (data from 1 trial only)	AIR2 trial (Castro et al. 2010): 30.9% of BT patients in the year after BT (and maintained during the 5 year follow-up) compared with 51.6% of BT patients in the 12 months before BT.

Conclusions	BT for patients with moderate to severe asthma provides a modest clinical benefit in quality of life and lower rates of asthma exacerbation, but no significant difference in asthma control scores. The quality of life findings are at risk of bias, as the main benefits were seen in the 2 studies that did not include a sham treatment arm. BT increases the risk of adverse events during treatment but has a reasonable safety profile after completion of the bronchoscopies. The overall quality of evidence is moderate. Patient data should be collected by independent clinical registries.
Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BT, bronchial thermoplasty; CI, confidence interval; LABA, long-acting β2-adrenergic agonists; NS, not statistically significant; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference. [a]Denominator is all randomised patients.	

Table 3 Summary of results from the Wu et al. (2011) systematic review and meta-analysis

Study component	Description
Objectives/ hypotheses	To evaluate the efficacy and safety of BT in the treatment of patients with moderate to severe persistent asthma.
Study design	Systematic review and meta-analysis.
Inclusion/ exclusion criteria	RCTs that compared BT versus any active control in adults with moderate or severe persistent asthma were included.
Primary outcomes	AQLQ scores.
Statistical methods	ITT analysis; heterogeneity assessed; when hypothesis of homogeneity was not rejected, a fixed-effects model used; otherwise random effects model used.

Participants	3 RCTs (421 participants) with differences in design (2 RCTs compared BT vs. medical management and the other vs. a sham intervention) and participant characteristics (1 RCT included only participants with severe difficult to control asthma; the other 2 included patients with less severe asthma).
Results: Quality of life (AQLQ change scores) at 12 months	BT vs. maintenance medication (2 trials): WMD 0.86 (95% CI 0.47 to 1.25); p<0.01. BT vs. sham BT treatment (1 trial): BT: 1.35 ± 1.10; sham: 1.16 ± 1.23 (posterior probability of superiority, 96.0%).
Results: Mean improvements in morning PEF at 12 months	BT vs. either comparator (3 trials): WMD 21.78 l/min; 95% CI 8.06 to 35.50, p = 0.002.
Results: Total number of respiratory adverse events in treatment period (6 weeks)	BT vs. either comparator (3 trials): BT: 1113/257; control: 369/164, p value not stated.
Results: Total number of respiratory adverse events in post-treatment period (6 weeks to 1 year)	No increase with BT (data not shown).
Results: Hospitalisations for adverse respiratory events during treatment period	BT: 24/257,[a] control: 4/164;[a] RR 3.78 (95% CI 1.39 to 10.24); p=0.009.

Results: Hospitalisations for adverse respiratory events during post-treatment period	BT: 11/257,[a] control: 7/164;[a] RR 1.15 (95% CI 0.47 to 2.79); NS.
Results: NNH for hospitalisations for adverse respiratory events with BT	15 per year (95% CI 5 to 106).
Conclusions	BT significantly improved morning PEF and quality of life at 12 months post-treatment, and was generally well tolerated and safe. The increased risk of transient adverse events after BT was outweighed by the benefits of BT that lasted for more than 1 year. Additional long-term RCTs are required to evaluate further the efficacy and safety of BT.
Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; BT, bronchial thermoplasty; CI, confidence interval; ITT, intention to treat; NNH, number needed to harm; NS, not significant; PEF, peak expiratory flow; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference. [a]Denominator excludes patients lost to follow-up.	

Table 4 Summary of the Zhou et al. (2015) systematic review and meta-analysis

Study component	Description
Objectives/hypotheses	Evaluate the long-term efficacy and safety of BT for patients with moderate to severe asthma.
Study design	Systematic review and meta-analysis.
Inclusion/exclusion criteria	Clinical trials including adults with moderate to severe persistent asthma who had received BT at least once using Alair system.

Primary outcomes	Pre- and post-bronchodilator FEV_1, adverse respiratory events, ER visits and hospitalisations for adverse events.
Statistical methods	ITT analysis; heterogeneity assessed; when hypothesis of homogeneity was not rejected, a fixed-effects model used; otherwise random effects model used.
Participants	3 RCTs (n=249 at 1 year and n=216 at 5 years).
Results: Change between end of year 5 and end of year 1 in pre-bronchodilator FEV_1	WMD -0.75, 95% CI -3.36 to +1.85, p=0.57.
Results: Change between end of year 5 and end of year 1 in post-bronchodilator FEV_1	WMD -0.62, 95% CI -3.32 to +2.08, p=0.65.
Results: Change between end of year 5 and end of year 1 in ER visits for respiratory adverse events	RR 1.06, 95% CI 0.77 to 1.46, p=0.71.
Results: Change between end of year 5 and end of year 1 in hospitalisation for respiratory adverse events	RR 1.47, 95% CI 0.69 to 3.12, p=0.32.
Results: Number of adverse events among patients at year 5 compared to year 1	Year 5: 201/1715 (12%) vs. year 1: 686/1715 (40%); RR 3.41, 95% CI 2.96 to 3.93, p<0.01.[a]
Results: Number of people who experienced adverse events	Year 5 111/216 (51%) vs. year 1 184/249 people (74%).
Conclusions	The authors state that these data demonstrate reasonable long-term benefits of BT with regard to safety and efficacy for patients with moderate to severe asthma. A large clinical study is required to confirm findings.

Abbreviations: BT, bronchial thermoplasty; CI, confidence interval; ER, emergency room; FEV_1, forced expiratory volume in 1 second; ITT, intention to treat; NS, not significant; RCT, randomised controlled trial; RR, risk ratio; WMD, weighted mean difference.

[a]Denominator for the comparison is reported as 1715 at both 1 year and 5 years, but there were only 249 patients at 1 year and 216 patients at 5 years, so it is unclear what the denominator represents.

Search strategy and evidence selection

Search strategy

The search strategy was designed to identify evidence on the clinical and cost effectiveness of the Alair BT System in adults with severe asthma which remains uncontrolled despite the use of inhaled steroids and long-acting beta agonists.

The strategy was developed in MEDLINE (Ovid interface). The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool. The strategy reflected the nature of the MIB assessments as rapid evidence reviews, with a relatively pragmatic approach being taken.

The main structure of the draft strategy comprised 2 concepts:

- Severe persistent asthma in adults
- BT.

The search concepts were combined as follows: severe persistent asthma in adults AND BT.

The strategy also used 3 stand-alone lines which included the asthma subject heading combined with the surgery subheading, the device name, and the previous manufacturer name. These lines were designed to retrieve any studies that may have been missed by the 2 concept approach.

The strategy excluded animal studies using a standard algorithm. Non-English language publications were also excluded from the search results. The search was restricted to studies published from 2006 to date. This date was identified by the research team as the earliest date from which relevant studies on the device would be published.

The performance of the draft Ovid MEDLINE strategy was assessed by checking retrieval of the 9 known, relevant studies identified by the research team at project start. The draft strategy successfully retrieved all 9 of the studies which were included in Ovid MEDLINE.

The final Ovid MEDLINE strategy was translated appropriately for the other databases searched. The PubMed search was limited to records not fully indexed for MEDLINE. Reflecting the scope of MIBs, records indexed as conference-related publication types (conference abstract, conference paper, conference proceeding, conference review) were excluded from the Embase search.

The following databases were searched:

- Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)
- Cochrane Database of Systematic Reviews (Cochrane Library, Wiley)
- Database of Abstracts of Reviews of Effects (Cochrane Library, Wiley)
- Embase (Ovid SP)
- Health Technology Assessment Database (Cochrane Library, Wiley)
- MEDLINE and MEDLINE in Process (Ovid SP)
- NHS Economic Evaluation Database (Cochrane Library, Wiley)
- PubMed.

Evidence selection

A total of 561 records were retrieved from the literature search. After de-duplication, 395 records remained. Two reviewers independently sifted these records and excluded 374 based on the following exclusion criteria:

- articles of poor relevance against the search terms

- publication types that are out of the project scope
- non-English language studies
- conference abstracts
- review protocols
- articles in which neither the abstract nor the full text is freely available online.

Full records were retrieved for the remaining 21 papers, and a second sift was undertaken. Papers were excluded at this stage if they were not randomised controlled trials, systematic reviews of randomised controlled trials or economic evaluations of BT; did not address the population, intervention, comparator and outcomes needed to inform the review; or failed quality assessment. The second sift was also undertaken independently by 2 reviewers. Following the second sift 10 papers were excluded (systematic reviews: Calhoun 2015, Singh 2015, Wilhelm 2015, CADTH 2014, NIHR 2012, Hayes 2012, Hayes 2011, Hayes 2010; economic analyses: Cangelosi 2015 and Menzella 2014.)

The remaining 11 papers comprised 2 systematic reviews and meta-analyses of RCT data (Torrego et al. [2014], Wu et al. [2011]), 1 economic analysis (Zein et al. [2015]), 3 RCTs (Cox et al. [2007; AIR trial], Pavord et al. [2007; RISA trial] and Castro et al. [2010; AIR2 trial]) with their 3 follow-up studies (reported in 4 publications: Thomson et al. [2011], Pavord et al. [2013], Castro et al. [2011] and Wechsler et al. [2013]) and one further systematic review that reported data only from intervention group patients (not controls) that compared data from the 5-year follow-up with that from 1 year after thermoplasty (Zhou et al. 2015). Synthesised evidence from the systematic review was used when appropriate. The underlying RCTs and follow-up studies were not described on a study-by-study basis as they were included in the systematic reviews.

The last paper (Zafari et al. 2016) was published and identified after the search date.

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths

and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

Development of this briefing

This briefing was developed for NICE by Newcastle and York External Assessment Centre. The interim process & methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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Declarations of interest

No relevant interests declared.

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