NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of bronchial thermoplasty for severe asthma

Asthma affects the small tubes (airways) that carry air in and out of the lungs. In severe asthma the lining of the airways becomes inflamed and swollen. This narrows them and makes it harder for air to pass through. Muscle tissue lining the airways may become thickened, narrowing the airways even more. This procedure involves applying thermal energy (heat) to the airway lining. The aim is to reduce the amount of muscle, so there is less to contract and narrow the airway.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the

medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in September 2017.

Procedure name

- Bronchial thermoplasty for severe asthma

Specialist societies

- British Thoracic Society
- Royal College of Paediatrics and Child Health
- British Paediatric Respiratory Society
- Royal College of Physicians.

Description of the procedure

Indications and current treatment

Asthma is a long-term condition of the airways in the lungs that affects children, young people and adults. It consists of inflammation and constriction of the smooth muscle in the airway walls (bronchoconstriction). This is triggered by increased responsiveness of the airways to various allergic stimuli, leading to airflow obstruction. Symptoms include recurring episodes of wheezing, breathlessness, chest-tightness and coughing.

Asthma is diagnosed and its severity assessed on the basis of symptoms and objective tests of lung function.

Treatment, including advice about lifestyle changes, aims to reduce the frequency and severity of attacks, allowing the person to lead a normal and active life. In the UK, treatment for asthma follows NICE guideline 80 and guidelines from the Global Initiative for Asthma.

Asthma is managed using a step-up approach. Mild intermittent asthma is treated using inhaled short-acting beta-2 agonists (bronchodilators) as needed (step 1). Step 2 includes inhaled corticosteroids in the treatment. Step 3 adds an additional therapy such as inhaled long-acting beta-2 agonists. At step 4, high-dose inhaled corticosteroids are used and an additional drug may be added such

as a leukotriene receptor antagonist or theophylline. At step 5, continuous or frequent courses of oral corticosteroids are needed.

What the procedure involves

The aim of bronchial thermoplasty for severe asthma is to reduce the smooth muscle mass lining the airways, decreasing their ability to constrict.

The procedure is usually done with the patient under sedation or general anaesthesia. A catheter is introduced into the bronchial tree. Short pulses of radiofrequency energy are applied circumferentially to sequential portions of the airway wall, moving from the distal to the proximal bronchi. Treatment is usually delivered in 3 sessions with an interval of at least 3 weeks between each session. After the first session, treated airways are evaluated by bronchoscopy before proceeding with further treatment.

Outcome measures

Asthma Specific Quality of Life Questionnaire (AQLQ)

Questionnaire used to assess functional problems (physical, emotional, social and occupational) associated with asthma in adults. There are 32 questions in 4 domains: symptoms, activity limitation, emotional function and environmental stimuli. The activity domain contains 5 ‘patient-specific’ questions. This allows patients to select 5 activities in which they are most limited and these activities are assessed at each follow-up. Patients are asked to think about how they have been during the previous 2 weeks and to respond to each of the 32 questions on a Likert scale from 7 (not impaired at all) to 1 (severely impaired). The overall AQLQ score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains. Higher scores indicate better quality of life. A difference in score of 0.5 for overall quality of life and for each of the individual domains is often considered the minimally important clinical difference.

Asthma Control Questionnaire (ACQ)

The ACQ has 7 questions (the top scoring 5 symptoms, forced expiratory volume in 1 second [FEV_1] percentage of predicted, and daily rescue bronchodilator use).

Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale from 0 (no impairment) to 6 (maximum impairment). Clinic staff score the FEV_1 percentage predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

Short Form (SF) 36

The SF-36 is an indicator of overall health status composed of 10 items. It has 8 scaled scores, which are the weighted sums of the questions in each section. Scores range from 0 to 100 with lower scores meaning more disability and higher scores less disability. The sections included in the questionnaire are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

Lung function tests

Spirometry

Forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) ratio of less than 70% (or below the lower limit of normal if this value is available) is interpreted as positive test for obstructive airway disease (obstructive spirometry). The FEV_1 can be expressed as a percentage of the predictive value which allows classification of the severity of the impairment:

FEV_1 % predicted	**Stage**
More than 80%	Mild
50 to 79%	Moderate
30 to 49%	Severe
Less than 30%	Very severe

Bronchodilator test

The presence of reversible airways obstruction is frequently used to diagnose asthma. This is assessed by looking for change in the person's normal airway indices following administration of a bronchodilator, such as 2.5 mg of nebulised salbutamol. A positive response in adults is defined as a 12% increase in baseline (pre-bronchodilator) FEV_1. An increase of 200 ml or more following the administration of a bronchodilator indicates asthma.

Hospital Anxiety and Depression Scale (HADS)

Questionnaire used to assess anxiety (7 questions) and depression (7 questions) in a general medical population. In both scales, scores less than 7 indicate no anxiety or depression.

Score	Severity
8 to 10	Mild
11 to 14	Moderate
15 to 21	Severe

EuroQoL quality of life questionnaire (EQ-5D)

Standardised instrument for measuring generic health status. The EQ-5D-3L has the following 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has 3 levels: no problems, some problems, or extreme problems. The respondent self-rates their health on a vertical visual analogue scale, with the endpoints labelled 'best imaginable health state' and 'worst imaginable health state'. The score is often converted into an index, with 1 representing perfect health and 0 representing death.

Efficacy summary

Quality of life

In a systematic review (SR) of 3 randomised control trials (RCTs, n=429), quality of life assessed by the Asthma Quality of Life Questionnaire (AQLQ) was

statistically significantly better in patients who had bronchial thermoplasty (BT) compared with standard medical care (SMC) or sham (mean difference [MD] 0.28, 95% confidence interval [CI] 0.07 to 0.5, p=0.0099; I^2=0%), at 12-month follow-up. Mean AQLQ score was 0.28 (0.07 to 0.5) higher in the BT group compared with controls (5.1 to 5.7)[1].

In a case series of 131 patients who had BT, mean AQLQ scores were statistically significantly higher from baseline values by 0.75 at 12-month follow-up (n=28, p=0.0003) but not at 24-month follow-up (mean increase 0.39, n=16, p=0.148). EQ-5D scores were not statistically significantly higher from baseline at 12-month follow-up (mean increase 0.008, n=18, p=0.909) or at 24-month follow-up (mean increase 0.029, n=13, p=0.706). Hospital Anxiety and Depression Scale (HADS) anxiety scores were also not statistically significantly lower from baseline at 12-month follow-up (mean decrease -1.6, n=20, p=0.078) or at 24-month follow-up (mean decrease -0.93, n=14, p=0.216). Also, HADS depression scores were not statistically significantly lower from baseline at 12-month follow-up (mean decrease -1.6, n=20, p=0.047) or at 24-month follow-up (mean decrease -0.57, n=14, p=0.336)[8].

Asthma control

In the SR of 3 RCTs (n=429) asthma control measured using the Asthma Control Questionnaire (ACQ) was not statistically significantly different between patients who had BT and SMC or sham controls (MD -0.15, 95% CI -0.40 to 0.10, p=0.23; I^2=32%) at 12-month follow-up[1].

In the case series of 131 patients who had BT, ACQ scores were not statistically significantly reduced from baseline at 12-month follow-up (mean reduction -0.43, n=36, p=0.083) or at 24-month follow-up (mean reduction -0.26, n=19, p=0.370)[8].

In a case series of 24 patients who had BT, ACQ scores were statistically significantly reduced from baseline (3.3 ± 1.1) at 6-month follow-up (1.5 ± 1.1, p<0.001)[9].

Exacerbations

In 1 RCT (n=112) reported in the SR of 3 RCTs, the mean reduction in mild asthma exacerbations was statistically significantly higher from baseline in patients who had BT (-0.16 ± 0.37 per week) compared with SMC (0.04 ± 0.29 per week, p<0.05) at 12-month follow-up. In the same RCT the number of severe exacerbations was not statistically significantly different in patients who had BT (0.01 ± 0.08 per week) compared with SMC (0.06 ± 0.24 per week, p>0.05). In another RCT (n=288) reported in the same SR, the number of severe exacerbations was statistically significantly lower in patients who had BT (0.48 ± 0.067) than sham (0.70 ± 0.122, p<0.05) at 12-month follow-up[1].

In the case series of 162 patients who had BT there was no statistically significantly difference in the proportion of patients experiencing severe exacerbations at 1-year follow-up compared with 5-year follow-up[3, 4].

A non-randomised comparative study (NRCS) of 380 patients compared outcomes for patients who had BT during the Post-Food and Drug Administration Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma study (PAS 2, n=190) and the Asthma Intervention Research 2 study (AIR 2, n=190). There was a statistically significant reduction in the rate of severe exacerbations from baseline in PAS 2 (74% [141/190] to 40% [67/168], p<0.0001) and in AIR 2 (52% [98/190] to 33% [55/165], p<0.0001) at 3-year follow-up[7].

In the case series of 24 patients who had BT, median rate of exacerbations was statistically significantly reduced from baseline (2, interquartile range [IQR] 2.75) at 6-month follow-up (0, IQR 1, p<0.001)[9].

Lung function tests

The SR of 3 RCTs reported no statistically significant difference in forced expired volume in 1 second (FEV_1) percentage predicted, morning peak expiratory flow and pre-bronchodilator FEV_1 between patients who had BT compared with sham and SMC at 12-month follow-up[1].

In a SR of 6 studies, pre-bronchodilator FEV_1 percentage predicted was not statistically significantly different between 1-year and 5-year follow-up in patients who had BT (weighted mean difference [WMD] 0.75, 95% CI 3.36 to 1.85, p=0.57; I^2=0%). There was also no statistically significant difference in post-bronchodilator FEV_1 percentage predicted between 1-year and 5-year follow-up (WMD 0.62, 95% CI 3.32 to 2.08, p=0.65; I^2=0%)[2].

In an RCT of 69 patients FEV_1, forced vital capacity, total lung capacity and residual volumes remained stable and showed no deterioration over 5 years of follow-up[5].

In a case series of 14 patients mean pre-bronchodilator and post-bronchodilator values did not change over 5 years of follow-up[6].

The NRCS of 380 patients reported no statistically significant difference in spirometric measures of lung function in either PAS 2 or AIR 2. In both studies the post-bronchodilator FEV_1 remained higher than pre-bronchodilator values at all times, indicating reversibility of asthma[7].

In a case series of 131 patients who had BT there was no statistically significant change in FEV_1 percentage predicted from baseline to 12-month follow-up (mean

increase 3.51, n=49, p=0.152) and at 24-month follow-up (mean increase 2.57, n=30, p=0.560)[8].

The case series of 24 patients reported a statistically significant reduction in FEV_1 percentage predicted from baseline (61.8 ± 15.9) at 6-month follow-up (68.7 ± 15.6, p<0.05)[9].

Reduction in asthma medication

In an RCT (n=34) in the SR of 3 RCTs, complete wean from regular corticosteroids was not statistically significantly different in patients who had BT (50% [4/8]) compared with SMC (14% [1/7], p>0.05). In the same RCT, mean reduction in regular oral corticosteroid (OCS) doses was also not statistically significantly different between patients who had BT (63.5 ± 45.4%) and controls (26.21 ± 40.70%, p>0.05) at 12-month follow-up[1]. The SR of 3 RCTs reported that the mean use of rescue medication was not statistically significantly different between patients who had BT compared with SMC or sham (MD -0.68, 95% CI -3.63 to 2.28), p=0.65; I^2=0%) at 12-month follow-up[1].

The SR of 6 studies reported that most patients reduced their doses of inhaled corticosteroids (ICS) and long-acting β-adrenergic agonists (LABA). More than 10% (range 12 to 49%) of patients were weaned off LABA treatment, without further maintenance medication for symptom control[2].

In the case series of 162 patients, use of maintenance ICS statistically significantly reduced by 50% or more in 28% (45/162, p<0.001) of patients from baseline to 5-year follow-up. An increase in maintenance ICS equal to or greater than 50% was reported in 5% (8/162, p<0.001) of patients. This is an average overall reduction in ICS dose of 18%. The same study reported that 12% (20/162) of patients were completely weaned off LABA, 9% (15/162) were weaned off ICS and 7% (12/162) had completely stopped all asthma medication[3, 4].

In the RCT of 69 patients the rate of OCS usage and the proportion of patients having BT who needed OCS did not change over the 5-year period compared with baseline, p value not reported. During 3 years of follow-up, 49% of patients in the BT group and 47% of patients in the control group stopped using LABA. The reduction in ICS was not significantly different between the groups at year 2 (p=0.93) and year 3 (p=0.92)[5].

In the case series of 14 patients there were no statistically significantly changes to inhaled asthma medication use from baseline to year-5 follow-up[6].

In the NRCS of 380 patients ICS daily doses (micrograms per day) statistically significantly reduced from baseline in patients who had BT in PAS 2 (2,301.0 ± 807.5 to 2,069.7 ± 1,158.2, p=0.003) and in AIR 2 (1,960.7 ± 745.2 to 1,840.9 ±

901.8, p=0.006) at 3-year follow-up. The proportion of patients having BT who needed OCS daily was statistically significantly reduced from baseline in PAS 2 (19% [36/190] to 10% [17/166], p=0.0004) but not in AIR 2 (4% [8/190] to 4% [6/162], p=0.52), at 3-year follow-up[7].

In the case series of 131 patients there was no statistically significant change in the use of rescue corticosteroids from baseline to 12-month follow-up (mean decrease -0.26, n=49, p=0.151) or at 24-month follow-up (mean decrease -1.42, n=27, p=0.129)[8].

In the case series of 24 patients who had BT, the median daily dose of prednisolone had statistically significantly reduced from baseline (10, IQR 7.5) at 6-month follow-up (0, IQR 4.5, p<0.001)[9].

Admissions to hospital in the post-treatment period (period following the 6 weeks after BT)

In the SR of 3 RCTs (n=429) admissions to hospital in the post-treatment period were not statistically significantly different between patients who had BT compared with sham or SMC (risk ratio [RR] 1.12, 95% CI 0.44 to 2.85, p=0.82; I^2=0%) at 12-month follow-up. This resulted in 6% (6/100) of patients who had BT needing hospitalisation because of a respiratory adverse event (95% CI 1 to 21) compared with 5% (5/100) in the control group[1].

In the SR of 6 studies, the frequency of hospital admissions for respiratory events was not statistically significantly different between 1-year and 5-year follow-up (RR 1.47, 95% CI 0.69 to 3.12, p=0.32; I^2=36%) in patients who had BT[2].

In the case series of 162 patients the rate of hospital admissions for respiratory symptoms was 2% (0 to 3.96) at 5-year follow-up compared with 4% (1.4 to 7.1) in the 12 months before BT, p value not reported[3, 4].

In the RCT of 69 patients, the rate of admission to hospital was higher but not statistically significantly different in patients who had BT in years 1 and 2 (6.7%) compared with SMC (0%, p=0.55)[5].

In the case series of 14 patients, the rate of hospitalisations per patient per year reduced from 0.71 at baseline to 0.23 at 5-year follow-up, corresponding to a 68% reduction (p value not reported)[6].

In the NRCS of 380 patients there was no statistically significant reduction in the rate of patients having hospital admissions compared with baseline in PAS 2 (15% [29/190] to 7% [12/168], p =0.0547) or in AIR 2 (4% [8/190] to 6% [10/165], p=0.6769), at 3-year follow-up[7].

In the case series of 131 patients who had BT there was a statistically significant reduction in the frequency of hospital admissions from baseline to 12-month follow-up (mean decrease -2.0, n=51, p=0.05) and at 24-month follow-up (mean decrease -1.0, n=26, p<0.006)[8].

Visits to the emergency department in the post-treatment period

In the SR of 6 studies, the frequency of visits to the emergency department (ED) because of respiratory events was not statistically significantly different between 1-year and 5-year follow-up (RR 1.06, 95% CI 0.77 to 1.46, p=0.71; I^2=0%) in patients who had BT[2].

In the case series of 162 patients who had BT, the percentage of patients needing visits to the ED because of respiratory symptoms reduced by 78% from baseline to 5-year follow-up (p value not reported)[3,4].

In the RCT of 69 patients, the rate of visits to ED was not statistically significantly different for patients who had BT compared with SMC at 1-year to 3-year follow-up[5].

In the case series of 14 patients there was a total of 11 respiratory-related hospitalisations in 5 patients (years 2 to 5), 7 asthma exacerbations, 1 lower respiratory tract infection, 1 wheeze and 2 semi-elective admissions for prophylactic aminophylline[6].

In the NRCS of 380 patients there was a statistically significant reduction in the rate of ED visits compared with baseline in PAS 2 (27% [52/190] to 11% [18/168], p =0.0003) and in AIR 2 (29% [55/190] to 8% [13/165], p<0.0001) at 3-year follow-up[7].

In the case series of 131 patients who had BT there was a statistically significant reduction in the frequency of unscheduled healthcare visits (asthma clinic, general practitioner or ED) from baseline to 12-month follow-up (mean decrease -0.93, n=47, p=0.018) and at 24-month follow-up (mean decrease -1.55, n=24, p=0.031)[8].

Patient satisfaction

In the case series of 14 patients, 91% (10/11) of patients stated that they would definitely have the procedure again and 1 patient reported that they would probably have the procedure again, at 5-year follow-up[6].

Radiological changes

The case series of 162 patients reported on 93 evaluable high resolution computed tomography scans (HRCT) pairs (year-1 and year-5 imaging). In 82%

there were either no radiological changes or improvement from baseline, and 71% showed no radiological changes of clinical significance. Improvement was shown in 14% of patients, and deterioration was shown in 15% of patients. In 2% (3/162) of patients increased or new bronchiectasis was noted[3, 4].

In the RCT of 69 patients annual chest x-ray imaging showed no clinically significant structural changes in the BT or SMC groups[5].

In the case series of 14 patients, 12 patients had unremarkable radiographs at 5-year follow-up[6].

Respiratory adverse events

In the SR of 3 RCTs the rate of respiratory adverse events was similar between the BT and control groups in the AIR and RISA trials, p value not reported[1].

In the case series of 162 patients, the rate of patients having 1 or more respiratory adverse events was 73% (66.5 to 79.4) in year-1, which continuously decreased to 48% (range 39.8 to 55.2) at year-5. Respiratory adverse events that occurred at a rate of 3% or greater in any of the follow-up years included sinusitis, asthma (multiple symptoms), bronchitis, cough, lower respiratory tract infections, influenza, nasopharyngitis, pneumonia, rhinitis, upper respiratory tract infections, and wheezing[3, 4].

In the RCT of 69 patients the proportion of patients having respiratory adverse events was higher in the BT group (84% [38/45]) compared with SMC (75% [18/24]) at 1-year follow-up, but similar at 3-year follow-up (56% [24/43] BT group, 57% [12/21] SMC group)[5].

Safety summary

The case series of 162 patients reported no incidence of pneumothorax, intubation or mechanical ventilation, cardiac arrhythmias, or death as a result of BT treatment over the 5 years of follow-up[3-6, 9].

Admissions to hospital during treatment period (up to 6 weeks after BT)

Admission to hospital during the treatment period was statistically significantly higher in patients who had BT compared with SMC or sham (RR 3.5, 95% CI 1.26 to 9.68, p=0.016; I^2=0%, n=429) in a pooled analysis reported in the SR of 3 RCTs[1].

Hospital admissions during the treatment period were not statistically significantly more frequent for patients who had BT in PAS 2 (13% [25/190] of patients) compared with AIR 2 (8% [16/190] of patients, p=0.1854) in the NRCS of 380 patients[7].

Intensive care admission for monitoring was reported in 1 patient in the case series of 24 patients. The patient needed admitting on 2 occasions and had non-invasive ventilation in 1 of the admissions[9].

Respiratory adverse events during treatment period (from first BT session to 6 weeks after last BT)

Respirator adverse events during the treatment period were more frequent in patients who had BT (407 events) compared with SMC or sham (106 events) in the RCT of 112 patients reported in the SR of 3 RCTs. This was similar in the RCT of 32 patients (136 events in the BT group, 57 events in controls) and in the RCT of 288 patients (85% patients BT group, 76% patients in control group) included in the same SR. Most adverse events happened within 1 day after bronchoscopy and were resolved within 7 days[1].

The frequency of respiratory adverse events was not statistically significantly different at 1-year and 5-year follow-up (RR 3.41, 95%CI 2.96 to 3.93, $p<0.00001$; $I^2=70\%$) in the pooled analysis of patients who had BT, reported in the SR of 6 studies. The author reported that the most common side effects were airway irritation, including worsening asthma symptoms (wheezing, chest discomfort, cough and chest pain) and upper respiratory tract infections. The majority of respiratory adverse events occurred within 1 day of the bronchoscopy and resolved within 7 days[2].

Respiratory-related serious adverse events during the treatment period were not statistically significantly more frequent in PAS 2 (13% [25/190] of patients) compared with AIR 2 (8% [16/190] of patients, p=0.1854) in the NRCS of 380 patient. Similarly, respiratory-related adverse events during the treatment period were not statistically significantly more frequent in PAS 2 (82% [155/190] of patients) compared with AIR 2 (85% [161/190] of patients, p=0.4933)[7].

Bilateral upper lobe atelectasis and acute respiratory failure after BT was reported in 1 case report (n=1)[10].

Bleeding

Massive haemoptysis following BT was reported in 1 case report (n=1)[12].

Visits to the emergency department during the treatment period

Emergency department visits during the treatment period were statistically significantly higher for patients who had BT in PAS 2 (16% [30/190] of patients) compared with AIR 2 (5% [10/190] of patients, p=0.0012) in the NRCS of 380 patients[7].

Asthma exacerbations during treatment period

Severe asthma exacerbations during the treatment period were statistically significantly more frequent in PAS 2 (56% [106/190] of patients) compared with AIR 2 (41% [77/190] of patients, p=0.004) in the NRCS of 380 patients[7].

Asthma exacerbation during the treatment period was reported in 9% (11/128) of patients and asthma-related symptoms (decreased FEV_1, wheeze, shortness of breath and desaturation) in 15% (19/128) in the case series of 131 patients who had BT[8].

Infection

Lung abscess at 14 months after BT requiring surgical resolution was reported in 1 patient in the RCT of 69 patients. Histological examination did not reveal obstruction or any other potentially contributory abnormality in the airways as a result of thermoplasty treatment, and the abscess was considered to be secondary to infection. At 5-year follow-up the patient had a post-bronchodilator FEV_1 of 1.78 L compared with the baseline value of 2.27 L[5].

Infection during the treatment period was reported in 6% (8/128) of patients in the case series of 131 patients who had BT[8].

Lung abscess after BT was reported in 1 case report[11].

Events preventing treatment completion

Excessive cough, discomfort, pain or bronchospasm preventing treatment completion were reported in 4% (5/128) of patients in the case series of 131 patients who had BT[8]. The same study reported incomplete course of treatment because of inability to perform BT (2 patients had 1 BT only, 2 patients had the first and second session only, and 4 patients did not complete any of the 3 BT sessions)[8].

Procedure related symptoms

Symptoms related to BT (bronchospasm, dry cough, chest twinges, tightness, discomfort or pain) were reported in 13% (16/128) of patients in the case series of 131 patients. The third BT treatment was postponed for 2 months because of inflamed airways and pain in 1 patient. Tracheomalacia was reported in 2 patients, central bronchiectasis in 1 patient and 'other' bronchiectasis in 2 patients in the same case series[8].

Device related

Catheter needing replacement during BT was reported in 2 occasions in the case series of 131 patients[8].

Other symptoms

Left rib fracture, metabolic acidosis, airway inflammation, medial basal bronchi bleeding, and procedure-related bradycardia were reported in 1 patient each in the case series of 131 patients who had BT. Lung collapse was reported in 3% (4/128) of patients in the same case series[8].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed no anecdotal or theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to bronchial thermoplasty for severe asthma. The following databases were searched, covering the period from their start to 11 September 2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with severe asthma.
Intervention/test	Bronchial thermoplasty.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 777 patients from 2 systematic reviews and meta-analysis, 1 randomised controlled trial, 3 case series (2 of which were extensions of randomised trials; 1 case series was reported in 2 separate publications), 1 registry, 1 non-randomised comparative study and 3 case reports. [1–12]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in the appendix.

Table 2 Summary of key efficacy and safety findings on bronchial thermoplasty for severe asthma

Study 1 Torrego A (2014)

Details

Study type	**Systematic review and meta-analysis (Cochrane)**
Country	Canada, Colombia, Spain
Recruitment period	Databases searched up to 2014
Study population and number	**n=3 RCTs**, 429 adults with moderate to severe asthma treated by BT
Age and sex	
Patient selection criteria	Studies inclusion criteria: - Studies comparing BT with any active control in adults with moderate or severe persistent asthma according to the Global Initiative for Asthma (GINA) criteria.
Technique	Pooled quantitative synthesis was attempted when possible.
Follow-up	**12 months**
Conflict of interest/source of funding	The main author is member of the Scientific Steering Committee of an international registry of patients treated with bronchial thermoplasty and performs the procedure in patients with severe asthma.

Analysis

Follow-up issues: AIR: at the 12-month follow-up data was available for 93% (52/56) of patients in the BT group and 88% (49/56) in the comparators group. RISA: there were 12% (2/17) of patients randomised to BT that withdrew from the intervention group without having received treatment. AIR 2: missing data for secondary outcomes were imputed using the last observation carried forward. At the 12-month follow-up data was missing on 9% (9/98) of patients in the BT group and 1/190 patient in the controls.

Study design issues: Two authors independently extracted data and assessed risk of bias. The risk of bias was independently assessed for each study using the Cochrane Handbook for Systematic reviews of Interventions. Disagreements were reviewed and discussed with a third author. The AIR and RISA studies were at high risk for performance and attrition bias because of lack of blinding.

Treatment effects were reported using MD or SMD for continuous outcomes and RR for dichotomous outcomes. Standard deviations at the end of follow-up were imputed from baseline data. ITT was used when available. Heterogeneity was explored using the I^2 statistic with a cut-off point of 50%, sensitivity analysis and subgroup analysis were used reason the causes of heterogeneity. Meta-analysis used a random-effect model and the inverse variance method.

The primary outcomes were quality of life, asthma exacerbation and adverse events. Secondary outcomes were lung function tests, doses of regular medication for asthma control, use of rescue medication, asthma symptom-free days, days missed from work or school and adverse events.

Study population issues:

Study	Design	Comparators	n	FU
AIR Trial **Cox** (2010, 2009, 2007, 2006a, 2006b), **Thomson** (2011), **Rubin** (2006), **Prys-Picard** (2010), **Pavord** (2010), **Niven** (2009, 2010), **Laviolette** (2004)	RCT, computer randomisation, closed envelopes	BT plus medical management (n=56) versus medical management alone (n=56).	112	3, 6 and 12 months
AIR 2 Trial **Castro** (2011, 2010a, 2010b, 2009), **Shah** (2009), **Wechsler** (2013a, 2013b)	RCT, double blinded, computer randomisation, concealment not described	Sham (n=190) versus BT (98)	288	3, 6, 9 and 12 months

RISA Trial **Pavord** (2011, 2007)	RCT, computer randomisation, closed envelopes	BT plus medical management (n=17) versus medical management alone (n=17), after BT, patients entered a steroid stable phase, followed by weaning phase and a reduced steroid treatment period.	34	12 months

Key efficacy and safety findings

Efficacy

n=3 RCTs (n=429)

Quality of life - AQLQ

MD 0.28, 95% CI 0.07 to 0.5, p=0.0099; I^2=0% (3 trials, n=429) [favours BT][1]

Mean quality of life (AQLQ) was 0.28 (0.07 to 0.5) higher in the BT group compared with controls (5.1 to 5.7) [GRADE=moderate, 3 RCTs, n=429]

Mean AQLQ scores per study

	Follow-up	BT	Controls	p*
AIR	Baseline	4.91±1.23	5.15±1.19	NR
	12 months	6.18±0.88	5.72±1.11	0.003
	Difference	0.46		
RISA	12 months	1.21±1.05	0.15±0.75	<0.05
	% patients with MCI improvement ≥0.5	77%	35%	NR
	% patients with MCI deterioration ≥0.5	8%	18%	NR
AIR 2	Baseline	4.30±1.21	4.32±1.21	
	12 months	5.66±1.60	5.48±1.15	>0.05
	% patients with MCI improvement ≥0.5	79%	64%	<0.05

Asthma control

MD -0.15, 95% CI -0.40 to 0.10, p=0.23; I^2=32% (3 trials, n=429) [no difference in mean ACQ symptom control scores between BT and comparator groups]

Mean change in asthma control measure (ACQ) was 0.15 (-0.4 to 0.1) in the BT group compared with controls (-0.55 to -0.01) [GRADE=moderate, 3 RCTs, n=429]

Mean ACQ and AQLQ symptom control scores by trial

	Follow-up	BT	Controls	p*
AIR	Baseline (AQLQ)	2.5±0.92	2.16±0.86	NR
	12 months (AQLQ)	1.32±0.85	1.69±0.99	<0.05[2]
RISA[3]	Improvement in symptom based AQLQ scores	1.53±0.79	0.42±0.82	0.001
	Improvement in symptom based ACQ scores	-0.99±0.83	-0.22±0.78	0.01
AIR 2	Baseline	2.13±0.87	2.09±0.9	NR
	Improvement in ACQ symptom based scores	1.31±0.94	1.32±0.91	>0.05

Safety

Serious adverse events

Hospitalisations because of respiratory adverse events in patients who had BT

During treatment period

RR 3.5, 95% CI 1.26 to 9.68, p=0.016; I^2=0%, (3 RCTs, n=429) [favours controls]

	BT	Controls
AIR[5]		
Hospitalisation (treatment period)	4 patients, 6 admissions	2 patients, 2 admissions
RISA		
Hospitalisation (treatment period)	4 patients, 7 admissions	0
AIR 2		
Hospitalisation (treatment period)	16 patients, 19 admissions	2 patients, 2 admissions

Respiratory adverse events

	BT	Controls
AIR[6]		
During treatment period	407 events	106 events
Mild	69%	-
RISA[7]		
During treatment period	136 events	57 events
Mild	49%	-
Moderate	41%	-
AIR 2[8]		
During treatment period	85%	76%
Asthma symptoms	52 patients	39 patients

For all trial in the review, most adverse events experienced by patients who had BT occurred within 1 day after bronchoscopy and were resolved within 7 days.

[5]The trialists reported that over 5 years of follow-up, the number of participants who received bronchial thermoplasty and required hospitalisation and the number of hospitalisations required for a respiratory

	Difference	-0.82±0.95	-0.77±1.08	

Exacerbations

Mean number of mild exacerbations (per participant/week)

	Follow-up	BT	Controls	p*
AIR	Baseline	0.35±0.32	0.28±0.31	NR
	12-month	0.18±0.31	0.31±0.46	NR
	Difference	-0.16±0.37	0.04±0.29	<0.05[4]

Mean number of severe exacerbations

	Folllow-up	BT	Controls	p*
AIR	Baseline	0.07±0.18	0.09±0.31	
	12-month	0.01±0.08 (exacerbations per participant per week)	0.06±0.24 (exacerbations per participant per week)	>0.05
AIR 2	12 months	0.48±0.067 (exacerbations per patient year)	0.70±0.122 (exacerbations per patient year)	<0.05
	% severe exacerbations	26% (50/190)	40% (39/98)	<0.05

Lung function tests

	Test	Follow-up	BT	Controls	p*
RISA	FEV_1 (% predicted)	22 weeks	14.9±17.4	-0.9±22.3	<0.05
		12 months	NR	NR	>0.05
AIR	Morning PEF (L/min)	Baseline	369±97.9	394±98.2	
		12 months	397.4±100.7	395.4±88.6	>0.05
	Pre-bronchodilator FEV_1	12 months	NR	NR	>0.05
AIR 2	Morning PEF	12 months	NR	NR	>0.05
	Pre-bronchodilator FEV_1	12 months	NR	NR	>0.05

Medication

Doses of regular medication

		Follow-up	BT	Controls	p*
RISA	Complete wean from regular steroids	52 weeks	50% (4/8)	14% (1/7)	>0.05
	Mean % reduction in regular oral steroid dose	52 weeks	63.5±45.4%	26.21±40.70%	>0.05

Use of rescue medication (short-acting bronchodilator puffs/week)

adverse event did not get worse compared with the first 12 months of follow-up within the formal trial.

[6]Most common adverse events: dyspnoea, wheezing and cough.

[7]Most common adverse events: wheeziness, cough and chest discomfort.

[8]Most common adverse events: wheeziness, chest discomfort, cough and chest pain.

Mean reductions use of rescue medication was MD -0.68, 95% CI -3.63 to 2.28, p=0.65; I^2=0% in the BT group compared with controls (-9.99 to -0.1) puffs/week [GRADE=low, 3 RCTs, n=429]

		Follow-up	BT	Controls	p*
AIR	Short-acting bronchodilator (puffs/week)	Baseline	19.8±17.2	16±18.8	
		12 months	10.9±15	14.8±21.2	<0.05
RISA	Short-acting bronchodilator reduction (puffs/week)	Steroid stable phase (22 weeks)	26.6±40.1	1.5±11.7	<0.05
		52 weeks	25.6±31.2	6.1±12.4	<0.05
AIR 2	Short-acting bronchodilator (puffs/week)	Baseline	13.4±19.2	11.8±11.2	
		12 months	7.4±15	7.5±12.6	>0.05

Asthma symptom-free days

	Follow-up	BT	Controls	p*
AIR	12 months	41±40%	17±40%	<0.05

Days missed from work or school

	Follow-up	BT	Controls	p*
AIR 2	12 months	1.3±0.36	3.92±1.55	NR

Admissions to hospital (post-treatment period)

RR 1.12 95% CI 0.44 to 2.85, p=0.82; I^2=0%, (3 RCTs, n=429) [no difference]

This would result in 6% (6/100) of patients who had BT needing hospitalisation because of a respiratory adverse event (95% CI 1 to 21).

	BT	Controls
Admissions to hospital	8%	15%
Absolute risk reduction (hospitalisation)	**7%**	
AIR[5]		
Hospitalisations (during follow-up)	3 admissions	3 admissions
Asthma exacerbation requiring hospitalisation	4 admissions	
RISA		
Hospitalisations (during follow-up)	1 patient 4 admissions	3 patients, 5 admissions
Asthma exacerbation requiring hospitalisation	4 patients, 5 admissions	
AIR 2		
Hospitalisations (during follow-up)	5 patients, 6 admissions	4 patients, 12 admissions
Asthma exacerbation requiring hospitalisation	10 patients, 12 admissions	2 patients, 2 admissions

Respiratory adverse events

The rate of respiratory adverse events was similar between the BT and control groups in the AIR and RISA trials, p value not reported.

*between group difference in change from baseline

[1]Results driven by the AIR and RISA trials. Results from the AIR 2 trial suggest a large placebo effect without the sham intervention.

[2]Strong Hawthorne effect: alteration of the behaviour of a subject because of the effect of knowing he is being observed. [3]At the end of the reduced steroids phase (52 weeks). [4]Exacerbations were counted only from 2-week periods in which LABA was withdrawn from both groups at 3, 6 and 12 months.	
Abbreviations used: ACQ, Asthma Control Questionnaire; AIR study, Asthma Intervention Research study; AQLQ, Asthma Specific Quality of Life Questionnaire; BT, bronchial thermoplasty; CI, confidence interval, FEV_1, forced expiratory volume in 1 second; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; ICS, inhaled corticosteroid; ITT, intention-to-treat; LABA, long-acting β-adrenergic agonist; MCI, minimum clinical important increase; MD, mean difference; NR, not reported; PEF, peak expiratory flow; RCT, randomised control trial; RISA study, Research in Severe Asthma study; RR, risk ratio; WMD, weighted mean difference; µg, microgram.	

Study 2 Zhou JP (2015)

Details

Study type	**Systematic review and meta-analysis**
Country	China
Recruitment period	Studies published between 2000 and 2014
Study population and number	**n=6 studies**, (3 RCTs and 3 extension studies) reporting on 249 patients with moderate to severe asthma treated by BT
Age and sex	Mean 38.6 to 51.5 years, 42 to 43% males
Patient selection criteria	Inclusion criteria: - Patients aged between 18 and 65 years - Diagnosis of moderate to severe persistent asthma according to the Global Initiative for Asthma - Patients requiring daily therapy with inhaled corticosteroids equivalent to a dose ≥ 200 µg of beclomethasone and LABA, and a dose ≥ 100 µg of salbutamol or the equivalent. - Patients who received BT at least once, using the Alair system.
Technique	All patients were treated with the Alair system, Boston Scientific.
Follow-up	**1 to 5 years**
Conflict of interest/source of funding	The study was supported by the National Natural Science Foundation of China. No conflict of interest.

Analysis

Follow-up issues: Data on 87% (216/249) of patients was available at the 5-year follow-up.

Study design issues: The study followed the Cochrane collaboration protocol. The authors reported a comprehensive literature search. Two physicians independently extracted the data from all included trials. An ITT analysis was used when available. Study heterogeneity was explored using the I^2 statistic. A random-effect model was used when the hypothesis of homogeneity was rejected. The author has graded the studies as high quality.

Outcomes of interest assessed after BT included spirometric data, adverse respiratory events, emergency room visits and hospitalisation for respiratory illness.

Study population issues: A majority of patients included in the original trials are white (83% [206/249]) with only 17% (43/249) being African American or other race. The patient included in the AIR 2 trials were receiving an higher mean quantity of inhaled corticosteroids (1960.7±745.2) compared with patients in the RISA study (1,179±421) and AIR (1,305±880), p value not reported.

Study	Design	n	Follow-up (years)	Jadad scale*
Pavord 2007 [RISA study]	Multicentre RCT, parallel group study	14	1	3
Pavord 2013 [RISA study]	Extension study	12	5	-
Cox 2007 [AIR study]	Multicentre RCT, parallel group study	45	1	3
Cox 2011 (Thomson 2011) [AIR study]	Extension study	42	5	-
Castro 2010 [AIR 2 study]	Multicentre RCT, double blind	190	1	3
Castro 2013 (Wechsler 2013) [AIR 2 study]	Extension study	162	5	-

**A Jadad scale of <3 is considered to indicate low-quality trial.*

Other issues: This study compared the outcomes in patients who had BT at 1 (V_1) and 5 years (V_2) post-treatment period follow-up and it did not report on the control groups. The study population is the same as reported in paper 1.

Key efficacy and safety findings

Efficacy	Safety
n= 249 patients (1 year follow-up, V_1), **216 patients** (5 years follow-up, V_2) **Maintenance medication changes:** Most patients presented with different level of reduction of ICS and LABA doses. More than 10% (range 12 to 49%) of patients was weaned off LABA treatment, without further maintenance medication for symptom control. **Spirometric stability:** Pre-bronchodilator FEV_1 (% predicted) WMD 0.75, 95% CI 3.36 to 1.85, p=0.57; I^2=0% [no difference between V_1 and V_2] Post-bronchodilator FEV1 (% predicted) WMD 0.62, 95% CI 3.32 to 2.08, p=0.65; I^2=0% [no difference between V_1 and V_2] **Emergency department visits for adverse events** RR 1.06, 95% CI 0.77 to 1.46, p=0.71; I^2=0% [no significant difference between V_1 and V_2] **Hospitalisation for adverse respiratory events** RR 1.47, 95% CI 0.69 to 3.12, p=0.32; I^2=36% [no significant increase between V_1 and V_2]	**Total adverse respiratory events** RR 3.41, 95%CI 2.96 to 3.93, p<0.00001; I^2=70% [no significant decrease between V_1 and V_2] The author reported that the most common side effects were airway irritation, including worsening asthma symptoms (wheezing, chest discomfort, cough and chest pain), and upper respiratory tract infections. The majority of respiratory adverse events occurred within 1 day of the bronchoscopy and resolved within 7 days.
Abbreviations used: AIR study, Asthma Intervention Research study; BT, bronchial thermoplasty; CI, confidence interval, FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; ITT, intention-to-treat; LABA, long-acting β-adrenergic agonist; RCT, randomised control trial; RISA study, Research in Severe Asthma study; RR, risk ratio; WMD, weighted mean difference; µg, microgram;.	

Study 3 & 4 Wechsler ME (2013), Castro M (2011)

Details

Study type	**Case series (AIR 2 study extension)**
Country	Australia, Brazil, Canada, Netherlands, UK, US
Recruitment period	2005 to 2012
Study population and number	**n=162** patients with severe asthma treated by BT
Age and sex	41.5±118 years, 42% (68/162) males
Patient selection criteria	Inclusion criteria: - 18–65 years of age - diagnosis of asthma requiring regular maintenance medications of ICS 1,000 µg/day beclomethasone or equivalent) and LABA >100 µg/day salmeterol or equivalent). - other medications were allowed, including leukotriene modifiers, omalizumab (if used for at least 1 year prior), and OCS 10 mg/day or less - subjects on stable maintenance asthma medications for at least 4 weeks before entry - baseline AQLQ score 6.25 or lower - pre-bronchodilator FEV_1 >60% of predicted, - airway hyperresponsiveness (methacholine provocative concentration causing a 20% drop in FEV_1 <8 mg/ml), - at least 2 days of asthma symptoms during the 4-week baseline period - being a non-smoker for at least 1 year with less than 10 pack-years smoking history Exclusion criteria: - life-threatening asthma - chronic sinus disease - respiratory diseases such as emphysema - use of immunosuppressants - β-adrenergic blocking agents or anticoagulants - history in the previous year of 3 or more hospitalisations for asthma, 3 or more lower respiratory tract infections, and 4 or more pulses of OCS use for asthma
Technique	After the 12-months follow-up of the AIR 2 study, patients who had BT were evaluated annually for 5 years to assess long-term safety and efficacy of the treatment. Patients were instructed to maintain the use of controller medications, unless changes were medically indicated, and were contacted by phone every 3 months.
Follow-up	**5 years**
Conflict of interest/source of funding	The study was supported by Boston Scientific, manufacturer of the Alair device. Some of the authors declared having received financial support or remuneration for services provided to different companies manufacturing medical devices or pharma.

Analysis

Follow-up issues: Of the 190 patients who had BT during the AIR 2 trial, 85% (162/190) completed the 5 years follow-up. Of the 28 patients not completing the follow-up 18 were lost to follow-up, 4 were withdrawn by the investigators (1 terminal illness, 3 non-compliance with physician's instructions), 5 were withdrawn for nonmedical reasons and 1 died in motor vehicle accident. Four subjects missed the year 4 visit but remained in the study. Data from patients who terminated during the follow-up were still counted in those years that the subject provided data.

Study design issues: The definition of severe exacerbation consisted of treatment with systemic corticosteroids, a doubling of the baseline ICS dose for at least 3 days or any temporary increase in the dose of corticosteroids in patients taking regular OCS. No imputations were made for missing data.

Outcomes of interest were: severe exacerbations, adverse events, hospitalisations and ED visits for respiratory symptoms, maintenance medication, spirometric data and HRCT scans.

Study population issues: The 28 patients not completing the 5 years follow-up were younger than the remaining 168 subjects (p=0.019). There were no other statistically significant differences in baseline demographic characteristics.

The mean number of activations for the 3 treatment procedures were 44±1.2, 47±1.2 and 60±1.6. Patients completing the 5-year follow-up had a total of 151 activations (during the 3 bronchoscopies).

Key efficacy and safety findings

Efficacy

n=162

Severe exacerbations

There was no statistically significant difference in the proportion of patients experiencing severe exacerbations in year 1 compared with the subsequent years of follow-up.

Severe exacerbations (% patients)

	Baseline (year before BT)	**Year 1*** (Reduction from baseline)	**Year 5** (Reduction from baseline)
Severe exacerbations (% patients)	52%	-31%	-44%
Severe exacerbation (% patients) (matched, n=162)[1]	53%	NR	-48%

(p values not reported)

Lung function

Percent predicted pre-bronchodilator FEV1 values remained unchanged over the 5 years after BT. Post-bronchodilator FEV1 remained higher at all times. Increase in percent predicted FEV1 at baseline of 8% and at 5 years 6%.

Changes in maintenance medication

Baseline*	ICS + LABA[2]	≥3 maintenance asthma medications
	72% (116/162)	28% (45/162)
Year 5		
Decrease ICS ≥50%	28% (45/162)**	
Increase ICS ≥50%	5% (8/162)**	
Reduction of ICS to ≤ 500 µg/day	13% (21/162)	
Overall reduction in average ICS dose (at year 5)	18%	
Weaned off LABA	12% (20/162)	
Weaned off ICS	9% (15/162)	
Weaned off all asthma medication	7% (12/162)	

**p<0.001

HRCT

There were 93 evaluable HRCT pairs at year 5. In 82% there were either no radiological changes or improvement from baseline, 71% show no radiological changes of clinical significance. There were 14% of patients showing improvements and 15% showing deterioration. There were 2% (3/162) of patients noted to have increased or new bronchiectasis.

ED visits for respiratory symptoms

The proportion of patients having ED visits for respiratory symptoms was reduced from baseline values after BT and this reduction was maintained at the 5 years follow-up.

	Baseline (12 months before BT)	**Year 1*** (Reduction from baseline)	**Year 5** (Reduction from baseline)
ED visits for respiratory symptoms (% patients)	28.9%	NR	-78%
ED visits (% patients)	NR	NR	-88%

ED visits during years 2 to 5 were lower when compared with the annualised rate of the approximately 64-week year 1 period that included both treatment period (12 weeks from first BT until 6 weeks after the last bronchoscopy) and post-treatment period (52 weeks beginning 6 weeks after BT).

Adverse events and hospitalisation for respiratory symptoms

	% patients who had BT having ≥1 AE		
	Respiratory	Asthma	Hospitalisation for respiratory symptoms
Baseline (n=190)	-	-	4% (1.4-7.1)
Year 1	73% (66.5-79.4)	29% (22.1-35.3)	3% (0.7-5.9)
Year 2	59% (51.3-66.3)	28% (21.0-34.7)	4% (1.2-7.3)
Year 3	58% (50.4-65.6)	30% (22.6-36.7)	6% (2.5-9.9)
Year 4	55% (47.0-62.5)	31% (24.2-38.7)	6% (2.1-9.3)
Year 5	48% (39.8-55.2)	25% (18.1-31.3)	2% (0.0-3.9)
5 Years mean	59% (53.4-63.8)	28% (23.7-33.6)	4% (2.3-6.6)

	Events rate (events/subject/year)		
	Respiratory	Asthma	Hospitalisation for respiratory symptoms
Baseline (n=190)	-	-	0.053 (0.04-0.08)
Year 1	2.02 (1.764-2.318)	0.481 (0.379-0.609)	0.04 (0.025-0.060)
Year 2	1.22 (1.013-1.465)	0.461 (0.357-0.594)	0.061 (0.042-0.087)
Year 3	1.25 (1.037-1.499)	0.506 (0.396-0.646)	0.068 (0.048-0.096)
Year 4	1.18 (0.971-1.424)	0.503 (0.393-0.644)	0.076 (0.054-0.105)
Year 5	0.78 (0.616-0.982)	0.321 (0.236-0.436)	0.025 (0.014-0.044)
5 Years mean	1.30 (1.149-1.481)	0.45 (0.374-0.554)	0.053 (0.038-0.073)

Respiratory AEs that occurred at an incidence rate of 3% or greater of subjects in any of years 1 through 5 included sinusitis, asthma (multiple symptoms), bronchitis, cough, lower respiratory tract infections, influenza, nasopharyngitis, pneumonia, rhinitis, upper respiratory tract infections, and wheezing.

Event rates (event/patient/year) were higher in non-responders that in responders:

	Non-responders	Responders
Severe exacerbations	0.720	0.389
Respiratory AEs	1.487	1.012
Asthma (multiple symptoms)	0.745	0.376
ED visits for respiratory symptoms	0.214	0.068
Hospitalisations for respiratory symptoms	0.079	0.051

*Baseline=12 months before BT. Year 1 began 6 weeks after the last bronchoscopy (end of treatment period)

[1]Matched-pair analysis comparing 162 patients completing the 5-year evaluation with the same group in previous years.

[2]High dose ICS (>1,000 µg beclomethasone equivalent) + LABA.

Safety

There was no incidence of pneumothorax, intubation/mechanical ventilation, cardiac arrhythmias, or death as a result of BT treatment over the 5 years of follow-up.

Abbreviations used: AE, Adverse event; AIR 2, Asthma Intervention Research 2; AQLQ, Asthma Quality of Life Questionnaire; BT, bronchial thermoplasty; ED, emergency department; HRCT, high-resolution computed tomography; ICS, inhaled corticosteroid; LABA, Long-acting b2-agonist; NAEPP; National Asthma Education and Prevention Program; OCS, Oral corticosteroid; µg, microgram.

Study 5 Thomson (2011)

Details

Study type	**RCT (5 years follow-up of the AIR trial)**
Country	Canada, UK, Brazil, Denmark
Recruitment period	2002 to 2004
Study population and number	**n = 69** (45 bronchial thermoplasty plus medical management versus 24 medical management alone)
Age and sex	Mean: 40 years (BT group), 41 years (controls); 41% males (28/69)
Patient selection criteria	Inclusion criteria: - patients with moderate or severe persistent asthma - requiring daily therapy with inhaled corticosteroids equivalent to a dose of 200 µg or more of beclomethasone and long-acting β2-agonist at a dose of 100 µg or more of salmeterol or equivalent to maintain reasonable asthma control - airflow obstruction (pre-bronchodilator FEV_1 of 60 to 85% of predicted value, - airway hyperresponsiveness by challenge with methacholine - stable asthma during the 6 weeks before enrolment - worsening asthma control after abstention from LABA for 2 weeks (either increase in ACQ score of ≥ 0.5, or a decline in average PEF during second week of abstinence). Exclusion criteria: - 3 or more lower-respiratory-tract infections requiring antibiotics during previous 12 months or a respiratory tract infection within previous 6 weeks
Technique	Patients in the BT group were treated with the Alair device.
Follow-up	**5 years**
Conflict of interest/source of funding	There were 10 authors receiving industry-sponsored grant funding from Asthmatx Inc, for participating in clinical trials. One of the authors was an employee of Asthmatx Inc.

Analysis

Follow-up issues: After 12-month visit, adverse events were actively solicited during an annual evaluation and medical chart review. There were 13% (7/52) of patients in the BT group and 51% (25/49) in the control group declining to participate in the extension study for personal reasons. By year 5, 1 patient in the bronchial thermoplasty group was lost to follow-up and 1 withdrew consent.

Study design issues: AIR trial (11 centres in 4 countries). Patients in the control group were evaluated at year 2 and year 3 and then exited from the study. In year 1, multiple symptoms associated with an adverse event were recorded as separate adverse events. In years 2 to 5, an adverse event with multiple symptoms was recorded as a single adverse event. The study aim was to evaluate long-term safety; no efficacy data were reported. Pulmonary function tests were performed when patients were taking only inhaled corticosteroids as their maintenance asthma medication (patients on LABA went through a 2-week withdrawal period).

Study population issues: There were no statistically significant differences between the groups with regard to baseline demographic information and clinical characteristics.

Other issues: None

Key efficacy and safety findings

Efficacy

Number of patients analysed: **69 (45 BT versus 24 controls)**

Oral corticosteroid use for asthma symptoms

Neither the rate of OCS usage nor the proportion of patients requiring OCS pulses showed any worsening over the 5-year period in the BT group.

Maintenance asthma medication use

Over the course of 3 years, 49% of patients in the BT group and 47% of patients in the control group stopped using LABA as controller medication.

The reduction in ICS was not significantly different between the groups at years 2 and 3 (p=0.93 and 0.92, respectively).

Pulmonary function tests

Both measures of lung function (FEV_1 and forced vital capacity) remained stable and showed no deterioration over the 5-year follow-up period. Total lung capacity and residual volumes also remained stable.

Review of annual chest X-rays

There were no clinically significant structural changes noted in either group.

Summary of respiratory adverse events

	Proportion of patients		*Events per patient*	
	BT	**Controls**	**BT**	**Controls**
Year 1	84% (38/45)	75% (18/24)	4.5	3.1
Year 2	53% (24/45)	54% (13/24)	1.2	1.2
Year 3	56% (24/43)	57% (12/21)	1.3	1.3
Year 4	53% (23/43)	N/A	1.2	N/A
Year 5	52% (22/42)	N/A	1.1	N/A

Proportion of patients admitted to hospital or visiting the emergency room

	Admission to hospital			*Emergency room visits*		
	BT	**Controls**	**p**	**BT**	**Controls**	**p**
Year 1	6.7%	0%	0.55	4.4%	0%	0.54
Year 2	6.7%	0%	0.55	6.7%	12.5%	0.41
Year 3	2.3%	4.8%	1.00	4.7%	4.8%	1.00
Year 4	2.3%	NA		9.3%	NA	
Year 5	2.4%	NA		4.8%	NA	

The respiratory adverse events were typical of asthma. The most common were dyspnoea, cough, wheeze, nasal congestion and upper respiratory tract infection.
One patient was hospitalised 14 months after BT for surgical resection of a lung abscess in left upper lobe, considered to be secondary to an infection.

Subjects with respiratory adverse events reported at ≥3%/year

	Year 1		Year 2		Year 3		Year 4	Year 5
Adverse event	**BT (n=45)**	**Control (n=24)**	**BT (n=45)**	**Control (n=24)**	**BT (n=45)**	**Control (n=21)**	**BT (n=43)**	**BT (n=42)**
Dyspnoea	42% (19/45)	50% (12/24)	9% (4/45)	13% (3/24)	9% (4/43)	14% (3/21)	9% (4/43)	10% (4/42)
Cough	38% (17/45)	29% (7/24)	9% (4/45)	1/24	5% (2/43)	14% (3/21)	7% (3/43)	5% (2/42)
Wheeze	31% (14/45)	17% (4/24)	4% (2/45)	1/24	7% (3/43)	1/21	7% (3/43)	5% (2/42)

Safety

There were no reports of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias, or death as a result of BT.

Abscess

One patient in the treatment group developed a lung abscess at 14 months after BT, which required surgical resolution. Histological examination did not reveal obstruction or any other potentially contributory abnormality in the airways as a result of thermoplasty. The abscess was considered to be secondary to infection. At the end of the 5-year follow-up the patient had a post-bronchodilator FEV^1 of 1.78 L compared with the baseline value of 2.27 L.

Nasal congestion	29% (13/45)	21% (5/24)	4% (2/45)	0	0	0	0	1/42
Upper RTI	22% (10/45)	8% (2/24)	24% (11/45)	17% (4/24)	19% (8/43)	19% (4/21)	19% (8/43)	10% (4/43)
Productive cough	20% (9/45)	21% (5/24)	4% (2/45)	1/24	5% 2/43)	0	0	1/42
Chest discomfort	18% (8/45)	13% (3/24)	4% (2/45)	8% (2/24)	7% (3/43)	1/21	1/43	5% (2/42)
Nasopharyngitis	13% (6/45)	0	1/45	0	0	0	1/43	1/42
Nocturnal dyspnoea	13% (6/45)	8% (2/24)	0	0	0	0	0	0
RTI	11% (5/45)	21% (5/24)	7% (3/45)	8% (2/24)	12% (5/43)	1/21	12% (5/43)	10% (10/42)
Pharyngolaryngeal pain	11% (5/45)	13% (3/24)	0	0	0	0	0	0
Respiratory tract congestion	9% (4/45)	8% (2/24)	0	0	0	0	0	0
Discoloured sputum	9% (4/45)	0	7% (3/45)	0	0	0	0	0
Rhinitis	4% (2/45)	0	0	0	1/43	0	0	5% (2/42)
Bronchitis	1/45	0	1/45	1/24	1/43	10% (2/21)	1/43	1/42
Pharingitis	1/45	1/24	0	0	0	0	0	0
Pleuritic pain	1/45	1/24	0	0	0	0	0	0
Rhinorrhea	1/45	1/24	0	0	1/43	0	0	0
Asthma symptoms	0	0	9% (4/45)	8% (2/24)	16% (7/43)	1/21	16% (7/43)	14% (6/42)
Sinusitis	0	0	1/45	1/24	5% (2/43)	0	5% (2/43)	5% (2/42)
Nasal polyp	0	0	1/45	0	0	0	5% (2/43)	0
Pneumonia	0	0	0	0	1/43	1/21	0	0

Abbreviations used: AIR, Asthma Intervention Research; BT, bronchial thermoplasty; FVC_1 functional vital capacity in 1 second; ICS, inhaled corticosteroid; LABA, Long-acting b2-agonist; NAEPP; National Asthma Education and Prevention Program; OCS, Oral corticosteroid; RTI, respiratory tract infection.

Study 6 Pavord (2013)

Details

Study type	**Case series (RISA trial extension)**
Country	Canada, UK, US
Recruitment period	2004 to 2010
Study population and number	**n=14** patients with severe asthma treated by BT during the RISA trial
Age and sex	Mean 38.6±13.3, 43% (6/14) males
Patient selection criteria	Inclusion criteria: - patients with asthma aged 18–65 years - requirement of high-dose ICS and LABA with or without oral prednisone, leukotriene modifiers, or theophylline - Pre-bronchodilator FEV_1 ≥ 50% of predicted - demonstrable airway hyperresponsiveness by challenge with methacholine or reversible bronchoconstriction during prior 12 months - uncontrolled symptoms despite taking maintenance medication - abstinence from smoking for at least 1 year and past smoking history < 10 pack-years Exclusion criteria - participation in another clinical trial involving any respiratory intervention - new diagnosis of psychiatric disorder that could interfere with provision of informed consent, completion of tests or therapy -
Technique	All patients had BT using the Alair device.
Follow-up	**5 Years**
Conflict of interest/source of funding	Conflict of interest/source of funding: the trial was funded by Asthmatx, Boston Scientific. Some of the authors have reported having received honoraria from medical technology companies.

Analysis

Follow-up issues: On the 15 patients who had BT during the RISA trial, 14 chose to participate in the extension study. One patient declined to participate and died 3 years after the last BT treatment, the family refused permission for review of the medical records. All 14 patients completed the 3-year follow-up and 12 patients completed the 5-year follow-up. One patient died from a recreational drug overdose unrelated to the patient asthma, 1 patient missed the year-4 follow-up, both were recorded as lost to follow-up.

Study design issues: Annual evaluations consisted of physical examination, pre-bronchodilator and post-bronchodilator spirometry, chest radiography, information of any ED visits or hospitalisation for respiratory symptoms, OCS pulses for worsening of asthma symptoms and changes in asthma medication. Chest radiographs were reviewed by a radiologist who was unblinded to the intervention, and compared with the radiographs done at baseline.

Information on AEs was collected differently in year 1: 12 office visits and 9 phone contacts throughout the year.

Study population issues: None

Other issues: None

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>

n=14

Maintenance asthma medication
No statistically significant changes were found in inhaled asthma medication use overall.

Chest radiographies
All 12 patients had unremarkable radiographs at year 5.

Pulmonary function tests
Mean pre-bronchodilator and post-bronchodilator values had no deterioration over the 5-year follow-up.

Patient satisfaction (11 patients)
In response to the question: “Would you undergo BT if you had to do it all over again?”
“Definitely yes”: 91% (10/11) patients
“Probably yes”: 1/11 patient

Respiratory related hospitalisations outside treatment period
There were a total of 11 respiratory related hospitalisations in 5 patients (year 2 to 5): 7 asthma exacerbations, 1 lower RTI, 1 wheeze, and 2 semi-elective for prophylactic aminophylline.

Hospitalisations per year

	Admissions	Per patient/year
Baseline*	10 (6 patients)	0.71
Year 1 (n=14)	5 (3 patients)	0.36
Year 2 (n=14)	6 (4 patients)	0.43
Year 3 (n=14)	3 (2 patients)	0.21
Year 4 (n=12)	1 (1 patient)	0.08
Year 5 (n=12)	1 (1 patient)	0.08
Total		0.23 (-68%)

Visits to ED

	Per patient/year
Baseline*	0.36
Mean at 5 years	0.12

*12 months before BT.

Adverse events per year

	Events	Number of patients	Events per patient per year
Year 1 (n=14)	118	100% (14/14)	8.4
Year 2 (n=14)	20	79% (11/14)	1.4
Year 3 (n=14)	34	86% (12/14)	2.4
Year 4 (n=12)	20	83% (10/12)	1.7
Year 5 (n=12)	29	100% (10/10)	2.4

</td><td>There was no incidence of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias or death as result of BT.</td></tr>
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Adverse events and patients affected

	Year 1		Year 2	Year 3	Year 4	Year 5
	Events	Patients	Patients	Patients	Patients	Patients
Respiratory, thoracic and mediastinal	118	100% (14/14)	79% (11/14)	86% (12/14)	83% (10/12)	100% (12/12)
Asthma	2	1/14	36% (5/14)	50% (7/14)	17% (2/12)	42% (5/12)
Bronchitis	1	1/14	14% (2/14)	21% (3/14)	1/12	1/12
Bronchospasm	0	0	1/14	0	0	0
Chest discomfort	3	21% (3/14)	0	0	0	1/12
Chest pain	1	1/14	0	14% (2/14)	1/12	1/12
Cough	13	43% (6/14)	0	1/14	0	0
Dyspnoea	20	64% (9/14)	0	0	1/12	0
Dyspnoea exacerbated	3	14% (2/14)	0	0	0	0
Epistaxis	2	14% (2/14)	0	0	0	0
Haemoptysis	1	1/14	0	0	0	0
Hoarseness	1	1/14	0	1/14	0	0
Lower RTI	8	43% (6/14)	25% (5/14)	29% (4/14)	42% (5/12)	58% (7/12)
LRT inflammation	0	0	0	0	0	1/12
Nasal congestion	5	36% (5/14)	0	0	0	0
Nasopharyngitis	7	29% (4/14)	0	1/14	1/12	1/12
Nocturnal dyspnoea	3	21% (3/14)	0	0	0	0
Pharyngolaryngeal	2	14% (2/14)	0	0	1/12	0
Productive cough	14	64% (9/14)	0	1/14	0	0
Rhinitis	1	1/14	0	14% (2/14)	0	0
Sinusitis	0	0	0	1/14	1/12	0
Sputum discoloured	3	21% (3/14)	0	0	0	0
Throat irritation	0	0	0	0	0	1/12
Upper RTI	9	36% (5/14)	0	14% (2/14)	17% (2/12)	17% (2/12)
Wheezing	19	71% (10/14)	1/14	14% (2/14)	0	1/12

Abbreviations used: BT, bronchial thermoplasty; FVC_1 functional vital capacity in 1 second; ED, emergency department; ICS, inhaled corticosteroid; LABA, Long-acting β2-agonist; OCS, oral corticosteroid; RISA, Research in Severe Asthma study; RTI, respiratory tract infection.

Study 7 Chupp G (2017)

Details

Study type	**Non-randomised comparative study**
Country	US
Recruitment period	**PAS 2**: 2011 to 2014 **AIR 2**: 2005 to 2008
Study population and number	**n=380** (190 AIR 2, 190 PAS 2) patients with severe asthma treated by BT
Age and sex	**PAS 2**: mean 45.87±11.39 years, 38% males **AIR 2**: 40.69±11.89 years, 43% males
Patient selection criteria	Inclusion criteria (PAS 2): - Age 18-65 - Inadequately controlled asthma despite optimise treatment with ICS and LABA. - Patients were allowed to take additional medication including low dose oral corticosteroids. - Able to provide written informed consent and willing and able to comply with study protocol - ICS >1,000 µg/day (beclomethasone equivalent), LABA ⩾80 µg salmeterol or equivalent - May also be taking leukotriene modifiers and/or anti-IgE - OCS ⩽10 mg/day - Pre-bronchodilator FEV1 % predicted ⩾60% - Non-smoker for ⩾1 year (if former smoker, <10 pack-years total smoking history) - Able to undergo outpatient bronchoscopy procedures - Has had at least 2 days of asthma symptoms in the last 4 weeks - AQLQ score ⩽6.25 during baseline period Exclusion criteria: - Participation in another trial within 6 weeks of baseline period involving respiratory intervention - Over the last 7 days of a 4-week medication stable period, rescue medication usage exceeds an average of 8 puffs/day - SABA, 4 puffs·day−1 rescue bronchodilator or 2 nebuliser treatments·day−1 - Post-bronchodilator FEV1 % pred <65% - History of life-threatening asthma (previous intubation or ICU admission in prior 2 years) - ⩾4 lower respiratory tract infections in previous 12 months - ⩾3 hospitalisations for asthma in the previous 12 months - ⩾4 pulses of systemic corticosteroids in the past 12 months - Known sensitivity to medications required to perform bronchoscopy - Other respiratory diseases including emphysema, cystic fibrosis, vocal cord dysfunction, mechanical upper airway obstruction, Churg–Strauss syndrome, allergic aspergillosis - Segmental atelectasis, lobar consolidation, significant or unstable pulmonary infiltrate, or pneumothorax confirmed by chest radiography - Cardiovascular disease including myocardial infarction, angina, cardiac dysfunction, cardiac dysrhythmia, conduction defect, cardiomyopathy or stroke - Known aortic aneurysm - Significant comorbid illness including cancer, renal failure, liver disease or cerebral vascular disease - Uncontrolled hypertension - Implanted electrical stimulation device - Known coagulopathy - Any other medical condition that could interfere with study participation in the opinion of the investigator Inclusion and exclusion criteria for the AIR 2 trial are described in papers 3 and 4 in table 2
Technique	The study compares outcomes of the first 190 patients included in the PAS 2 study with the 190 patients on the treatment arm in the AIR 2 trial. All patients received BT using the Alair device.
Follow-up	**3 years**
Conflict of interest/source of funding	The study was founded by Boston Scientific, manufacturer of the Alair device.

Analysis

Follow-up issues: PAS 2 patients were evaluated at each bronchoscopy visit and at 6 weeks after last procedure (end of treatment period). Patients also attended annual visits up to 5 years after BT and were contacted by phone every 3 months.

Study design issues: The AIR 2 trial was a randomised sham-controlled trial of BT in patients with severe asthma. The PAS 2 study is a prospective, open-label, observational multicentre (23 US centres, 4 Canadian centres) clinical study designed to demonstrate the short and long term efficacy and safety of BT in the clinical practice. The study was part of the FDA requirements for pre-market approval. PAS 2 expected completion date is January 2020 (5 years follow-up).

Primary endpoints of the PAS 2 study was the occurrence of severe exacerbations (worsening of asthma symptoms requiring systemic corticosteroids or increased dose corticosteroids if the patients was already on a regular dose). Other endpoints were respiratory adverse events, serious adverse events and measurements of pre and post-bronchodilator FEV_1.

The AIR2 trial included doubling of ICS dose as part of the definition of a severe exacerbation.

Study population issues: The PAS 2 subjects were older (mean age 45.9 versus 40.7 years, $p < 0.0001$) and more obese (mean body mass index 32.5 versus 29.3 $kg/m^{2,}$ $p<0.0001$), took higher doses of inhaled corticosteroids (mean dose 2,301 versus 1,961 µg/day, $p<0.0001$). Patients in the PAS 2 study also had statistically significantly more severe exacerbations and hospitalisations in the 12 months previous to BT.

Other issues: None.

Key efficacy and safety findings

Efficacy

n=380 (190 PAS 2, 190 AIR 2)

Medication reduction (3 years)

	Follow-up	PAS 2 (n)	AIR 2 (n)
ICS (µg/day)	Baseline[1]	2,301.0±807.5 (189)	1,960.7±745.2 (157)
	3 years	2,069.7±1,158.2 (189)	1,840.9±901.8 (151)
	p*	**0.003**	**0.006**
LABA (µg/day)	Baseline	106.9±39.4 (189)	122.2±50.6 (190)
	3 years	104.9±53.5 (149)	116.7±42.7 (143)
SABA (µg/day)	Baseline	2.4±1.5 (182)	2.2±1.3 (168)
	3 years	2.4±1.5 (162)	2.0±0.9 (134)
OCS (mg/day)	Baseline	19% (36/190) 9.1±2.7 (36)	4% (8/190) 11.9±15.5 (8)
	3 years	10% (17/166) 14.6±6.9 (15)	4% (6/162) 7.3±2.5 (6)
	p*	**0.0004**	**0.52**
Leukotriene modifier	Baseline	44% (84/190)	0% (0/190)
	3 years	43% (72/166)	0% (0/162)
Omalizumab	Baseline	16% (30/190)	1% (2/190
	3 years	15% (24/166)	2% (3/162)

Severe exacerbations

	PAS 2	AIR 2	p (between studies)
Severe exacerbations (% subjects)			
Baseline	74% (141/190)	52% (98/190)	<0.0001
3 years	40% (67/168)	33% (55/165)	0.2554
p*	<0.0001 (-45%)	<0.0001	
Severe exacerbations (Events)			
Baseline	1.57±1.15 (190)	0.88±1.03 (190)	<0.0001
3 years	0.64±0.96 (168)	0.54±0.93 (165)	0.3575
p*	<0.0001	0.0003	

Other end-points

	PAS 2	AIR 2	p (between studies)
Emergency department visits (% patients)			
Baseline	27% (52/190)	29% (55/190	0.8196
3 years	11% (18/168)	8% (13/165)	0.4517
p*	-55%, p=0.0003	-72% , p<0.0001	
Emergency department visits (Events)			

Safety

Respiratory related adverse events during treatment period

	PAS 2		AIR 2		
	AE	**Patients with ≥1 AE**	**AE**	**Patients with ≥1 AE**	**p**
Respiratory related SAEs					
Treatment phase	32	13% (25/190)	19	8% (16/190)	0.1854
Respiratory related AEs					
Treatment phase	561	82% (155/190)	573	85% (161/190)	0.4933

AEs during treatment period

	PAS 2	AIR 2	p
Severe exacerbations (% subjects)	56% (106/190)	41% (77/190)	0.004
Severe exacerbations (Events)	0.98±1.12 (190)	0.60±0.86 (190)	0.0002
Emergency department visit (% subjects)	16% (30/190)	5% (10/190)	0.0012
Emergency department visit (Events)	0.21±0.52 (190)	0.07±0.31 (190)	0.0023
Hospitalisation (% subjects)	13% (25/190)	8% (16/190)	0.1854
Hospitalisation (Events)	0.17±0.48 (190)	0.10±0.36 (190)	0.0983

Baseline	0.52±1.16 (190)	0.74±1.71 (190)	0.1289
3 years	0.18±0.63 (168)	0.13±0.64 (165)	0.4535
p*	0.0028	<0.0001	
Hospitalisation (% patients)			
Baseline	15% (29/190)	4% (8/190)	0.0004
3 years	7% (12/168)	6% (10/165)	0.8261
p*	-40%, p=0.0547	0.6769	
Hospitalisation (events)			
Baseline	0.21±0.53 (190)	0.05±0.27 (190)	0.0005
3 years	0.10±0.40 (168)	0.07±0.27 (165)	0.3698
p*	0.2494	0.8422	

FEV_1 (litres)

BT did not seem to an effect on spirometric parameters of lung function. In both studies the post-bronchodilator FEV_1 remained higher than pre-bronchodilator values at all times, indicating reversibility of asthma.

	PAS 2	AIR 2	p
Pre-bronchodilator			
Baseline	2.5±0.7 (190)	2.6±0.7 (190)	0.4517
% predicted	79.6±13.1 (190)	77.8±15.6 (190)	0.2255
3 years	2.4±0.8 (164)	2.5±0.8 (162)	0.5038
% predicted	76.3±18.6 (164)	75.8±19.1 (162)	0.7912
Post-bronchodilator			
Baseline	2.7±0.7 (190)	2.9±0.8 (190)	0.0225
% predicted	84.8±12.9 (190)	86.1±15.8 (190)	0.4009
3 years	2.6±0.8 (161)	2.7±0.8 (162)	0.3513
% predicted	82.3±17.1 (161)	82.3±17.9 (162)	0.9786

Respiratory related AEs

	PAS 2		AIR 2		
	AEs	Patients with ≥1 AE	AEs	Patients with ≥1 AE	p
Respiratory related SAEs					
1 year	28	10% (18/188)	7	4% (7/187)	0.0366
2 years	18	9% (17/181)	9	4% (7/168)	0.0592
3 years	19	8% (13/173)	11	6% (10/163)	0.6700
Respiratory related AEs					
1 year	301	65% (122/188)	369	72% (134/187)	0.1832
2 years	250	61% (111/181)	202	58% (98/168)	0.5862
3 years	204	59% (102/173)	203	58% (95/163)	0.9122

Respiratory related adverse events post-treatment period

	PAS 2		AIR 2		
	AEs	Patients with ≥1 AE	AEs	Patients with ≥1 AE	p
Respiratory related SAEs					
1 year	28	10% (18/188)	7	4% (7/187)	0.0366
2 years	18	9% (17/181)	9	4% (7/168)	0.0592
3 years	19	8% (13/173)	11	6% (10/163)	0.6700

Respiratory related AEs					
1 year	301	65% (122/188)	369	72% (134/187)	0.1832
2 years	250	61% (111/181)	202	58% (98/168)	0.5862
3 years	204	59% (102/173)	203	58% (95/163)	0.9122

*p value for the difference between baseline and follow-up

[1]The 12 months prior to BT were considered the baseline period.

Abbreviations used: AEs, adverse events; AIR study, Asthma Intervention Research study; BT, bronchial thermoplasty; FDA, Food and Drug Administration; FEV_1, forced expiratory volume in 1 second; PAS 2, Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma; ICS, inhaled corticosteroids; LABA, long acting β-agonists; OCS, Oral corticosteroids; SABA, short-acting β-agonist; SAEs, serious adverse events; µg, microgram.

Study 8 UK BTS Difficult Asthma Registry (unpublished)

Details

Study type	**Case series**
Country	UK
Recruitment period	2011 to 2016
Study population and number	**n=131** adults with severe asthma treated by BT in the UK (11 centres, 1 to 34 patients by centre)
Age and sex	Mean 43.7 (21-74) years, 31% (41/131) males
Patient selection criteria	**Efficacy study** - patients who received BT treatment, had a valid BT baseline record and at least one follow-up record in DAR (n=86) **Safety study** - patients who had at least one BT procedure record in DAR (n=128)
Technique	All patients were scheduled to receive 3 bronchoscopy procedures done approximately 3 weeks apart. All patients were treated with the same device (Alair Bronchial Thermoplasty System)
Follow-up	**0 to 5 years**
Conflict of interest/source of funding	Pilot funding for the Difficult Asthma Registry was provided as unrestricted research grants from Astra Zeneca, GlaxoSmithKline, Novartis and Medimmune. The extension of the Difficult Asthma Registry to include bronchial thermoplasty data collection and analysis was funded by NICE. JB, AJS and KK are employed by The Newcastle upon Tyne Hospitals NHS Foundation Trust which hosts an External Assessment Centre funded by NICE. RN was PI on several of the thermoplasty trials, and has received honoraria for lecturing & attending advisory boards from Boston Scientific. Other authors: TBA

Analysis

Follow-up issues: Data collection in the BTS Difficult Asthma Registry for patients undergoing BT in the UK was advised in NICE IPG419 but not mandatory. From active surveillance it was estimated that 11 patients (45 procedures) who had BT in the UK did not have data entered into the registry, and 1 did not give consent for data collection. For the study population, it was estimated that 12 BT procedures and 169 follow-up records were not entered into registry.

Study design issues: Observational data from routine UK clinical practice. Data collection in the BTS Difficult Asthma Registry for patients who had BT in the UK was advised in NICE IPG419 but not mandatory.

Study population issues: Study population included all adults selected to receive BT in routine UK clinical practice with varying baseline characteristics, comorbidities and medical history. Following BT, patients are prescribed a variety of drugs.

Other issues: Duration of procedure, minutes (10-96). Number of activations (2-115). Number of missed segments (0-8). Procedure carried out under GA: (8 procedures, 7 patients)

Key efficacy and safety findings

Efficacy

Efficacy study (patients who received BT treatment, had a valid BT baseline record and at least one follow-up record in DAR) n=86

Quality of life/Asthma control:

All data at BT baseline and follow-ups

(all values mean±SD)

	BTBL (n=86)	FU6 (n=76)	FU12 (n=60)	FU24 (n=34)	FU36 (n=15)	FU48 (n=8)	FU60 (n=2)
AQLQ score	3.64±1.26 (n=59)	4.16±1.47 (n=41)	4.24±1.45 (n=37)	4.40±1.62 (n=19)	4.56±1.57 (n=5)	4.92±2.11 (n=4)	- (0)
Euroqol Eq5d score	0.53±0.38 (n=42)	0.63±0.33 (n=30)	0.62±0.38 (n=29)	0.65±0.35 (n=18)	0.79±0.07 (n=4)	- (0)	- (0)
ACQ score	3.28±1.36 (n=49)	2.72±1.40 (n=47)	2.75±1.34 (n=40)	3.06±1.27 (n=21)	2.85±1.37 (n=6)	3.10±2.25 (n=3)	5.50 (n=1)
HADS score – Anxiety	8.52±5.54 (n=48)	7.73±5.0 (n=33)	6.46 ± 5.20 (n=28)	5.28±5.65 (n=18)	5.80±3.70 (n=5)	7.0±7.0 (n=3)	19.0 (n=1)
HADS score – Depression	6.46±5.25 (n=48)	5.94±4.87 (n=33)	5.07±4.50 (n=28)	4.67±4.85 (n=18)	7.0±3.74 (n=5)	6.33±7.09 (n=3)	11.0 (n=1)

Quality of life/Asthma control:

Paired data (change from BT baseline to 12 and 24 month follow-up)

	FU12: mean change from baseline (n, p)	FU24: mean change from baseline (n, p)
AQLQ score	0.75 (28, 0.0003)[1]	0.39 (16, 0.148)
Euroqol Eq5d score	0.008 (18, 0.909)	0.029 (13, 0.706)
ACQ score	-0.43 (36, 0.083)	-0.26 (19, 0.370)
HADS – Anxiety	-1.60 (20, 0.078)	-0.93 (14, 0.216)
HADS – Depression	-1.60 (20, 0.047)	-0.57 (14, 0.336)

[1]Significant with Bonferroni correction applied for 9 paired comparisons ($p < 0.006$) at each follow-up point (AQLQ score, Eq5D score, ACQ score, HADS Anxiety score, HADS Depression score, Rescue steroid courses, Unscheduled healthcare visits, Hospital admissions, FEV_1 % predicted)

Rescue steroids and Healthcare utilisation:

All data at BT baseline and follow-ups

(all values median [range], annualised)

	BTBL (n=86)	FU6 (n=76)	FU12 (n=60)	FU24 (n=34)	FU36 (n=15)	FU48 (n=8)	FU60 (n=2)
Rescue steroid courses	4 (0-15) (n=75)	2.0 (0-11.7) (n=67)	3.1 (0-18.8) (n=55)	1.9 (0-12.1) (n=29)	3.1 (0-7.5) (n=14)	2.9 (0-8.7) (n=8)	5.8 (2.2-9.3) (n=2)
Unscheduled healthcare visits (asthma clinic/GP/A&E)	5 (0-20) (n=71)	2.0 (0-12.1) (n=61)	3.2 (0-11.5) (n=52)	1.3 (0-11.8) (n=29)	3.0 (0-10.6) (n=14)	4.1 (0-6.1) (n=8)	6.3 (3.3-9.3) (n=2)
Hospital admissions	2 (0-11) (n=76)	0 (0-7.2) (n=68)	0 (0-11.2) (n=55)	0 (0-3.9) (n=29)	0 (0-4.2) (n=14)	0 (0-4.8) (n=8)	0.7 (0-1.3) (n=2)

Rescue steroids and Healthcare utilisation:

Paired data (change from BT baseline to 12 and 24 month follow-up)

	FU12: median change from baseline (n, p)	FU24: median change from baseline (n, p)
Rescue steroid courses	-0.26 (49, 0.151)	-1.42 (27, 0.129)
Unscheduled healthcare visits (asthma clinic/GP/A&E)	-0.93 (47, 0.018)	-1.55 (24, 0.031)
Hospital admissions	-2.0 (51, 0.05)	-1.0 (26, 0.0) †

†Significant with Bonferroni correction applied for 9 paired comparisons ($p < 0.006$) at each follow-up point (AQLQ score, Eq5D score, ACQ score, HADS Anxiety score, HADS Depression score, Rescue steroid courses, Unscheduled healthcare visits, Hospital admissions, FEV1 % predicted)

Lung function:

All data at BT baseline and follow-ups

(all values mean±SD)

	BTBL (n=86)	FU6 (n=76)	FU12 (n=60)	FU24 (n=34)	FU36 (n=15)	FU48 (n=8)	FU60 (n=2)
FEV1 % predicted	69.6± 21.71 (n=82)	71.47±21.62 (n=59)	74.90±21.34 (n=52)	72.71±21.08 (n=31)	76.50±18.78 (n=12)	77.86±25.39 (n=7)	81.5±13.44 (n=2)

Lung function:

Paired data (change from BT baseline to 12 and 24 month follow-up)

	FU12: mean change from baseline (n, p)	FU24: mean change from baseline (n, p)
FEV1 % predicted	3.51 (49, 0.152)	2.57 (30, 0.560)

Safety

Safety study (patients who had at least one BT procedure record in DAR) n=128

Adverse symptoms: Peri-procedural

Event	Number of procedures affected (n=370)	Number of patients affected (n=128)
Events preventing treatment completion (Excessive cough, discomfort and pain/bronchospasm)	5	4% (5/128)
Infection	8	6% (8/128)
Exacerbation	13	9% (11/128)
Asthma-related symptoms (Drop in FEV1, wheeze, sob, low Sao2)	24	15% (19/128)
Procedure related symptoms (Bronchospasm, dry cough, chest twinges/tightness/discomfort/pain)	20	13% (16/128)
Other (Left rib fracture)	1	1/128
Other (Metabolic acidosis)	1	1/128
Other (Inflamed airways, medial basal bronchi bleed)	1	1/128
Other (Lung collapse, one slight)	4	3% (4/128)
Other (Procedure-related bradycardia)	1	1/128

Additional reports

Device-related: 2 catheters needed replacement

Prolonged stay (>7 days) with no reason given): (3 procedures, 2 patients)

A & E attendance: no details given (1 procedure, 1 patient)

BT3 postponed 2 months because of inflamed airways & pain: (1 procedure, 1 patient)

Airway tracheomalacia reported: (2 procedures, 2 patients)

All 3 procedures not able to be performed:

- BT1 only - 2 patients
- BT1 and BT2 only – 2 patients

All 3 procedures not completed at 30/09/2016 – 4 patients

Incomplete data entry – 3 patients

Adverse symptoms: Reported at follow-up

Unexpected events:

There were no unexpected adverse events reported at follow-up that could be attributed directly to BT

CT scan reports at follow-up: 24 CT scans (21 patients)

One report of 'central bronchiectasis'

Two reports of 'other bronchiectasis'
Abbreviations used: BT, bronchial thermoplasty; BTS, British Thoracic Society; DAR, Difficult Asthma Registry; BTBL, BT baseline; BT1, 1st BT procedure; FU6, follow-up at 6 months following BT3; AQLQ, Asthma Quality of Life Questionnaire; ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1st second; HADS, Hospital Anxiety and Depression Scale; IPG, Interventional procedures guidance; SD, standard deviation.

Study 9 Langton D (2017)

Details

Study type	**Case series**
Country	Australia
Recruitment period	2014 to 2016
Study population and number	**n=24** consecutive patients with severe asthma treated by BT
Age and sex	Mean 55.4±12.6 years, 33% (8/24) males
Patient selection criteria	Patients were chosen for BT at the discretion of the treating team. Included patients had to fulfil at least one of the ERS/ATS criteria of severe asthma.
Technique	All patients had BT using the Alair device. BT was done in 3 treatments, 3 to 4 weeks apart, starting with the right lower lobe, then left lower lobe, and, at the last treatment, both upper lobes. Patients were treated with oral prednisolone for 3 days before and 3 days after the procedure.
Follow-up	**6 months**
Conflict of interest/source of funding	None.

Analysis

Follow-up issues:

Study design issues: The primary response measure was change in the ACQ-5 score measured at 6 months post BT. The nurses administering the questionnaire were blinded to intraoperative care (number of activations). Spirometer was done in an accredited respiratory laboratory. Safety events were recorded for any patients requiring admission for longer than 48 hours or was readmitted for any cause within 30 days of procedure.

An improvement greater than 0.5 points (responders) in ACQ-5 score was considered the minimal clinically significant difference.

Study population issues: All participants had been prescribed high doses of ICS, mean beclomethasone equivalent dose of 2095 ± 450 µg daily (range: 1000-3000 µg). Twelve patients (50%) were taking maintenance oral prednisolone (median dose 10 mg/day, range 4-20 mg). All patients (100%) were taking LABA and long-acting muscarinic antagonists. Additional preventative therapy included leukotriene receptor antagonists (42%), omalizumab (29%), and methotrexate (17%).

Other issues: A mean of 211±50 (range 121 to 305) radiofrequency activations per patient were delivered.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>

n=24 (21 responders, 3 non-responders)

The number of activations was statistically significantly lower in the non-responders group (139±11.4) compared with responders (221±45, p<0.01). All other demography characteristic were similar.

Response to treatment

<table>
<tr><th></th><th>Baseline</th><th>6 months</th><th>p</th></tr>
<tr><td>ACQ-5</td><td>3.3±1.1</td><td>1.5±1.1</td><td><0.001</td></tr>
<tr><td>FEV₁% predicted</td><td>61.8±15.9</td><td>68.7±15.6</td><td><0.05</td></tr>
<tr><td>Salbutamol puffs/day Median (IQR)</td><td>8 (11)</td><td>2 (2)</td><td><0.001</td></tr>
<tr><td>Exacerbations Median (IQR)</td><td>2 (2.75)</td><td>0 (1)</td><td><0.001</td></tr>
<tr><td>Prednisolone (mg/day) (n=12) Median (IQR)</td><td>10 (7.5)</td><td>0 (4.5)</td><td><0.001</td></tr>
</table>

The authors reported a statistically significantly different change in ACQ-5 between surgeon A (-0.9±2.1) and surgeons B and C (-2.3±1.0, p<0.05). The number of activations was also statistically significantly different between surgeon A (155±24) and surgeons B and C (241±33, p<0.001).

</td><td>There were no pneumothorax, airway haemorrhage, deaths and no readmissions for any cause within 30 days of BT. One patients required monitoring in intensive care on 2 occasions, receiving non-invasive ventilation in 1 of them.</td></tr>
<tr><td colspan="2">Abbreviations used: ACQ-5, Asthma Control Questionnaire 5; ATS, American Thoracic Society; BT, bronchial thermoplasty; ERS, European Respiratory Society; IQR, interquartile range; µg, microgram..</td></tr>
</table>

Case reports on adverse events (10, 11, 12)

Safety
Aparnath M (2014) **Case report** **US** **n=1** **Bilateral upper lobe atelectasis and acute respiratory failure after BT** A 74-year-old woman with history of severe persistent asthma had completed the third session of BT on the previous day to presenting with acute dyspnoea. The patient required intubation and developed worsened hypoxaemia on day 3. CT revealed left upper lobe atelectasis with mediastinal shift and right upper lobe consolidation. Bronchoscopy revealed complete endobronchial occlusion of both upper lobes. The endobronchial mucosal debris were removed, treatment with corticosteroids and bronchodilators was started and she was weaned from ventilation. The patient required extended rehabilitation because of steroid-related myopathy. **Balu A (2015)** **Case report** **UK** **n=1** **Lung abscess as a complication of BT** A 43-year old female with a background of poorly controlled severe asthma presented 3 days post BT with left sided chest pain radiating to the back associated with shortness of breath, wheeze and dry cough. The patient was admitted to high dependency unit and despite 5 days of oral antibiotics and high dose steroids, her symptoms continued to worsen. High-resolution CT-chest was done on day 11 and demonstrated a lung abscess. The patients was continued with intravenous tazocin and had a bronchoscopy with bronchoalveolar lavage on day 19. Post bronchoscopy, the patient was started on a 6 week course of oral clindamycin to treat her lung abscess. The abscess was completely resolved but asthma symptoms remained uncontrolled. **Egressy KVL (2014)** **Case report** **US** **n=1** **Massive haemoptysis following BT** A 57-years old female with history of persistent severe asthma had BT, completing all 3 sessions. During the third session she was noted to have a white raised mucosal lesion that was biopsied and confirmed to contain aspergillus fungal hyphae and necrotic debris. She was started on variconazole because of concerns of possible semi-invasive disease. Three weeks after starting the anti-fungal she presented with a massive haemoptysis. Bronchoscopy revealed multiple areas of mucosal necrosis in the upper airways and a glistening pulsatile mass in the right bronchus. She had particle embolisation of the right upper lobe artery. The patient recovered and was discharged home, 1 year after she reported improvement of asthma symptoms.
Abbreviations used: BT, bronchial thermoplasty; CT, computed tomography.

Validity and generalisability of the studies

- None of the studies included children.
- Several of the main outcome measures are subjective patient-centred outcomes such as the AQLQ scores.The results from non-blinded studies may be affected by a placebo effect.
- Only a proportion of eligible patients participated in the long-term follow-up study[3-6]. The follow-up period in this study was longer for patients in the bronchial thermoplasty group than for the controls.
- The long-term follow-up study relied on eliciting adverse events on a yearly basis and there may have been some under reporting because of recall bias[4].
- There was some heterogeneity in the patient populations; the AIR trial included patients who were less symptomatic than the RISA trial.
- Data from the UK difficult asthma registry was made available ahead of publication[8].
- Follow-up data up to a 5-year period is now available[3-6].

Existing assessments of this procedure

Professional Societies British Thoracic Society (BTS) – British guideline on the management of asthma

A BTS October 2016 guideline on the management of asthma states that bronchial thermoplasty may be considered for the treatment of adult patients who have poorly controlled asthma despite optimal therapy. Assessment and treatment for bronchial thermoplasty should be undertaken in centres that have expertise in the assessment of difficult to control asthma and in fibreoptic bronchoscopic procedures. The balance of risks and benefits of bronchial thermoplasty treatment should be discussed with patients being considered for the procedure. Longer term follow up of treated patients is recommended. Further research is recommended into factors that identify patients who will or will not benefit from bronchial thermoplasty treatment (Grade A – highest rating).

European Respiratory Society and American Thoracic Society (ERS/ATS) - International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

In a joint guideline on severe asthma, the ERS and the ATS recommend that bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board-approved independent systematic registry or a clinical study (strong recommendation, very low quality evidence). The guidelines also include data regarding the increased risk of adverse events. Three studies on bronchial thermoplasty demonstrated increased risk of hospitalisation (relative risk [RR]: 2.3, 95% confidence interval [CI]: 1.3–3.9). All studies reported adverse effects related to respiration only. Bronchial thermoplasty increased the risk of respiratory adverse effects in the initial treatment phase (relative risk [RR]: 1.13, 95% CI: 0.99–1.28 [number of patients with at least 1 adverse event]; rate ratio: 3.3, 95% CI: 2.4–4.5 [number of adverse events]), irrespective of their severity. According to guideline authors, both the potential benefits and harms may be considerable and the long-term consequences are unknown regarding this new approach to asthma therapy with an invasive physical intervention. Well-designed clinical studies are needed to define its effects on relevant objective health outcomes such as exacerbation rates, and on lung function assessed over the long-term. Studies are also needed to better understand the phenotypes of responding patients and the effect of the technology in patients with severe obstructive asthma.

Global Initiative for Asthma – Global strategy for asthma management and prevention 2018

Bronchial thermoplasty is a potential treatment option at step 5 in some countries for adult patients whose asthma remains uncontrolled despite optimised therapeutic regimens and referral to an asthma specialty centre (Evidence B). Bronchial thermoplasty involves treatment of the airways during 3 separate bronchoscopies with a localised radiofrequency pulse. The treatment is associated with a large placebo effect. In patients taking high-dose ICS/LABA, bronchial thermoplasty was associated with an increase in asthma exacerbations during the 3 month treatment period, and a subsequent decrease in exacerbations, but no beneficial effect on lung function or asthma symptoms compared with sham-controlled patients. Extended follow up of some treated patients reported a sustained reduction in exacerbations compared with pre-treatment. However, longer-term follow up of larger cohorts comparing effectiveness and safety, including for lung function, in both active and sham-treated patients is needed. Caution should be used in selecting patients for this procedure. The number of studies is small, and people with chronic sinus disease, frequent chest infections or FEV1 <60% predicted were excluded from the sham-controlled study. Task Force on Severe Asthma recommends that bronchial thermoplasty should be performed in adults with severe asthma only in the context of an independent Institutional Review Board-approved systematic registry or a clinical study, so that further evidence about effectiveness and safety of the procedure can be accumulated.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Technology appraisals

- Mepolizumab for treating severe refractory eosinophilic asthma. NICE technology appraisal 431 (2017). Available from https://www.nice.org.uk/search?q=asthmaNICE guidelines

- Asthma (uncontrolled) – omalizumab. NICE technology appraisal 278 (2013). Available from https://www.nice.org.uk/guidance/ta278

Clinical guidelines

- Asthma. NICE quality standard QS25 (2013). Available from https://www.nice.org.uk/guidance/qs25

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Advisor Questionnaires for bronchial thermoplasty for severe asthma were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials:

- NCT02241265 Spirometric response to bronchial thermoplasty in patients with severe asthma. US, case series, n=20, FU= 12 months, start date: February 2014; estimated completion date: June 2018 [recruiting]
- NCT02965807 Effect of bronchial thermoplasty on moderate bronchial asthma in China. China, case series, n=50, FU= 12 months, start date: February 2015; estimated completion date: December 2017 [recruiting]
- NCT02225392 Unravelling targets of therapy in bronchial thermoplasty in severe asthma. Netherlands, RCT, n=50, FU= 25 weeks, start date: April 2014; estimated completion date: April 2018 [recruiting]
- NCT02464995 Bronchial thermoplasty in severe asthma with frequent exacerbations. France, RCT, n=34, FU= 12 months, start date: June 2015; estimated completion date: November 2020 [recruiting]
- NCT01777360 Bicentric prospective study, evaluating bronchial thermoplasty in a patient presenting severe uncontrolled asthma. France, interventional case series, n=46, FU= 12 months, start date: December 2012, estimated completion date: September 2017 [Active, not recruiting]
- NCT01974921 Study of physiopathological mechanisms and results of treatment with bronchial thermoplasty in severe asthma. Spain, interventional case series, n=15, FU= 6 months, start date: September 2013, estimated completion date: September 2016. [Recruiting]
- NCT02975284 Unravelling targets of therapy in bronchial thermoplasty in severe asthma (TASMA) Extension Study. Netherlands, case series, n=40,

FU= 5 years, start date: August 2015, estimated completion date: September 2024 [Recruiting]

- NCT01350336 Bronchial thermoplasty in severe persistent asthma. US, interventional case series, n=284, FU= 5 years, start date: April 2011, estimated completion date: January 2020 [Active, not recruiting]
- NCT02104856 Bronchial Thermoplasty Global Registry. Multi-country, case series, O2, n=160, FU= 2 years, start date: January 2014, estimated completion date: June 2019. [Active, not recruiting]
  NCT03243292 Bronchial Thermoplasty 10+ Year Study. Multi-country, case series, n=196, FU=, 10 years, start date: October 2017, estimated completion date: October 2018. [Not yet recruiting]
- NCT02206269 China Alair system registry study-CARE study. China, case series, n=225, FU= 1 year, start date: April 2015, estimated completion date: June 2019. [Recruiting]

References

1. Torrego A, Sola I, Munoz AM et al. (2014) Bronchial thermoplasty for moderate or severe persistent asthma in adults. The Cochrane database of systematic reviews (3), CD009910
2. Zhou JP, Feng Yu Wang Q et al. (2016) Long-term efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma: a systemic review and meta-analysis. The Journal of asthma: official journal of the Association for the Care of Asthma 53(1), 94-100
3. Wechsler ME, Laviolette M, Rubin AS et al. (2013) Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. The Journal of allergy and clinical immunology 132(6), 1295-302
4. Castro M, Rubin AS, Laviolette M et al. (2011) Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, and & Immunology 107(1), 65-70
5. Thomson NC, Rubin AS, Niven RM et al. (2011) Long-term (5 year) safety of bronchial thermoplasty: asthma Intervention Research (AIR) trial. BMC pulmonary medicine 11, 8
6. Pavord ID, Thomson NC, Niven RM et al. (2013) Safety of bronchial thermoplasty in patients with severe refractory asthma. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, and & Immunology 111(5), 402-7
7. Chupp G, Laviolette M, Cohn L et al. (2017) Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. The European respiratory journal 50(2), 1-11
8. Analysis of unpublished data from the UK BTS Difficult Asthma Registry was commissioned by NICE MTEP as project reference IP675 from Newcastle and York External Assessment Centre (EAC), completed 31/03/2017. The work is intended for imminent submission to academic publication by representatives of NY EAC, NICE, BTS and the IP675 project steering group. It is therefore anticipated that by the time the NICE IP Programme conducts its systematic review of published evidence for a future update to IPG419, the unpublished data reported in this table will have been superseded by a published manuscript.
9. Langton D, Sha J, Ing A et al. (2017) Bronchial thermoplasty: activations predict response. Respiratory research 18(1), 134
10. Aparnath M, Aristide G, Liberman R et al. (2014) Bilateral upper lobe atelectasis and acute respiratory failure after bronchial thermoplasty. American Journal of Respiratory and Critical Care Medicine 189, C41

11. Balu A, Ryan D and Niven Robert (2015) Lung abscess as a complication of bronchial thermoplasty. The Journal of asthma : official journal of the Association for the Care of Asthma 52(7), 740-2

12. Egressy KVL and Ferguson JS (2014) Massive hemoptysis following bronchial thermoplasty. American Journal of Respiratory and Critical Care Medicine 189, A4445 (online)

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	11/09/2017	Issue 9 of 12, September 2017
HTA database (Cochrane)	11/09/2017	Issue 4 of 4, October 2016
Cochrane Central Register of Controlled Trials (Cochrane)	11/09/2017	Issue 8 of 12, August 2017
MEDLINE (Ovid)	11/09/2017	1946 to August Week 5 2017
MEDLINE In-Process (Ovid)	11/09/2017	September 08, 2017
EMBASE (Ovid)	11/09/2017	1996 to 2017 Week 37
PubMed	11/09/2017	n/a
BLIC (British Library)	11/09/2017	n/a

Trial sources searched 11 09 2017

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched 07 09 2017

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 exp Asthma/
2 asthma*.ti,ab.
3 1 or 2
4 (bronchial* adj4 (thermoplast* or thermograph* or thermal*)).ti,ab.
5 Alair*.tw.
6 or/4-5
7 Bronchi/su [Surgery
8 (bronchi* adj4 surg*).tw.
9 Bronchoscopy/
10 Bronchoscop*.tw.
11 or/7-10
12 muscle, smooth/su
13 Airway Remodeling/
14 (airway* adj4 (remodel* or (muscle* adj4 smooth))).ti,ab.
15 hot temperature/tu
16 ((thermal* or thermo* or heat* or hot*) adj4 (treat* or energ*)).ti,ab
17 or/12-16
18 11 and 17
19 6 or 18
20 3 and 19
21 animals/ not humans/
22 20 not 21
23 (20110824* or 20110825* or 20110826* or 20110827* or 20110828* or 20110829* or 2011083* or 201109* or 20111* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).ed.
24 22 and 23

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Arrigo R, Failla G, Scichilone N et al. (2016) How Effective and Safe Is Bronchial Thermoplasty in "real Life" Asthmatics Compared to Those Enrolled in Randomized Clinical Trials?. BioMed Research International 2016, 9132198	Case series n=7 Fu=12 months	No ED visits and hospitalisation occurred in the year after BT. No changes in functional parameters were recorded. Our investigation confirms the safety and efficacy of BT in severe asthmatics in real life settings.	Larger case series included in table 2. No new safety report.
Burn J, Sims AJ, Keltie K et al. (2017) Procedural and short-term safety of bronchial thermoplasty in clinical practice: evidence from a national registry and Hospital Episode Statistics. Journal of Asthma , 1-8	Case series n=83 FU=30 days	A higher proportion of patients experienced adverse events compared with clinical trials. The greater severity of disease amongst patients treated in clinical practice may explain the observed rate of post-procedural stay and readmission. Study of long-term safety and efficacy requires continuing data collection.	Study population overlaps with papers 8 in table 2.
Castro M, Rubin AS, Laviolette M et al. (2010) Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. American journal of respiratory and critical care medicine 181(2), 116-124	RCT n=288 FU=12 months	BT in subjects with severe asthma improves asthma-specific quality of life with a reduction in severe exacerbations and healthcare use in the post-treatment period.	Study reported in paper 1 and 2 in table 2.
Castro M, Rubin AS, Laviolette M et al. (2010) Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. American Journal of Respiratory	RCT n=288 FU=12 months	BT in subjects with severe asthma improves asthma-specific quality of life with a reduction in severe exacerbations and healthcare use in the post-treatment period.	Study reported in paper 1 and 2 in table 2.

and Critical Care Medicine 181: 116–24.			
Cox G, Thomson NC, Rubin AS et al. (2007) Asthma control during the year after bronchial thermoplasty. New England Journal of Medicine 356: 1327–37.	RCT n=112 FU=12 months	Bronchial thermoplasty in subjects with moderate or severe asthma results in an improvement in asthma control.	Study reported in paper 1 and 2 in table 2.
Cox G, Miller JD, McWilliams A et al. (2006) Bronchial thermoplasty for asthma. American Journal of Respiratory & Critical Care Medicine 173: 965–9.	RCT n=112 FU=16 months	BT is well tolerated in patients with asthma and results in decreased airway hyperresponsiveness that persists for at least 2 yr.	Larger case series in table 2.
Doeing DC, Mahajan AK, White SR et al. (2013) Safety and feasibility of bronchial thermoplasty in asthma patients with very severe fixed airflow obstruction: a case series. The Journal of asthma : official journal of the Association for the Care of Asthma 50(2), 215-8	Case series n=8 FU=12 months	We suggest that BT may be safe for asthma patients with severe airflow obstruction and higher hospitalisation rates than previously reported.	Larger case series included in table 2. No new safety report.
Doeing DC, Husain AlN, Naureckas ET et al. (2013) Bronchial thermoplasty failure in severe persistent asthma: a case report. The Journal of asthma : official journal of the Association for the Care of Asthma 50(7), 799-801	Case report n=1 FU= 6 months	This case is the first to describe a failure of BT to reduce or eliminate airway smooth muscle in a patient with severe persistent asthma. It suggests the potential for treatment failure in the management of these patients after BT and highlights the need for further study of potential BT-refractory patients.	Larger case series included in table 2. No new safety report.
Facciolongo N, Menzella F, Lusuardi M et al. (2015) Recurrent lung atelectasis from fibrin plugs as a very early complication of bronchial thermoplasty: a case report. Multidisciplinary respiratory medicine 10(1), 9	Case report n=1 FU= 12 months	The originality of our case report is related to the recurrence of bronchial plugging with lobar atelectasis within one and 5 hours respectively, after 2 sequential BT procedures. At the histological evaluation the bronchial plugs appeared very different from the typical mucoid asthma plugs, being composed prevalently by fibrin. It can be hypothesised that intense thermal stimulation of the bronchial mucosa may represent a strong boost for inflammation in susceptible patients, with microvascular alteration induced directly by heat or through the release of mediators. Although in severe asthma a risk of	Larger case series included in table 2. No new safety report.

		atelectasis from the classical asthma mucoid plugs may be expected, the peculiarity of our case resides in the formation of fibrin plugs whose direct correlation with BT should be considered.	
Kirby M, Ohtani K, Lopez L et al. (2015) Bronchial thermoplasty in asthma: 2-year follow-up using optical coherence tomography. The European respiratory journal 46(3), 859-62	Case series n=2 FU=2 years	In summary, we evaluated 2 severe asthmatics immediately prior to and longitudinally following BT, and demonstrated a reduction in airway wall thickness that persisted 2 years following treatment in the BT responder, as well as differences in airway wall features between the responder and non-responder prior to treatment. These observations generate hypotheses for a larger study to determine if airway changes defined by OCT imaging can identify asthma patients who will benefit from BT and to determine the long-term effects of the treatment.	Larger case series included in table 2. No new safety report.
McCambridge J and Kruklitis R (2016) Transient Bronchial Wall Thickening After Bronchial Thermoplasty for Asthma. Journal of bronchology & interventional pulmonology 23(1), 51-3	Case report n=1 FU= 6 months	The patient felt well 6 months after completion of BT. Subjectively, her asthma was less severe. She continued to take budesonide-formoterol fumarate 160-4.5 2 puffs twice daily and tiotropium 18 mcg one puff daily. She now rarely required albuterol and has only had 1 minor flare since the procedure. Her Asthma Therapy Assessment Questionnaire decreased from 4 points before her first procedure to 0 to 1 point 6 months after BT was completed	Larger case series included in table 2. No new safety report.
Niven RM, Simmonds MR, Cangelosi MJ et al. (2017) Indirect comparison of bronchial thermoplasty versus omalizumab for uncontrolled severe asthma. J Asthma 14:1-9	Systematic review and meta-analysis n=3 RCTs FU=32 weeks to 1 year	The ITC should be interpreted cautiously considering the differences between patient populations in the included trials. However, based on the analysis, BT compares well with a potentially more costly pharmacotherapy for asthma. Clinicians evaluating the relative merits of using these treatments should consider the totality of evidence and patient preferences to make an informed decision.	Indirect treatment comparison of BT and omalizumab. Evidence from the AIR 2 trial has been included in several papers in table 2.
Pavord ID, Cox G, Thomson NC et al. (2007) Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. American	RCT n=32 FU=12 months	BT is associated with a short-term increase in asthma-related morbidity. However, there is preliminary evidence of long-lasting improvement in asthma control.	Study reported in paper 1 and 2 in table 2.

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Wu Q, Xing Y, Zhou Xet al. (2011) Meta-analysis of the efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma. The Journal of international medical research 39(1), 10-22	Meta-analysis n=3 RCTs	This meta-analysis assessed the efficacy and safety of a novel intervention for asthma, bronchial thermoplasty (BT), in patients with moderate-to-severe persistent asthma. An electronic literature search identified 3 randomised controlled trials (RCT) of BT that recruited 421 patients in total. Outcomes of interest were the Asthma Quality of Life Questionnaire (AQLQ) score, morning peak expiratory flow (PEF), tolerability and safety. Compared with standard medications and sham BT treatment, BT significantly improved AQLQ scores and PEF from baseline to the end of the trials. There were more respiratory adverse events and hospitalisations for adverse respiratory events with BT than with medications or sham treatment during the treatment period, but most events resolved, on average, within a week. This effect of BT treatment was not seen during the post-treatment period. Additional long-term RCT are required to confirm whether BT provides benefit to patients with moderate-to-severe persistent asthma.	Study overlaps with the paper 1 and 2 in table 2.