

# Bronchial Thermoplasty for Asthma

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## Final Evidence Report

April 14, 2016

**Health Technology Assessment Program (HTA)**

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# **Bronchial Thermoplasty for Asthma**

***A Health Technology Assessment  
Prepared for Washington State Health Care Authority***

**Final Report  
April 14, 2016**

## **Acknowledgement**

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**List of Key Abbreviations**

<b>ACQ</b>	Asthma Control Questionnaire
<b>AQLQ</b>	Asthma Quality of Life Questionnaire
<b>ATC</b>	American Thoracic Society
<b>BT</b>	bronchial thermoplasty
<b>FEV<sub>1</sub></b>	forced expiratory volume in 1 second
<b>GINA</b>	Global Initiative for Asthma
<b>ICS</b>	inhaled corticosteroid(s)
<b>LABA</b>	long-acting $\beta_2$ -agonist
<b>QOL</b>	quality of life
<b>RCT</b>	randomized controlled trial

## EXECUTIVE SUMMARY

The **EXECUTIVE SUMMARY** summarizes background information, the methods and search results for this report, findings with respect to the Key Questions, and payer policies and practice guidelines. The **Executive Summary** also includes conclusions and an assessment of the quality of the evidence for each Key Question. In general, references are not cited in the **Executive Summary**. The **Executive Summary** ends with an **Overall Summary and Discussion**.

The **TECHNICAL REPORT** provides additional detail, with full citation, regarding background information, study results, and payer policies and guidelines, but does not include conclusions or quality assessment.

### Summary of Clinical Background

#### *Prevalence and Treatment of Asthma*

Asthma is a chronic inflammatory disorder of the airways characterized by episodes of impaired breathing caused by airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. It is estimated that 300 million persons suffer from asthma worldwide, with the highest prevalence in North America, Australia, and Western Europe. A total of 18.7 million adults in the United States suffer from asthma and it is a major health concern. According to recent estimates, in the United States, asthma is responsible for 14.2 million ambulatory care visits, 439,000 hospitalizations, and 3400 deaths per year. The prevalence of asthma has increased over the past 30 to 40 years and was at 8.2% in 2009; however, for the U.S. population as a whole, the prevalence of asthma attacks has reached a plateau in recent years and remains at approximately 4%. The prevalence of asthma varies among different population subgroups. Women have a higher asthma prevalence rate than men, boys have a higher rate than girls, and children have a higher rate than adults. Also, non-Hispanic whites and Hispanics have a lower asthma prevalence rate than non-Hispanic blacks. Asthma is more common in the poor than other socioeconomic groups. In 2008, asthma was responsible for 14.2 million lost workdays in adults and 14.4 million lost school days in children.

Current guidelines emphasize that asthma therapy should be selected on the basis of disease severity. For intermittent asthma, no daily medication is advised for the majority of patients. In order to relieve occasional symptoms, a rapid-acting, inhaled beta 2 ( $\beta_2$ )-agonist is prescribed. Patients with mild, persistent asthma require controller medication with a daily-inhaled glucocorticoid to achieve and maintain asthma control. Other treatment options include sustained-release theophylline, cromones, or a leukotriene modifier. For moderate, persistent asthma, the preferred therapy is a combination of inhaled glucocorticoid and a long-acting, inhaled  $\beta_2$ -agonist (LABA). Sustained-release theophylline or a leukotriene modifier can be used instead of the  $\beta_2$ -agonist. Primary therapy for severe, persistent asthma includes an inhaled glucocorticoid at higher doses, in addition to an inhaled LABA. Once asthma control is achieved



and maintained for 3 months, a gradual reduction of maintenance therapy should be attempted in order to identify the minimal therapy needed to maintain control (Bateman et al., 2008). Some patients with severe asthma do not achieve acceptable control despite high dosages of medication. The National Asthma and Education and Prevention Program Expert Panel Report recommends add-on therapy with LABAs, leukotriene modifiers, theophylline, and omalizumab in patients with difficult-to-treat asthma who take inhaled corticosteroids. These therapies reduce inflammation or decrease airway narrowing by relaxing airway smooth muscles. Unfortunately, therapeutic options for patients with severe asthma remain limited and adjunctive therapies (like those listed above) targeting other mediators of the inflammatory pathway have yielded variable results. Bronchial thermoplasty is intended for the treatment of severe, persistent asthma in patients who are age 18 years or older with asthma that has not been well controlled by long-acting bronchodilators and glucocorticoids.

The definition of severe asthma is complex and requires an assessment of asthma symptoms, short-acting rescue bronchodilator use, pulmonary function, requirement for and dosing of controller medications, and the number and severity of exacerbations. When evaluating severe asthma, physicians should rule out other potential causes, including poor inhaler technique, inadequate adherence to therapy, exposures to environmental triggers, cigarette smoking, gastroesophageal reflux disease, obstructive sleep apnea, chronic rhinitis or sinusitis, and obesity. The American Thoracic Society (ATS) and European Respiratory Society (ERS) define severe asthma as requiring treatment with high-dose inhaled corticosteroids plus a second controller medication (and/or systemic corticosteroids) to maintain asthma control. Additionally, patients who had required systemic corticosteroids for  $\geq 50\%$  of the previous year are also classified as having severe asthma.

### ***Bronchial Thermoplasty***

Bronchial thermoplasty is designed to reduce the smooth muscle that constricts the airway during asthma attacks. This procedure relies on a catheter that has an expandable array of electrodes that is delivered to the airway via a bronchoscope, which allows the physician to see inside the lung. After the catheter is threaded into the airway, a wire leading out of the back end of the catheter is attached to a radiofrequency generator and a lever is operated that causes the electrodes to curl into a ball shape around the front end of the catheter. The curved electrodes are held against the bronchial walls and an electrical current is applied to generate heat that destroys the smooth muscle underneath the lining of the bronchial passages. Bronchial thermoplasty is performed in 3 separate procedures in which all accessible airways located beyond the mainstream bronchi (average of 3 to 10 millimeters [mm] in diameter), except for the right middle lobe, are treated. The delivery of energy during bronchial thermoplasty uses continuous feedback to tightly control the degree and time of tissue heating to decrease airway smooth muscle mass without airway perforation or stenosis. Dividing the treatment into 3 procedures allows shorter procedure times and obviates the risks associated with widespread irritation of the airways in patients with severe asthma. Bronchial thermoplasty is typically performed by a pulmonologist with the patient under moderate sedation or general anesthesia.

### ***Safety of Bronchial Thermoplasty***

Bronchial thermoplasty has been associated with statistically significant increases in dyspnea, wheezing, chest discomfort, night awakenings, sputum discoloration, cough, productive cough, and need for hospitalization during the treatment period. Most of these complications were mild or moderate in severity. Other potential adverse events that may occur during or shortly after this procedure include the following: headache, fever, chest infection, pleurisy, bronchitis, hoarseness, throat irritation, bronchospasm, mucus production, retention of mucus, hypoxemia, pneumothorax, and exacerbation of asthma.

Labeling information approved by the Food and Drug Administration (FDA) warns that pneumothorax and respiratory failure requiring intubation are potential complications and the UK National Institute for Health and Care Excellence (NICE) has stated that bronchial stenosis is a potential long-term complication.

*Contraindications:* According to labeling information approved by the FDA, bronchial thermoplasty is contraindicated under any of the following circumstances:

- Presence of a pacemaker, internal defibrillator, or similar implanted electronic device.
- Known sensitivity to the drugs employed during bronchoscopy such as lidocaine, atropine, or benzodiazepines.
- Prior bronchial thermoplasty procedure.
- Active respiratory infection.
- An asthma attack or alteration of the dose of systemic glucocorticoids in the preceding 14 days.
- Known bleeding disorder.
- Need for aspirin, anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory drugs that cannot be interrupted.

The latter 4 contraindications listed here are relative rather than absolute and, in some cases, may only require delay of bronchial thermoplasty.

### **Policy Context**

Bronchial thermoplasty is a procedure used to treat asthma that is not well-controlled by medication. Smooth muscle in the lungs is altered by placement of a radiofrequency catheter that heats the muscle tissue, reducing the likelihood of bronchoconstriction during an asthma reaction. The specific catheter for the procedure was approved for marketing by the FDA in 2010. There are high concerns related to the safety and efficacy of bronchial thermoplasty, and medium concerns for the cost-effectiveness of the procedure.

## Summary of Review Objectives and Methods

### *Review Objectives*

**Population:** Adults diagnosed with moderate or severe asthma.

**Interventions:** Bronchial thermoplasty.

**Comparisons:** Medical management; sham treatment; no comparator.

**Outcomes:** Quality of life; asthma control, including medication use; asthma exacerbations; lung function; safety; emergency department visits; hospitalizations; mortality; cost and cost-effectiveness.

### *Key Questions*

1. What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma?
  - a. Is there clinically meaningful improvement for patients with severe asthma?
2. What are the harms associated with bronchial thermoplasty?
3. Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)?
4. What are the cost implications and cost-effectiveness of bronchial thermoplasty?

## Methods

See the **Methods** section of the **TECHNICAL REPORT**, [Appendix I](#), and [Appendix II](#) for additional detail.

### *Search Strategy and Selection Criteria*

Core databases, PubMed, and the websites of relevant specialty societies were searched for systematic reviews, meta-analyses, economic evaluations, and practice guidelines published in the last 10 years. Systematic reviews were selected if they reviewed studies considered eligible for answering the Key Questions or if they provided useful background information. Three systematic reviews of direct evidence pertinent to the Key Questions were discovered. The PubMed and OVID-Embase databases (searched on October 2, 2015) were searched for primary studies and economic evaluations designed to answer the Key Questions. Update searches were conducted on December 15, 2015, and January 25, 2016.

### *Inclusion/Exclusion Criteria*

Studies were selected for inclusion if they assessed the safety or efficacy of bronchial thermoplasty, were conducted in patients diagnosed with moderate or severe asthma, and

were published in English-language journals. Although bronchial thermoplasty has only been approved by the FDA for severe asthma, 1 of the 3 randomized controlled trials (RCTs) assessed in the current report included patients with moderate or severe asthma. Therefore study inclusion was not limited to studies assessing use of bronchial thermoplasty in severe asthma. Studies were excluded if they were conference abstracts, were conducted in nonhumans, or were case studies or series of case reports.

### **Quality Assessment**

The process used by Hayes for assessing the quality of primary studies and bodies of evidence is in alignment with the methods recommended by the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) Working Group. Like the GRADE Working Group, Hayes uses the phrase *quality of evidence* to describe bodies of evidence in the same manner that other groups, such as the Agency for Healthcare Research and Quality (AHRQ), use the phrase *strength of evidence*. A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines. See the **Methods** section of the **TECHNICAL REPORT** and [Appendix II](#) for details on quality assessment methods.

### **Summary of Search Results**

Eleven studies reported in 15 publications were selected for detailed analysis as evidence pertaining to the Key Questions. No unique studies were identified for Key Question #2 (safety) or Key Question #3 (differential effectiveness). Four studies were identified for Key Question #4 (cost-effectiveness). See [Appendix III](#) for a list of 11 studies that were excluded from analysis after full-text review. Four relevant practice guidelines published in the last 10 years were identified.

### **Findings**

Summary of Findings tables follow each Key Question. See **EXECUTIVE SUMMARY**, **Methods**, *Quality Assessment* and the corresponding section in the **TECHNICAL REPORT**, as well as [Appendix II](#), for details regarding the assessment of bodies of evidence. See [Appendix IV](#) for full evidence tables.

**Key Question #1**

**Key Question #1: What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma? #1a: Is there clinically meaningful improvement for patients with severe asthma?**

*Clinical Effectiveness of Bronchial Thermoplasty for Asthma (Key Question #1)*

The searches identified a total of 7 studies (reported in 11 articles) that evaluated the effectiveness of bronchial thermoplasty treatment in patients with asthma. The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3 very-poor-quality case series. Outcome measures included laboratory-collected respiratory parameters (e.g., forced expiratory volume in 1 second [FEV<sub>1</sub>]; provocation challenge causing 20% decrease in FEV<sub>1</sub> [PC<sub>20</sub>]), quality-of-life assessments (Asthma Quality of Life Questionnaire [AQLQ]; Asthma Control Questionnaire [ACQ]), patient self-report data collected in daily diaries (e.g., peak expiratory flow, asthma symptoms, asthma exacerbations, rescue medication use), changes in medication requirements, and hospitalizations and emergency department visits.

See [Table 1](#) for a summary of findings.

**RCTs (3 studies)**

The literature search identified 3 RCTs that evaluated the Alair Bronchial Thermoplasty System for treatment of moderate or severe asthma. One trial used sham bronchial thermoplasty in the control group (Castro et al., 2010) and 2 studies used asthma maintenance medication in the control group (Cox et al., 2007; Pavord et al., 2007). One study enrolled less than 50 patients and 2 studies did not involve blinding or placebo controls. Two RCTs enrolled patients with severe asthma, and 1 RCT enrolled patients with moderate or severe asthma. All of the RCTs evaluated thermoplasty as an adjunct to continued drug therapy. The initial reports of the RCTs involved only 1 year of follow-up; however, subsequent reports for the RCTs extended this follow-up to 5 years for patients who underwent thermoplasty and one of these extensions included a subset of control group patients with 3 years of follow-up. All of the RCTs were supported by the device manufacturer and performed in part by investigators who had financial relationships with the device manufacturer. Industry-supported funding of clinical trials does not introduce automatic bias into the results of the study, and was not considered a limitation when evaluating the quality of the evidence; however, this information may be of interest to the reader.

Patient selection criteria varied across studies. The highest-quality sham-controlled RCT enrolled patients with severe asthma (Castro et al., 2010). This pivotal trial was the primary basis for FDA premarket approval (PMA) of bronchial thermoplasty. For study inclusion, patients were required to use daily high-dose inhaled corticosteroids and a long-acting  $\beta$ 2-agonist (LABA), and have been on stable maintenance asthma medication for  $\geq$  4 weeks. Oral corticosteroids were acceptable in doses  $<$  10 milligrams per day (mg/day). In addition, patients

were required to have a low AQLQ score,  $\geq 2$  days of asthma symptoms per week, and have a pre-bronchodilator  $FEV_1 \geq 60\%$  of the predicted value. A small RCT enrolled 32 patients with severe asthma (Pavord et al., 2007). For inclusion in the study, patients were required to use high-dose inhaled glucocorticoids and LABA. In addition, patients were required to have a pre-bronchodilator  $FEV_1 \geq 50\%$  of the predicted value. The third RCT enrolled 109 patients with moderate or severe stable asthma (Cox et al., 2007). For study inclusion, patients were required to have an absence of unscheduled physician visits for asthma care, unchanged use of asthma medication for maintenance treatment, and stable use of rescue medication ( $\leq 4$  puffs in a 24-hour period of a short-acting bronchodilator). In addition, patients were required to use daily inhaled corticosteroids and LABA, as well as have a mean pre-bronchodilator  $FEV_1$  60% to 85% of the predicted value.

The largest available controlled study of thermoplasty for severe asthma was a double-blind, sham-controlled good-quality RCT that randomized 190 patients to thermoplasty and 98 patients to placebo treatment (Castro et al., 2010). Outcomes of this study were evaluated using Bayesian methods rather than traditional statistical tools, thus the term “posterior probability of superiority (PPS)”, rather than “statistically significant” will be used to describe the strength of the results. A meaningful improvement was defined as  $PPS > 0.964$  for the primary AQLQ outcome, and  $> 0.95$  for all other outcomes. It is unclear whether significant between-group differences would be observed using traditional statistical tools. The primary outcome measure for this study was mean change from baseline in AQLQ at 12-months following the procedure. Throughout the study, all patients continued drug therapy with no intentional or directed changes in medication use. Limitations of this study include that 3% of patients were lost to follow-up (primarily from thermoplasty group), mild exacerbations were not reported, some outcome measures were self-reported in daily diaries (i.e., rescue medication use, asthma symptoms, peak expiratory flow), lack of daily diary compliance data although daily diaries were electronic, and lack of controlled follow-up after 1 year. In addition, the peer reviewed publication did not provide information on the source of the prior distribution data used in the Bayesian model making it difficult to determine if the prior distribution data was appropriate for the purpose of the study. At 1-year follow-up, the primary outcome measure of improvement from baseline in AQLQ score (mean  $\pm$  SD) was greater in the bronchial thermoplasty group than the sham group ( $1.35 \pm 1.10$  versus  $1.16 \pm 1.23$ ;  $PPS=0.96$ ), but this difference did not reach the PPS planned of 96.4% thereby narrowly failing to meet the study’s primary outcome. However, the thermoplasty group had meaningful improvements compared with the control group for the following measures: severe exacerbations (0.48 versus 0.70 per patient annually;  $PPS=0.96$ ); emergency department visits (0.07 versus 0.43 per patient annually;  $PPS=0.999$ ); days lost from work, school, or other activities due to asthma (1.3 versus 3.9 per year;  $PPS=0.993$ ); and significantly more patients in the bronchial thermoplasty group showed a clinically meaningful improvement of 0.5 or greater in AQLQ scores compared with the sham group (78.9% versus 64.3%;  $PPS=0.996$ ). Despite these improvements, no meaningful improvements were noted between the thermoplasty group and the control group for the following measures at 1-year follow-up: morning peak expiratory flow; total symptom scores; symptom-free days; rescue medication use; unscheduled physician visits; hospitalizations; ACQ scores; and the primary outcome measure of improvement from baseline in AQLQ scores.

Scores (mean  $\pm$  SD) were greater in the bronchial thermoplasty group than the sham group (1.35  $\pm$  1.10 versus 1.16  $\pm$  1.23; PPS=0.96). However, this difference did not reach the PPS planned of 96.4%. The AQLQ is designed to measure the within-subject change in quality of life over time, and the results demonstrated meaningful improvements (i.e. within-subject change of  $\geq 0.5$ ) in 78.9% of patients in the bronchial thermoplasty group and in 64.3% of subjects in the sham group with a PPS of 0.996. The likelihood of improvement was therefore found to be greater for subjects having undergone bronchial thermoplasty. There was a higher than expected improvement in the sham group (0.5 anticipated vs. 1.16 observed), which was likely due, as noted by the study authors, to a higher than expected placebo effect in patients undergoing the sham procedure. It is important to note that mean change in AQLQ scores were averaged over the 6 to 12 months follow-up; all other outcomes were reported as mean at 12 months follow-up. An additional year of uncontrolled follow-up of the thermoplasty group evaluated with traditional statistical tools showed no statistically significant differences within this group from 1 to 2 years follow-up in severe exacerbations, asthma symptoms, emergency department visits, or hospitalizations. Uncontrolled follow-up of the thermoplasty group was extended to 5 years and found no significant increase in respiratory adverse events or need for hospitalization, and compute tomography (CT) findings were unchanged except for development of bronchiectasis in 3 (2%) patients.

A fair-quality RCT that enrolled 109 patients who had moderate to severe, persistent asthma found improvements similar to those reported above despite differences in study design (Cox et al., 2007). This trial was not blinded or placebo controlled and most of the outcomes were measured after attempted withdrawal of patients from LABA use. The primary outcome measure of this study was frequency of mild exacerbations during a 2-week period of abstinence from LABA. Data on exacerbations were self-report data collected using daily diaries. The authors did not note whether the study was sufficiently powered to detect between-group differences for any secondary outcomes. Limitations of this study included a lack of blinding, a lack of sham treatment in the control group, 5% of patients lost to follow-up, most outcomes with the use of LABA were not reported, follow-up was only 1 year, and several outcome measures were self-report data collected using daily diaries (i.e., exacerbations, peak expiratory flow, asthma symptoms). At 1-year follow-up, compared with the control group, thermoplasty was associated with statistically significant improvements in mean change in the following measures: mild exacerbations without LABA ( $-0.16$  versus  $+0.04$ ;  $P < 0.01$ ); mild exacerbations with LABA ( $-0.17$  versus  $+0.03$ ;  $P < 0.05$ ); AQLQ (higher score better) ( $+1.3$  versus  $+0.6$ ;  $P < 0.005$ ); ACQ (lower score better) ( $-1.2$  versus  $-0.5$ ;  $P < 0.005$ ); symptom-free days ( $+41\%$  versus  $+17\%$ ;  $P < 0.01$ ); symptom scores (lower score better) ( $-1.9$  versus  $-0.7$ ;  $P < 0.05$ ); rescue bronchodilator use ( $-8.9$  versus  $-1.2$  puffs per week;  $P < 0.05$ ); morning peak expiratory flow ( $+39$  versus  $+9$  liters per minute [L/min];  $P < 0.005$ ). In contrast, at 1-year follow-up, no significant differences were seen between the thermoplasty group and the control group on the following measures: severe exacerbations; airway responsiveness; FEV<sub>1</sub>. A second report of this study extended follow-up to 5 years for 45 (82%) thermoplasty group patients and to 3 years for 24 (44%) control group patients. Thermoplasty was not associated with any serious long-term adverse events and at 3 years follow-up, airway responsiveness (measured based on doublings of methacholine dose giving a 20% decrease in FEV<sub>1</sub>) increased 1.3 doublings for the

thermoplasty group versus a decrease of 0.4 doublings for the control group ( $P<0.05$ ). However, at 3 years follow-up, there were no significant differences between the thermoplasty group and the control group in other respiratory parameters, oral glucocorticoid use, worsening of asthma, emergency department visits, or hospitalizations. The apparent loss of benefits of thermoplasty during longer follow-up may indicate loss of effectiveness over time or may be an artifact of selective dropping out of control group patients who had the most poorly controlled asthma.

A fair-quality RCT that enrolled 32 patients who had severe asthma also reported that thermoplasty provided benefits despite differences in study design relative to the other available RCTs (Pavord et al., 2007). This trial was not blinded or placebo controlled and patients underwent attempted weaning from oral and inhaled glucocorticoids during weeks 22 to 36 of the study followed by maintenance of reduced steroid use during weeks 37 to 52 of the study. The primary outcome measure of the study was occurrence of adverse events, which were collected by during study visits and by telephone (12 office visits and 9 telephone contacts throughout the year). It was unclear whether complications were strictly self-reported in the patients' daily diaries, or if data were supplemented using more objective data from medical charts. The authors did not state if a power analysis was conducted. Outcomes from safety data are discussed in the results for Key Question #2 (safety). The study did not appear to be sufficiently powered to detect between-group differences for efficacy outcomes. Limitations of this study included a lack of blinding, a lack of sham treatment in the control group, small sample size, no power analysis was reported, 12% of thermoplasty patients ( $n=2$ ) withdrew from the study before undergoing bronchial thermoplasty (2 patients were not candidates for thermoplasty due to possible Churg-Strauss syndrome in 1 patient and post-bronchodilator  $FEV_1 < 55\%$  predicted in 1 patient), only 1 year of controlled follow-up, and several outcome measures were self-report data collected using daily diaries (i.e., medication use, peak expiratory flow, asthma symptoms). Compared with the control group at 22 weeks follow-up (before steroid weaning), thermoplasty was associated with statistically significant improvements in the following measures:  $FEV_1$  (+15% versus -1%;  $P<0.05$ ); AQLQ (higher score better) (+1.2 versus +0.2;  $P<0.05$ ); ACQ (lower score better) (-1.0 versus -0.1;  $P<0.05$ ); rescue bronchodilator use (-27% versus -2%;  $P<0.05$ ). Except for  $FEV_1$ , improvements in these measures remained statistically significant at 52 weeks follow-up, after reduction of steroid dosages. Compared with the control group at 52 weeks, thermoplasty was associated with statistically significant improvements in the following measures: AQLQ (higher score better) (+1.5 versus +0.4;  $P<0.05$ ); ACQ (lower score better) (-1.0 versus -0.2;  $P<0.05$ ); mean rescue bronchodilator use (-26% versus -6%;  $P<0.05$ ). Uncontrolled follow-up of 14 (93%) thermoplasty group patients found that in years 2 through 5, respiratory adverse events, hospitalizations, emergency department visits, asthma maintenance medication usage, and respiratory parameters were essentially unchanged compared with the first year after thermoplasty treatment. Outcomes during follow-up years 2 to 5 were collected once per year and may be subject to recall bias.



**Nonrandomized Studies (4 studies)**

Four very-poor-quality nonrandomized studies assessed efficacy outcomes in patients following bronchial thermoplasty. Two of these studies suggested that there were some favorable outcomes in patients following bronchial thermoplasty. However, caution should be exercised in interpreting results of these studies, as they do not include a control or comparison group, and are subject to several additional limitations.

Please see the [Literature Review](#) for in-depth study details.

**Table 1. Summary of Findings, Key Question #1: Asthma**

**Key:** ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BD, bronchodilator; BT, bronchial thermoplasty; FEV<sub>1</sub>, forced expiratory volume in 1 second; f/u, follow-up; grp, group; LABA, long-acting β<sub>2</sub>-agonist; MCID, minimal clinically important difference; PEF, peak expiratory flow; PICO, population-intervention-comparator-outcome; pt(s), patient(s); QOL, quality of life; RCT(s), randomized controlled trial(s); sx, symptom(s); tx, treatment

Number, Size, Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
<b>KQ #1. Effectiveness of BT for Asthma</b>			
7 studies (n=480) Cox 2007 (RCT, Fair) Pavord 2007 (RCT, fair) Castro 2010 (RCT, good) Cox 2006 (case series, very poor) Doeing 2013 (case series, very poor) Bicknell 2015 (retrospective cohort study, very poor) Chakir 2015 (case series, very poor)	<b>OVERALL: LOW</b> <b>Study quality:</b> Very poor – good <b>Quantity and precision:</b> Small body of evidence, some studies w/ small sample sizes <b>Consistency:</b> Studies demonstrated that BT was superior to sham tx or control tx w/ some inconsistency across outcome measures <b>Applicability to PICO:</b> ✓ <b>Publication bias:</b> Unknown	Asthma-related QOL improved relative to control (2 of 3 RCTs)  Severe exacerbations decreased (1 of 2 RCTs)  Asthma sx improved relative to control (1 of 3 RCTs)  Rescue medication use decreased compared w/ control (2 of 3 RCTs)  FEV <sub>1</sub> did not improve (3 RCTs)  No control or comparison grp (4 studies)	<i>Castro (2010) (Meaningful improvements compared w/ placebo grp at 1-yr f/u):</i> Secondary outcome measures: Severe exacerbations:0.48 vs 0.70 per pt annually, PPS=0.96 Emergency department visits: 0.07 vs 0.43 per pt annually, PPS=0.999 Days lost from work, school, or other activities due to asthma: 1.3 vs 3.9 per yr, PPS=0.993 <i>No meaningful improvements were found for these measures:</i> Primary outcome measure: AQLQ scores: 1.4±1.1 vs 1.2±1.2, PPS=0.96 However: More BT pts reached MCID (≥0.5) compared w/ sham grp (78.9% versus 64.3%; PPS=0.996). Secondary outcome measures: Morning peak expiratory flow; total sx scores; sx-free days; rescue medication use; unscheduled physician visits; hospitalizations; ACQ scores  <i>Cox (2007) (statistically significant improvements compared w/ control grp at 1-yr f/u):</i> Primary outcome measure:

Number, Size, Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
			<p>Mild exacerbations w/o LABA: -0.16 vs +0.04; <i>P</i>&lt;0.01</p> <p>Secondary outcome measures:</p> <p>Mild exacerbations w/ LABA: -0.17 vs +0.03; <i>P</i>&lt;0.05</p> <p>AQLQ: +1.3 vs +0.6; <i>P</i>&lt;0.005</p> <p>ACQ: -1.2 vs -0.5; <i>P</i>&lt;0.005</p> <p>Sx-free days: +41% vs +17%; <i>P</i>&lt;0.01</p> <p>Sx scores: -1.9 vs -0.7; <i>P</i>&lt;0.05</p> <p>Rescue BD use: -8.9 vs -1.2 puffs per wk; <i>P</i>&lt;0.05</p> <p>Morning PEF: +39 vs +9 L/min; <i>P</i>&lt;0.005</p> <p><i>No statistically significant improvements were found for these measures:</i> Severe exacerbations; airway responsiveness; FEV<sub>1</sub></p> <p><i>Pavord (2007) (statistically significant improvements at 1-yr f/u):</i></p> <p>Primary outcome measure: Adverse events (discussed in results for Key Question #2)</p> <p>Secondary outcome measures:</p> <p>AQLQ: +1.5 vs +0.4; <i>P</i>&lt;0.05</p> <p>ACQ: -1.0 versus -0.2, <i>P</i>&lt;0.05</p> <p>Mean rescue BD use: -26% vs -6%; <i>P</i>&lt;0.05</p> <p><i>No statistically significant improvements were found for these measures:</i> Morning or evening PEF; sx-free days; sx scores; airway responsiveness; FEV<sub>1</sub></p>
<b>KQ #1a. Clinically Meaningful Improvement Following BT for Patients with Severe Asthma?</b>			
<p>4 studies (n=439)</p> <p>Cox 2007 (RCT, Fair)</p> <p>Pavord 2007 (RCT, fair)</p> <p>Castro 2010 (RCT, good)</p> <p>Bicknell 2015 (retrospective cohort study, very poor)</p>	<p><b>OVERALL: LOW</b></p> <p><b>Study quality:</b> Very poor – good</p> <p><b>Quantity and precision:</b> Small body of evidence, some studies w/ small sample sizes</p> <p><b>Consistency:</b> Studies demonstrated that BT was superior to sham tx or control tx for QOL</p> <p><b>Applicability to PICO:</b> ✓</p> <p><b>Publication Bias:</b> Unknown</p>	<p>Asthma-related QOL improved to an extent that was clinically meaningful relative to control (2 of 3 RCTs)</p> <p>In a retrospective cohort study, 50% of pts met criteria for clinical improvement</p>	<p>3 RCTs defined clinical improvement by a single QOL measure. Change of 0.5 in scores on AQLQ is considered to be the MCID.</p> <p><b>Change in AQLQ scores from BL to 1-yr f/u (thermoplasty grp, control grp):</b></p> <p>Cox (2007): +1.3; +0.6 (difference of 0.69) (<i>P</i>&lt;0.005)</p> <p>Pavord (2007): +1.5; +0.4 (difference of 1.1) (<i>P</i>&lt;0.05)</p> <p>Castro (2010): +1.35; +1.16 (difference of 0.19) (NS)</p> <p><b>Bicknell (2015) defined clinical improvement as:</b></p> <ol style="list-style-type: none"> <li>(1) Reduction by ≥1 severe exacerbation or hospital admission for asthma</li> <li>(2) Improvement in ACQ or AQLQ score by the MCID,</li> </ol>

Number, Size, Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
			w/o worsening of the other (3) Stepdown in drug tx <b>5 of 10 clinic pts (50%) vs 73% of RCT pts</b> met the criteria for clinical improvement at 1-yr f/u.

***Is there clinically meaningful improvement for patients with severe asthma (Key Question #1a)?***

Three RCTs and 1 retrospective cohort study addressed whether improvements in outcome measures were clinically meaningful. All 4 studies included the AQLQ in their assessments. A *within-group* change of 0.5 in scores on the AQLQ is considered to be the MCID, with higher scores indicating improved asthma-related quality of life (Juniper et al., 1994). The study authors applied this MCID to *between-group* differences. Cox et al. (2007) found a between-group difference of 0.69 (+1.3 thermoplasty group versus +0.6 control group;  $P < 0.005$ ) at 12 months, which suggests that the increase in AQLQ is clinically meaningful. Likewise, Pavord et al. (2007) also found a clinically meaningful between-group difference of 1.1 in AQLQ (+1.5 thermoplasty group versus +0.4 control group). The most recent sham-controlled trial found that the AQLQ score improved from baseline to 1 year by 1.16 in the sham group and by 1.35 in the thermoplasty group, with a difference in AQLQ scores between the 2 groups of only 0.19 (PPS=0.96). The PPS did not reach the PPS planned of 0.964 (Castro et al., 2010). However, more thermoplasty patients (78.9%) met the MCID than sham patients (64.3%; PPS=0.996).

One very-poor-quality retrospective cohort study assessed clinically meaningful improvement in asthma-related outcomes (Bicknell et al., 2015). Clinical improvement was defined as achieving at least 1 of the following outcomes during the posttreatment period: (1) reduction by  $\geq 1$  severe exacerbation (requirement for high-dose oral corticosteroids) or hospital admissions for asthma; (2) improvement in ACQ or AQLQ score by the MCID, without worsening of the other (ACQ score decrease by  $\geq 0.5$ , AQLQ score increase by  $\geq 0.5$ ); (3) stepdown in treatment—half the maintenance oral prednisolone dose or stop omalizumab without a loss of asthma control (no increase in hospitalization or asthma exacerbations by  $\geq 1$  or worsening of ACQ/AQLQ scores by the MCID). At 1 year of follow-up, 5 of the 10 clinic patients (50%) met the criteria for clinical improvement. In comparison, 73% of RCT patients achieved the criteria for clinical improvement. AQLQ scores improved in 10 of 14 RCT patients that had AQLQ data (71%) and ACQ scores improved in 11 of 14 patients (79%). Asthma medications were reduced in 3 clinic patients (2 patients discontinued omalizumab and 1 patient discontinued prednisolone); changes in asthma medications were not reported in RCT patients. The number of severe exacerbations and hospitalizations was reduced in 3 of 10 clinic patients. Severe exacerbations decreased in 5 of 15 (33%) RCT patients and hospital admissions decreased in 2 of 15 RCT patients (13%).

The reviewed studies did not provide definitions for clinically meaningful changes for any outcome measures other than AQLQ.

*Quality of the Evidence:*

The quality of the evidence was assessed taking into consideration the quality of the individual studies; the precision, directness, and consistency of data; and the applicability of the data to the relevant patient population in clinical practice. The evidence for the effectiveness of bronchial thermoplasty for treating asthma was considered to be of low quality because of some positive but inconsistent results regarding short-term benefits of bronchial thermoplasty, varied patient selection criteria across studies, small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long-term efficacy of bronchial thermoplasty.

## Key Question #2

### **Key Question #2: What are the harms associated with bronchial thermoplasty?**

*Complications during treatment period.* Seven studies reported on adverse events and/or rates of hospitalizations that occurred during the treatment period (i.e., treatment period plus 6-week follow-up). The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3 very-poor-quality case series.

Three studies reported on the rate of specific adverse events occurring during the bronchial thermoplasty treatment period. Bronchial thermoplasty was associated with statistically significant increases in dyspnea (60% to 71% of thermoplasty patients), wheezing (50% to 73%), chest discomfort (40% to 56%), night awakenings (40%), sputum discoloration (11% to 33%), cough (53% to 94%), productive cough (40% to 53%), bronchial irritation (9% to 13%), and nasal congestion (13% to 20%). Most of these complications were mild or moderate in severity. Other potential adverse events that may occur during the treatment period are headache, fever, chest infection, upper respiratory infections, pleurisy, bronchitis, hoarseness, throat irritation, bronchospasm, mucus production, retention of mucus, hypoxemia, pneumothorax, atelectasis, and exacerbation of asthma.

*Hospitalizations during treatment period.* Seven studies reported on an increased need for hospitalization during the treatment period. The 3 RCTs found that 5% to 27% of thermoplasty patients compared with 0% to 4% of control patients required hospitalization during the treatment period. However, only 1 fair-quality small RCT found that the between-group difference was significant. The rate of hospitalization in thermoplasty patients among the nonrandomized studies ranged from 0% to 62.5%. The rate of hospitalization appeared to be higher in studies that enrolled patients with more severe asthma. The percentage of patients hospitalized ranged from 0% to 5.5% in studies that included patients with mild and/or moderate asthma. The percentage of patients hospitalized ranged from 5% to 62.5% in studies

that included patients with mild and/or moderate asthma. The study with 0% hospitalizations enrolled only patients with stable mild to moderate asthma. The study with 62.5% of patients hospitalized during the treatment period enrolled patients with severe asthma with obstructed airflow ( $FEV_1 < 50\%$ ).

*Complications during long-term follow-up.* Thomson et al. (2011) reported controlled follow-up data on complications occurring during 1 to 5 years following bronchial thermoplasty for 69 of 109 patients (63%) that were enrolled in Cox et al. (2007). Control patients were followed for only 3 years. Between-group differences in worsening of asthma, hospitalizations, and emergency department (ED) visits were not statistically significant. During the 5 years of follow-up, no patients had pneumothorax or cardiac arrhythmias, were intubated or mechanically ventilated, or died due to thermoplasty.

Pavord et al. (2007) reported that at 1-year follow-up, between-group differences in complications were not significant. Five hospitalizations occurred in 3 bronchial thermoplasty patients, and 4 hospitalizations occurred in a single patient in the control group. Uncontrolled follow-up of 14 thermoplasty patients (93%) found that in years 2 to 5, rates of respiratory adverse events (1.4, 2.4, 1.7, and 2.4 events per patient), respiratory-related hospitalizations (21% of patients in year 1, 29% of patients in year 2, 14% of patients in year 3, 7% of patients in years 4 and 5), and ED visits (mean 0.36 ED visits per patient per year before thermoplasty versus mean 0.12 ED visits per patient per year for 5 years of follow-up) were essentially unchanged (Pavord et al., 2013). There were no deaths during the study. There were no incidences of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias, or deaths as a result of bronchial thermoplasty.

An additional year of uncontrolled follow-up of thermoplasty patients enrolled in Castro et al. (2010) showed no statistically significant differences within this group from 1 to 2 years follow-up in ED visits or hospitalizations (Castro et al., 2011). Uncontrolled follow-up of the thermoplasty group was extended to 5 years and found no significant increase in respiratory adverse events or need for hospitalization, and bronchiectasis developed in 3 (2%) patients (Wechsler et al., 2013).

Three of the nonrandomized studies reported on adverse events occurring during 1 to 2 years follow-up. Cox et al. (2006) reported that over a 2-year follow-up period, 312 adverse events occurred. More than half of these (155 events) were directly related to the procedure and occurred during the treatment period. Of these events, 230 (74%) were mild, 79 (25%) were moderate, and 3 (1%) were severe. All 3 severe adverse events involved hospitalization and were considered to be not related to the procedure. No ED visits related to thermoplasty or asthma exacerbation occurred. Doeing et al. (2013) reported that no patients had an increase in hospitalization rate up to 1-year follow-up. Mean hospitalizations for asthma in the year prior to bronchial thermoplasty was 2.88, compared to 0.50 hospitalizations during the median follow-up of 31 weeks following thermoplasty. Bicknell et al. (2015) reported that 1 patient was hospitalized during the 1-year follow-up period. No deaths occurred during the study period in any of the nonrandomized studies.

In addition to the complications listed above, labeling information approved by the FDA warns that pneumothorax and respiratory failure requiring intubation are potential complications (CDRH, 2010) and the NICE has stated that bronchial stenosis is a potential long-term complication (NICE, 2012).

According to labeling information approved by the FDA, bronchial thermoplasty is contraindicated under any of the following circumstances (Asthmatx Inc., 2010):

- Presence of a pacemaker, internal defibrillator, or similar implanted electronic device.
- Known sensitivity to the drugs employed during bronchoscopy such as lidocaine, atropine, or benzodiazepines.
- Prior bronchial thermoplasty procedure.
- Active respiratory infection.
- An asthma attack or alteration of the dose of systemic glucocorticoids in the preceding 14 days.
- Known bleeding disorder.
- Need for aspirin, anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory drugs that cannot be interrupted.

The latter 4 contraindications listed here are relative rather than absolute and, in some cases, may only require delay of bronchial thermoplasty (CDRH, 2010).

#### *Quality of the Evidence:*

The quality of the evidence was assessed taking into consideration the quality of the individual studies; the precision, directness, and consistency of data; and the applicability of the data to the relevant patient population in clinical practice. The evidence for the safety of bronchial thermoplasty for treating asthma was considered to be of low quality because of the small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long-term safety of bronchial thermoplasty.

#### **Key Question #3**

***Key Question #3: Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)?***

The literature search found no studies that were specifically designed to assess differential effects of bronchial thermoplasty. The analyzed studies varied considerably in patient selection criteria, which may have had an impact on study outcomes. In addition, several studies conducted post-hoc analyses investigating the impact of various patient characteristics and

other prognostic factors on clinical outcomes. These data were of very poor quality; therefore, all findings should be considered preliminary in nature.

Patient selection criteria varied considerably between studies, and the RCTs were selective in the patients that were enrolled in the study. Because the body of literature concerning safety and efficacy of bronchial thermoplasty for asthma is small, it is difficult to determine whether efficacy or safety or thermoplasty varied by baseline variables such as asthma severity, medication use, pulmonary function, or other characteristics.

- A good-quality sham-controlled RCT assessing thermoplasty in patients with severe asthma (Castro et al., 2010). For study inclusion, patients were required to use daily high-dose inhaled corticosteroids ( $\geq 1000$   $\mu\text{g}/\text{day}$  beclomethasone or equivalent) and LABA ( $\geq 100$   $\mu\text{g}/\text{day}$  salmeterol or equivalent), and have been on stable maintenance asthma medication for  $\geq 4$  weeks. Oral corticosteroids were acceptable in doses  $< 10$   $\text{mg}/\text{day}$ . Patients were required to need  $< 8$  puffs/day of short-acting bronchodilator,  $< 4$  puffs/day of long-acting rescue bronchodilator, and  $< 2$  nebulizer treatments per day. In addition, patients were required to have a low AQLQ score ( $\leq 6.25$ ), a low threshold percentage of symptom-free days ( $\geq 2$  days of asthma symptoms per week), and have pre-bronchodilator  $\text{FEV}_1 \geq 60\%$  of the predicted value; 86% of the bronchial thermoplasty group (163 patients) and 88% of the sham control group (86 patients) met ATS criteria for severe refractory asthma. Bronchial thermoplasty patients had a mean pre-bronchodilator  $\text{FEV}_1$  of 78% of the predicted value.
- A fair-quality small RCT enrolled patients with severe asthma (Pavord et al., 2007). All patients met the Global Initiative for Asthma (GINA) criteria for severe persistent asthma. All but 1 patient met ATS criteria for refractory asthma. For inclusion in the study, patients were required to use high-dose inhaled glucocorticoids ( $\geq 750$  micrograms [ $\mu\text{g}$ ] fluticasone propionate per day or equivalent) and LABA ( $\geq 100$   $\mu\text{g}$  of salmeterol or the equivalent). In addition, patients were required to have a pre-bronchodilator  $\text{FEV}_1 \geq 50\%$  of the predicted value. Bronchial thermoplasty patients had a mean pre-bronchodilator  $\text{FEV}_1$  of 63% of the predicted value.
- A fair-quality RCT enrolled patients with moderate or severe stable asthma (Cox et al., 2007). For study inclusion, patients were required to have an absence of unscheduled physician visits for asthma care, unchanged use of asthma medication for maintenance treatment, and stable use of rescue medication ( $\leq 4$  puffs in a 24-hour period of a short-acting bronchodilator). In addition, patients were required to need daily treatment with inhaled corticosteroids equivalent to a dose of  $\geq 200$   $\mu\text{g}$  of beclomethasone and LABA at a dose of  $\geq 100$   $\mu\text{g}$  of salmeterol or equivalent, to maintain reasonable asthma control. Patients were required to have a mean pre-bronchodilator  $\text{FEV}_1$  of 60% to 85% of the predicted value. Bronchial thermoplasty patients had a mean pre-bronchodilator  $\text{FEV}_1$  of 73% of the predicted value.
- A very-poor-quality case series enrolled patients with mild to moderate stable asthma (Cox et al., 2006). Patients were excluded if they used more than 4 puffs in a 24-hour period of a short-acting  $\beta_2$ -adrenergic agonist (e.g., albuterol 100  $\mu\text{g}/\text{puff}$  or equivalent)

except for exercise. Patients had a mean pre-bronchodilator FEV<sub>1</sub> of 82% of the predicted value.

- A very-poor-quality case series enrolled patients with severe asthma that had severe airflow obstruction (Doeing et al., 2013). For inclusion in the study, patients were required to use high-dose inhaled glucocorticoids ( $\geq 1000$   $\mu\text{g}/\text{day}$  fluticasone or equivalent) and LABA  $\geq 100$   $\mu\text{g}/\text{day}$ . Patients had a mean pre-bronchodilator FEV<sub>1</sub> of 52% of the predicted value.
- A small very-poor-quality retrospective cohort study enrolled patients with severe asthma requiring high-dose inhaled glucocorticoids ( $\geq 1000$   $\mu\text{g}/\text{day}$  beclomethasone equivalent daily) plus additional preventer medications (Bicknell et al., 2015). Patients had a mean pre-bronchodilator FEV<sub>1</sub> of 72% of the predicted value.
- A very-poor-quality case series enrolled patients with severe asthma requiring  $\geq 500$   $\mu\text{g}/\text{day}$  fluticasone plus salmeterol 100  $\mu\text{g}$  daily or equivalent (Chakir et al., 2015). Patients were required to have a pre-bronchodilator FEV<sub>1</sub>  $\geq 50\%$ , and were allowed a previous smoking history under certain conditions. Patients had a mean pre-bronchodilator FEV<sub>1</sub> of 64% of the predicted value.

Cox et al. (2007) conducted a post hoc analysis on 32 patients (16 thermoplasty, 16 control) who required  $> 1000$   $\mu\text{g}$  beclomethasone per day or equivalent at baseline. At 12 months follow-up, there were greater improvements observed relative to the between-group differences observed in the entire cohort for several outcome measures. Statistically significant improvements in the thermoplasty group compared with the control group were observed in morning PEF, airway hyperresponsiveness, AQLQ, and ACQ.

Pavord et al. (2007) conducted a post hoc analysis of covariance to investigate whether nonsignificant differences in baseline values of rescue medication use, AQLQ, and ACQ affected outcomes. Baseline ACQ score was found to have a statistically significant relationship to ACQ at 22 weeks, resulting in a loss of statistical significance for this one measure.

Castro et al. (2010) conducted a univariate logistic regression within the bronchial thermoplasty group to investigate whether baseline characteristics were statistically significant predictors of AQLQ response (responders versus nonresponders). Responders were defined as those patients that had a change in AQLQ score of 0.5 or greater. Responders were found to have lower (less favorable) baseline AQLQ scores than nonresponders and higher (less favorable) ACQ scores than nonresponders. Long-term follow-up data suggests that responders have fewer asthma-related adverse events and healthcare utilization than nonresponders (Wechsler et al., 2013). Average severe exacerbations), respiratory adverse events, asthma multiple symptoms, ED visits for respiratory symptoms, and hospitalizations for respiratory symptoms over years 2 through 5 follow-up were higher in nonresponders than in responders. Wechsler et al. (2013) also investigated the impact of reported seasonal allergy status and found that there was no difference in severe exacerbations over 5 years between those patients with seasonal allergy and those with no allergies. In addition, both patients with FEV<sub>1</sub> values of 60% to 70% of



predicted value and those with FEV<sub>1</sub> values of > 70% of predicted value had sustained improvements in exacerbations over the 5-year period.

Although no formal post hoc analyses were conducted, 2 of the nonrandomized studies commented on effects of baseline and procedural characteristics on study outcomes. Cox et al. (2006) reported that there was no relationship between rate or severity of adverse events and the anesthesia used, baseline medication use, or baseline airway hyperresponsiveness. Chakir et al. (2015) noted that patients with greater airway smooth muscle (ASM) mass ( $\geq 15\%$ ) had greater absolute reduction in ASM following bronchial thermoplasty.

#### *Quality of the Evidence:*

The quality of the evidence was assessed taking into consideration the quality of the individual studies; the precision, directness, and consistency of data; and the applicability of the data to the relevant patient population in clinical practice. The evidence for differential effectiveness of bronchial thermoplasty for treating asthma was considered to be of very low quality because of the lack of studies specifically designed to assess differential effects of bronchial thermoplasty.

#### **Key Question #4**

#### ***Key Question #4: What are the cost implications and cost-effectiveness of bronchial thermoplasty?***

Four studies were found that compared the cost of usual care with bronchial thermoplasty or assessed the cost effectiveness of bronchial thermoplasty. One of these studies was conducted in Italy; the other 3 studies were conducted in the United States.

#### ***Cost of Bronchial Thermoplasty***

Four of the economic evaluations provided estimated costs for the bronchial thermoplasty procedure. The below cost estimates varied widely:

- Menzella et al. (2014) assumed a cost of €6550 (USD 7864.18, year 2015\*) for the bronchial thermoplasty procedure, which was estimated from data provided by a single hospital in Italy, which included costs of physicians and staff, bronchial thermoplasty procedure, and hospital admission.
- Cangelosi et al. (2015) calculated the costs of bronchial thermoplasty to be \$50,470 (\$52,346.23, year 2015\*) based on private, commercial payer data and included both physician payments and procedure costs over a 5-year period. This is compared with \$49,510 (\$51,350.54, year 2015\*) for standard care. Thus, bronchial thermoplasty increased costs by \$960 (\$996.69, year 2015\*) over the 5-year period.
- Zein et al. (2015) calculated the costs of bronchial thermoplasty to be \$6690 (\$6938.70, year 2015\*) based on average Medicare reimbursement rates.

- Zafari et al. (2016) calculated the costs of bronchial thermoplasty to be \$14,900 (\$15,453.91, year 2015\*) based on data from a published trial, to estimate the average cost of 3 catheters, facility, and professional fee.

\*NOTE: The above conversions represent an approximate translation of the procedural cost and/or product price values to current U.S. values. These conversions do NOT provide an estimate of the current cost; they are based on January 30, 2016, use of the CCEMG - EPPI-Centre web-based cost converter with the International Monetary Fund (IMF) dataset for Purchasing Power Parity (PPP) values, available at: [click here](#) [last updated on January 27, 2014] (Shemilt et al., 2010).

### ***Cost of Usual Care Compared with Bronchial Thermoplasty***

Menzella et al. (2014) performed a budget impact analysis to project the costs of a hypothetical cohort of adult patients with severe asthma. During the first year of treatment, the bronchial thermoplasty procedure adds approximately €20,000 (USD 24,012.77, year 2015\*) to standard care. Bronchial thermoplasty was projected to reduce the rate of emergency room visits by 83.3% and reduce the rate of hospitalization by 74.2%. In terms of costs to the regional healthcare system, the cost of introducing bronchial thermoplasty would be approximately €17.7 million (USD \$21.25 million, year 2015\*) during the first year, but these costs would be offset by savings from avoided adverse events. Bronchial thermoplasty would produce savings of approximately €1 million (USD \$1.2 million, year 2016\*) after year 3, €10.5 million (USD \$12.6 million, year 2015\*) after year 4, and up to €19.2 million (USD \$23.1 million, year 2015\*) after year 5.

\*NOTE: The above conversions represent an approximate translation of the procedural cost and/or product price values to current U.S. values. These conversions do NOT provide an estimate of the current cost; they are based on January 30, 2016, use of the CCEMG - EPPI-Centre web-based cost converter with the International Monetary Fund (IMF) dataset for Purchasing Power Parity (PPP) values, available at: [click here](#) [last updated on January 27, 2014] (Shemilt et al., 2010).

### ***Cost-Effectiveness***

The literature search identified 3 cost-effectiveness assessments for bronchial thermoplasty for asthma. These studies provided a cost-effectiveness analysis for the use of bronchial thermoplasty from a payer perspective. In these studies, although bronchial thermoplasty increased costs in the short term, it was found to increase quality-adjusted life-years (QALYs) in the longer term. The studies are summarized in the following paragraphs.

Cangelosi et al. (2015) applied a Markov model to estimate the costs and quality-of-life (QOL) impact of bronchial thermoplasty compared with high-dose combination therapy among severe persistent asthma patients (i.e., those patients requiring high-dose combination therapy and required  $\geq 1$  asthma exacerbation-related ED visit in the past year). Over a 5-year period,

bronchial thermoplasty increased quality-adjusted life expectancy by approximately 0.18 QALYs (3.14 versus 2.96), driven primarily by the decrease in exacerbations. Bronchial thermoplasty increased costs by \$960 (\$995.69, year 2015\*) when considering both the procedural costs and costs of treating periprocedural exacerbations. These findings resulted in an incremental cost-effectiveness ratio (ICER) of \$5495 (\$5699.28, year 2015\*) per QALY.

Zein et al. (2015) applied a Markov model to estimate the costs and QOL impact of bronchial thermoplasty compared with usual care among severe persistent asthma patients whose asthma is not well-controlled with combination therapy of inhaled corticosteroids and LABA. Compared with Cangelosi et al. (2015), this study used a less severe patient population and estimated a lesser healthcare utilization without bronchial thermoplasty. Use of bronchial thermoplasty increased costs by \$5458 (\$5660.90, year 2015\*) compared with usual care at baseline. Treatment with bronchial thermoplasty resulted in 6.40 QALYs and \$7512 (\$7791.26, year 2015\*) in cost compared to 6.21 QALYs and \$2054 (2015 USD \$2130.36) for usual care. These findings resulted in an ICER of \$45,300 (2015 USD, \$ 46,984.04) per QALY at 5 years and an ICER of \$29,821 (2015 USD, \$30,929.60) per QALY at 10 years.

Zafari et al. (2016) applied a Markov model to estimate the costs and quality-of-life impact of bronchial thermoplasty compared with usual care and omalizumab treatment for moderate-to-severe allergic asthma patients whose asthma is not well-controlled despite therapy with inhaled corticosteroids, with or without LABA. This study was conducted from the healthcare system perspective. Treatment with bronchial thermoplasty resulted in 3.24 QALYs and \$28,100 (\$29,144.62, year 2015\*) in cost compared to 3.08 QALYs and \$15,400 (\$15,972.50, 2015\*) for usual care and 3.26 QALYs and \$117,000 (\$121,349.50, year 2015\*) for omalizumab. In the life-time analysis that assumed an exponentially declining effect for bronchial thermoplasty after the 5th year, the ICER of bronchial thermoplasty compared with usual care, omalizumab compared with bronchial thermoplasty, and omalizumab compared with usual care was \$12,500/QALY (\$12,964.69/QALY, year 2015\*), \$3.15 million/QALY (2015 USD, \$3.27 million/QALY), and \$529,000/QALY (\$548,665.67/QALY, year 2015\*), respectively.

\*NOTE: The above conversions represent an approximate translation of the procedural cost and/or product price values to current U.S. values. These conversions do NOT provide an estimate of the current cost; they are based on January 30, 2016, use of the CCEMG - EPPI-Centre web-based cost converter with the International Monetary Fund (IMF) dataset for Purchasing Power Parity (PPP) values, available at: [click here](#) [last updated on January 27, 2014] (Shemilt et al., 2010).

## Practice Guidelines

The search of the core sources and relevant specialty groups identified 4 guidelines with relevant recommendations regarding use of bronchial thermoplasty in treating asthma and published within the past 10 years. The general recommendations provided by the guidelines are summarized in [Table 2](#). Additional details, by guideline, are presented in [Appendix V](#). See

also [Practice Guidelines](#) in the **TECHNICAL REPORT** for additional background information on guidelines.

Four guidelines addressed the use of bronchial thermoplasty in treating asthma. These included guidelines from the European Respiratory Society (ERS) jointly with the ATS, British Thoracic Society (BTS), the Global Initiative for Asthma (GINA), and NICE.

Two of the 4 guidelines state that bronchial thermoplasty is a possible treatment option in highly-selected adult patients with severe asthma (BTS, GINA). One of these guidelines restricted its recommendation of use of bronchial thermoplasty to a few specialist centers (BTS). Two guidelines stated that bronchial thermoplasty for severe asthma should only be practiced in the context of a clinical trial or independent systematic registry, or after establishing clinical governance, including patient consent and research or audit (ERS/ATS, NICE). All guidelines encouraged caution in the use of this technology, as longer-term follow-up studies are needed to assess the safety and efficacy of bronchial thermoplasty. The place of bronchial thermoplasty in the treatment of asthma remains to be established.

## Table 2. Summary of Practice Guideline Recommendations

**Key:** ATS, American Thoracic Society; BT, bronchial thermoplasty; BTS, British Thoracic Society;; BTS, British Thoracic Society; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; GL(s), guideline(s); NICE, National Institute for Health and Clinical Excellence; pt(s), patient(s); QOL, quality of life; sx, symptoms; tx, treatment (or therapy)

Quantity of Individual GLs	Individual GL Quality	Recommendations
4 (BTS, ERS/ATS, GINA, NICE)	1 Good 3 Fair	<p><u>BTS (Good Quality)</u>: BT is a possible tx option in selected pts w/ severe persistent asthma already on maximal tx, although its place in the tx of asthma remains to be established (Grade A). Long-term safety and efficacy of BT remain unclear and BT should be limited to a few specialist centers in carefully selected pts.</p> <p><u>ERS/ATS (Fair Quality)</u>: The available evidence concerning this procedure is considered to be of very low quality. ERS/ATS strongly recommend that BT be performed only in adults with severe asthma and only in the context of a clinical trial or systematic registry (strong recommendation).</p> <p><u>GINA (Fair Quality)</u>: BT is a potential option for highly selected adult pts who have uncontrolled asthma despite use of recommended tx regimens and referral to an asthma specialty center (Evidence B). The long-term safety and efficacy of BT are unknown. Carefully controlled trials are important as a large placebo effect has been seen in studies to date.</p> <p><u>NICE (Fair Quality)</u>: For pts w/ severe asthma, BT has been shown to provide some improvements in sx and QOL and reductions in exacerbations and hospitalizations. Although evidence of safety is adequate in the short and medium term, more evidence of long-term safety is needed; therefore, BT should only be used after establishment of special arrangements for</p>

Quantity of Individual GLs	Individual GL Quality	Recommendations
		clinical governance, including pt consent and research or audit. The NICE encourages additional research to evaluate the long-term safety and efficacy of BT.

## Selected Payer Policies

No Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) was identified for bronchial thermoplasty. At the direction of Washington State HCA, the coverage policies for the following organizations were reviewed: Aetna, CMS, Oregon Health Evidence Review Commission (HERC), GroupHealth, and Regence Blue Cross/Blue Shield. The only payers found to have a policy were Aetna, GroupHealth, and Regence Group. Aetna and Regence Group consider bronchial thermoplasty experimental and investigational for the treatment of asthma. GroupHealth states that the use of bronchial thermoplasty does not meet the Group Health Medical Technology Assessment Criteria. No coverage policy for bronchial thermoplasty was identified on the Oregon HERC website.

See [Selected Payer Policies](#) in the **TECHNICAL REPORT** for additional details and links to policy documents.

## Systematic Reviews

Three systematic reviews and meta-analyses were found on the efficacy and safety of bronchial thermoplasty for asthma. All 3 studies analyzed data from the 3 RCTs that were analyzed in the current report. Two of the trials analyzed data from 1-year follow-up of bronchial thermoplasty. One trial analyzed results from uncontrolled long-term follow-up 1 to 5 years following thermoplasty. In general, the systematic reviews resulted in some positive but inconsistent results across outcome measures. See [Systematic Reviews](#) in the **TECHNICAL REPORT** for additional details on these reviews.

## Overall Summary and Discussion

### *Evidence-Based Summary Statement*

The Alair Bronchial Thermoplasty System (Boston Scientific Corp.) is regulated via the premarket approval (PMA) process as a Class III (high risk) device and is subject to the most stringent regulations enforced by the FDA. The FDA approved the bronchial thermoplasty system on April 27, 2010, for the treatment of severe persistent asthma in adults whose asthma is not well controlled with ICS and LABAs (CRDH, 2010). FDA PMA was primarily based on a pivotal double-blind sham-controlled RCT (Castro et al., 2010). The FDA concluded that bronchial thermoplasty had an acceptable safety profile, as adverse events were reversible and most were common in both active and control groups. Serious adverse events included hemoptysis, respiratory infections, atelectasis, pneumonia, and asthma symptoms. With the exceptions of atelectasis and hemoptysis, these serious complications occurred in both active and sham treatment groups. However, these are expected events in the patient population and

may be related to bronchoscopic procedures rather than the thermoplasty treatment; thus, it did not raise major concerns. The primary efficacy measure of AQLQ scores between treatment and sham groups did not meet prespecified success criteria. However, the FDA considered severe asthma exacerbations to be an important measure of clinical performance; there was a clinically important difference in favor of the thermoplasty group for this endpoint. In addition, several other clinically important endpoints that may be related to severe asthma exacerbations also showed differences in favor of the thermoplasty group (e.g., ED visits; hospitalizations; rescue medication use; asthma symptoms; days lost from work, school, or other activities; unscheduled physician office visits for respiratory symptoms).

The overall body of evidence concerning thermoplasty for treatment of asthma was small in size and low in quality. The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3 very-poor-quality case series. The evidence for the effectiveness of bronchial thermoplasty for treating asthma was considered to be of low quality because of some positive but inconsistent results regarding short-term benefits of bronchial thermoplasty, varied patient selection criteria across studies, small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long-term efficacy of bronchial thermoplasty.

Overall, the body of evidence suggests that during the first year after thermoplasty, some benefits were observed, including improved QOL, symptom relief, reduced medication use, and reductions in ED visits; however, the benefits varied somewhat across studies. These differences in benefits may have resulted from differences in study protocols (e.g., different primary outcome measures in all 3 RCTs, 2 RCTs involved partial discontinuation of certain asthma medications). Only one of the RCTs reported results of controlled follow-up for longer than 1 year. This study found that, at 3 years follow-up, the only statistically significant benefit of thermoplasty was an improvement in airway responsiveness. However, this follow-up may have been flawed since it involved only 69 patients and the dropout rate was much higher for the control group than for the thermoplasty group. The apparent loss of benefits of thermoplasty during longer follow-up may indicate loss of effectiveness over time or may be an artifact of selective dropping out of control group patients who have the most poorly controlled asthma.

Results from 4 very-poor-quality nonrandomized studies report some positive but mixed outcomes. In a single retrospective cohort study in patients with severe asthma, 5 of 10 clinic patients (50%) met criteria for clinical improvement at 1-year follow-up. Asthma medications were reduced in 3 of 10 (30%) patients and the number of severe exacerbations and hospitalizations was reduced in 3 of 10 (30%) patients. A case series of 16 patients with mild to moderate asthma found that mean pre-bronchodilator FEV<sub>1</sub> and airway responsiveness was significantly increased from baseline at 1 year post-thermoplasty; however, this increase in FEV<sub>1</sub> was not maintained at 2 years. A second case series assessed the effect of bronchial thermoplasty in 8 patients with severe asthma that had severe airflow obstruction and found that at 1-year follow-up, there were no changes in mean pre bronchodilator FEV<sub>1</sub> or mean hospitalizations for asthma. A third case series assessed the effect of bronchial thermoplasty in

17 patients with severe asthma and found that at 1-year follow-up, some medications were reduced relative to baseline, self-reported number of exacerbations decreased, and the Asthma Control Scoring System improved. However, there was no significant change in mean pre-bronchodilator FEV<sub>1</sub>.

The majority of complications associated with bronchial thermoplasty occurred within the treatment period. Bronchial thermoplasty was associated with statistically significant increases in dyspnea, wheezing, chest discomfort, night awakenings, sputum discoloration, cough, productive cough, bronchial irritation, and nasal congestion. Most of these complications were mild or moderate in severity. The 3 RCTs found that 5% to 27% of thermoplasty patients compared with 0% to 4% of control patients required hospitalization during the treatment period. However, only 1 fair-quality small RCT found that the between-group difference was significant. Uncontrolled follow-up of patients who underwent thermoplasty treatment found that, in years 2 to 5 versus the first year after treatment, there were no significant changes in respiratory adverse events, ED visits, need for hospitalization, maintenance asthma medication usage, respiratory parameters, or most computed tomography (CT) findings. One study reported that bronchiectasis occurred in 3 (2%) patients.

Labeling information approved by the FDA warns that pneumothorax and respiratory failure requiring intubation are potential complications. In addition, bronchial thermoplasty is contraindicated under any of the following circumstances: presence of a pacemaker, internal defibrillator or similar implanted electronic device; known sensitivity to the drugs employed during bronchoscopy such as lidocaine, atropine, or benzodiazepines; prior bronchial thermoplasty procedure; active respiratory infection; an asthma attack or alteration of the dose of systemic glucocorticoids in the preceding 14 days; known bleeding disorder; need for aspirin, anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory drugs that cannot be interrupted. The UK NICE has stated that bronchial stenosis is a potential long-term complication. In the available literature, no deaths were reported that were related to bronchial thermoplasty for treatment of asthma.

Patient selection criteria varied considerably between studies, and the RCTs were selective in the patients that were enrolled in the study. Although bronchial thermoplasty is indicated in patients with severe asthma, one RCT included patients with moderate and severe asthma. Because we did not want to exclude this important study, studies that included patients with moderate or severe asthma were eligible for inclusion in this report. Because the body of literature concerning safety and efficacy of bronchial thermoplasty for asthma is small, it is difficult to determine whether efficacy or safety of thermoplasty varied by baseline variables such as asthma severity, medication use, pulmonary function, or other characteristics. More data on differential effects of baseline characteristics are needed to better define patient selection criteria for bronchial thermoplasty.

***Gaps in the Evidence***

The following evidence is needed to better answer the Key Questions of this report:

- RCTs and long-term cohort studies of sufficient size, design and length to further investigate the safety and efficacy of bronchial thermoplasty in patients with severe asthma.
- Studies designed to systematically investigate differential effectiveness and safety according to patient characteristics (e.g., severity of asthma, baseline respiratory function and medication needs, and previous treatment history).
- Additional studies investigating the impact of bronchial thermoplasty on QOL and functional status.



## TECHNICAL REPORT

### Clinical Background

#### *Prevalence and Treatment of Asthma*

Asthma is a chronic inflammatory disorder of the airways characterized by episodes of impaired breathing caused by airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. It is estimated that 300 million persons suffer from asthma worldwide, with the highest prevalence in North America, Australia, and Western Europe (Sverrild et al., 2012). A total of 18.7 million adults in the United States suffer from asthma and it is a major health concern. According to recent estimates, in the United States, asthma is responsible for 14.2 million ambulatory care visits, 439,000 hospitalizations, and 3400 deaths per year (CDC, 2014). The prevalence of asthma has increased over the past 30 to 40 years and was at 8.2% in 2009; however, for the U.S. population as a whole, the prevalence of asthma attacks has reached a plateau in recent years and remains at approximately 4% (Akinbami et al., 2011; Myers and Tomasio, 2011). The prevalence of asthma varies among different population subgroups. Women have a higher asthma prevalence rate than men, boys have a higher rate than girls, and children have a higher rate than adults. Also, non-Hispanic whites and Hispanics have a lower asthma prevalence rate than non-Hispanic blacks (Akinbami et al., 2011; Myers and Tomasio, 2011; ALA, 2012). Asthma is more common in the poor than other socioeconomic groups. In 2008, asthma was responsible for 14.2 million lost workdays in adults and 14.4 million lost school days in children (Akinbami et al., 2011).

Current guidelines emphasize that asthma therapy should be selected on the basis of disease severity. For intermittent asthma, no daily medication is advised for the majority of patients. In order to relieve occasional symptoms, a rapid-acting, inhaled  $\beta$ 2-agonist is prescribed. Patients with mild, persistent asthma require controller medication with a daily-inhaled glucocorticoid to achieve and maintain asthma control. Other treatment options include sustained-release theophylline, cromones, or a leukotriene modifier. For moderate persistent asthma, the preferred therapy is a combination of inhaled glucocorticoid and a long-acting, inhaled  $\beta$ 2-agonist (LABA). Sustained-release theophylline or a leukotriene modifier can be used instead of the  $\beta$ 2-agonist. Primary therapy for severe, persistent asthma includes an inhaled glucocorticoid at higher doses, in addition to a LABA. Once asthma control is achieved and maintained for 3 months, a gradual reduction of maintenance therapy should be attempted in order to identify the minimal therapy needed to maintain control (Bateman et al., 2008). Some patients with severe asthma do not achieve acceptable control despite high dosages of medication. The National Asthma and Education and Prevention Program Expert Panel Report recommends add-on therapy with LABAs, leukotriene modifiers, theophylline, and omalizumab in patients with difficult-to-treat asthma who take inhaled corticosteroids. These therapies reduce inflammation or decrease airway narrowing by relaxing ASM. Unfortunately, therapeutic options for patients with severe asthma remain limited and adjunctive therapies (like those

listed above) targeting other mediators of the inflammatory pathway have yielded variable results.

The definition of severe asthma is complex and requires an assessment of asthma symptoms, short-acting rescue bronchodilator use, pulmonary function, requirement for and dosing of controller medications, and the number and severity of exacerbations (Laxmanan and Hogarth, 2015). When evaluating severe asthma, physicians should rule out other potential causes, including poor inhaler technique, inadequate adherence to therapy, exposures to environmental triggers, cigarette smoking, gastroesophageal reflux disease, obstructive sleep apnea, chronic rhinitis or sinusitis, and obesity. The American Thoracic Society (ATS) and European Respiratory Society (ERS) define severe asthma as requiring treatment with high-dose inhaled corticosteroids plus a second controller medication (and/or systemic corticosteroids) to maintain asthma control. Additionally, patients who had required systemic corticosteroids for  $\geq$  50% of the previous year are also classified as having severe asthma (Chung et al., 2014).

Bronchial thermoplasty has been approved by the Food and Drug Administration (FDA) intended for the treatment of severe, persistent asthma in patients who are age 18 years or older with asthma that has not been well controlled by long-acting bronchodilators and glucocorticoids (CDRH, 2010).

### ***Bronchial Thermoplasty***

Bronchial thermoplasty is designed to reduce the smooth muscle that constricts the airway during asthma attacks. This procedure relies on a catheter that has an expandable array of electrodes that is delivered to the airway via a bronchoscope, which allows the physician to see inside the lung. After the catheter is threaded into the airway, a wire leading out of the back end of the catheter is attached to a radiofrequency generator and a lever is operated that causes the electrodes to curl into a ball shape around the front end of the catheter. The curved electrodes are held against the bronchial walls and an electrical current is applied to generate heat that destroys the smooth muscle underneath the lining of the bronchial passages. Bronchial thermoplasty is performed in 3 separate procedures in which all accessible airways located beyond the mainstream bronchi (average of 3 to 10 mm in diameter), except for the right middle lobe, are treated. The delivery of energy during bronchial thermoplasty uses continuous feedback to tightly control the degree and time of tissue heating to decrease airway smooth muscle (ASM) mass without airway perforation or stenosis. Dividing the treatment into 3 procedures allows shorter procedure times and obviates the risks associated with widespread irritation of the airways in patients with severe asthma. Bronchial thermoplasty is typically performed by a pulmonologist with the patient under moderate sedation or general anesthesia.

### ***Safety of Bronchial Thermoplasty***

Bronchial thermoplasty has been associated with statistically significant increases in dyspnea, wheezing, chest discomfort, night awakenings, sputum discoloration, cough, productive cough, and need for hospitalization during the treatment period. Most of these complications were mild or moderate in severity. Other potential adverse events that may occur during or shortly

after this procedure include the following: headache, fever, chest infection, pleurisy, bronchitis, hoarseness, throat irritation, bronchospasm, mucus production, retention of mucus, hypoxemia, pneumothorax, and exacerbation of asthma (Cox et al., 2006; Cox et al., 2007; Pavord et al., 2007; Castro et al., 2010).

Labeling information approved by the FDA warns that pneumothorax and respiratory failure requiring intubation are potential complications (CDRH, 2010) and the National Institute for Health and Care Excellence (NICE) has stated that bronchial stenosis is a potential long-term complication (NICE, 2012).

*Contraindications:* According to labeling information approved by the FDA, bronchial thermoplasty is contraindicated under any of the following circumstances (Asthmatx Inc., 2010):

- Presence of a pacemaker, internal defibrillator, or similar implanted electronic device
- Known sensitivity to the drugs employed during bronchoscopy such as lidocaine, atropine, or benzodiazepines
- Prior bronchial thermoplasty procedure
- Active respiratory infection
- An asthma attack or alteration of the dose of systemic glucocorticoids in the preceding 14 days
- Known bleeding disorder
- Need for aspirin, anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory drugs that cannot be interrupted

The latter 4 contraindications listed here are relative rather than absolute and, in some cases, may only require delay of bronchial thermoplasty (CDRH, 2010).

## Washington Agency Utilization Data

### Bronchial Thermoplasty

The utilization of bronchial thermoplasty over five years is relatively small, therefore, to avoid releasing data that might be identifiable; the findings are release in aggregate for all agencies.

#### Data analysis based on patients from:

PEBB/UMP  
PEBB Medicare;  
Labor and Industries  
Medicaid Fee-for-Service;  
Medicaid Managed Care

**Population:** >17 years old

**Utilization:** 2010 - 2014

#### Coding:

31660, one lobe; 31661, two lobes,  
*C9730, C9731 (deleted 20111231)*  
*0276T, 0277T (deleted 20130101)*

**Average age:** 60 years old

Proportionally, more males than females receive bronchial thermoplasty.

#### Diagnosis for individuals receiving bronchial thermoplasty:

Asthma (493)  
Acute and chronic respiratory failure (518)

#### Amount submitted for CPT professional code:

Range \$4,500 to \$12,000

#### Associated inpatient stay with bronchial thermoplasty:

Range: \$20,000 to \$272,000 (submitted)  
Length of stay: 1 to 6 days

## Review Objectives and Analytic Framework

### *Scope*

The scope of this report is defined as:

**Population:** Adults diagnosed with moderate or severe asthma.

**Interventions:** Bronchial thermoplasty.

**Comparisons:** Medical management; sham treatment; no comparator.

**Outcomes:** Quality of life; asthma control, including medication use; asthma exacerbations; lung function; safety; emergency department (ED) visits; hospitalizations; mortality; cost and cost-effectiveness.

### *Key Questions*

The following key questions will be addressed:

1. What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma?
  - a. Is there clinically meaningful improvement for patients with severe asthma?
2. What are the harms associated with bronchial thermoplasty?
3. Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)?
4. What are the cost implications and cost-effectiveness of bronchial thermoplasty?

## Methods

### *Search Strategy and Selection Criteria*

See [Appendix I](#) for additional search details.

### *Systematic Reviews and Guidelines*

These sources were searched on October 2, 2015, for systematic reviews, meta-analyses, economic evaluations, and practice guidelines:

- Core online databases such as the Agency for Healthcare Research and Quality (AHRQ), Centre for Reviews and Dissemination (York University), and National Guidelines Clearinghouse (NGC).
- Websites of relevant professional societies.
- PubMed, using filters for Practice Guidelines, Guidelines, Meta-analyses, and Systematic Reviews.

Systematic reviews were selected if they reviewed studies considered eligible for answering the Key Questions or if they provided useful background information.

### *Primary Studies*

The PubMed and OVID-Embase databases were searched on October 2, 2015, for primary studies and economic evaluations designed to answer the Key Questions. Update searches were conducted on December 15, 2015, and January 25, 2016. Specific search strings are documented in [Appendix I](#). Additional studies were identified through manual searching of bibliographies of reviews and primary articles.

### *Inclusion/Exclusion Criteria*

Studies were selected for inclusion if they:

- Assessed the safety or efficacy of bronchial thermoplasty
- Were conducted in patients diagnosed with moderate or severe asthma
- Were published in English-language journals

Studies were excluded if they:

- Contained no quantitative data for assessing impact of bronchial thermoplasty
- Were conference abstracts
- Were case reports or series of case reports

Although bronchial thermoplasty has only been approved by the FDA for severe asthma, 1 of the 3 randomized controlled trials (RCTs) assessed in the current report included patients with moderate or severe asthma. Therefore study inclusion was not limited to studies assessing use of bronchial thermoplasty in severe asthma.

### **Quality Assessment**

#### *Clinical Studies*

[Appendix II](#) outlines the process used by Hayes for assessing the quality of individual primary studies and the quality of bodies of evidence. This process is in alignment with the methods recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Quality checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *good*, *fair*, *poor*, or *very poor*. For individual studies included in systematic reviews, this report relies on the quality assessment by review authors. To aid in interpreting the assessment by review authors, a systematic review quality checklist, the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007), was used.

Like the GRADE Working Group, Hayes uses the phrase *quality of evidence* to describe bodies of evidence in the same manner that other groups, such as AHRQ, use the phrase *strength of evidence*. The Hayes Evidence-Grading Guides ensure that assessment of the quality of bodies of evidence takes into account the following considerations:

- Methodological quality of individual studies, with an emphasis on the risk of bias within studies.
- Applicability to the population(s), intervention(s), comparator(s), and outcome(s) of interest, i.e., applicability to the PICO statement.
- Consistency of the results across studies.
- Quantity of data (number of studies and sample sizes).
- Publication bias, if relevant information or analysis is available.

NOTE: Two terms related to applicability are *directness* and *generalizability*. *Directness* refers to how applicable the evidence is to the outcomes of interest (i.e., health outcomes versus surrogate or intermediate outcomes) or to the comparator of interest (indirect comparison of 2 treatments versus head-to-head trials). *Generalizability* usually refers to whether study results are applicable to real-world practice. If the setting is not specified in a PICO (population-interventions-comparator-outcomes) statement, the issue of generalizability to real-world settings is not typically treated as an evidence quality issue. Another term used by some organizations is *imprecision*, which refers to findings based on such a small quantity of data that the CI surrounding a pooled estimate includes both clinically important benefits and clinically important harms, or such a small quantity of data that any results other than large statistically significant effects should be considered unreliable.

Bodies of evidence for particular outcomes are labeled as being of *high, moderate, or low quality*, or they are deemed to be *insufficient* to permit conclusions. These labels can be interpreted in the following manner:

**High:** Suggests that we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies.

**Moderate:** Suggests that we can have reasonable confidence that the results represent the true direction of effect but that the effect estimate might well change with the publication of new studies.

**Low:** We have very little confidence in the results obtained, which often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and, possibly, the direction of the results.

**Insufficient:** Suggests no confidence in any result found, which often occurs when there is a paucity of data or the data are such that we cannot make a statement on the findings.

### *Economic Evaluations*

A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. Sources are listed in [Appendix II](#).

### *Guidelines*

The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool (AGREE Enterprise, 2013), along with a consideration of the items related to commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines. Use of the AGREE tool was limited to these areas because they relate most directly to the link between guideline recommendations and evidence.

## **Search Results**

### *Included Studies*

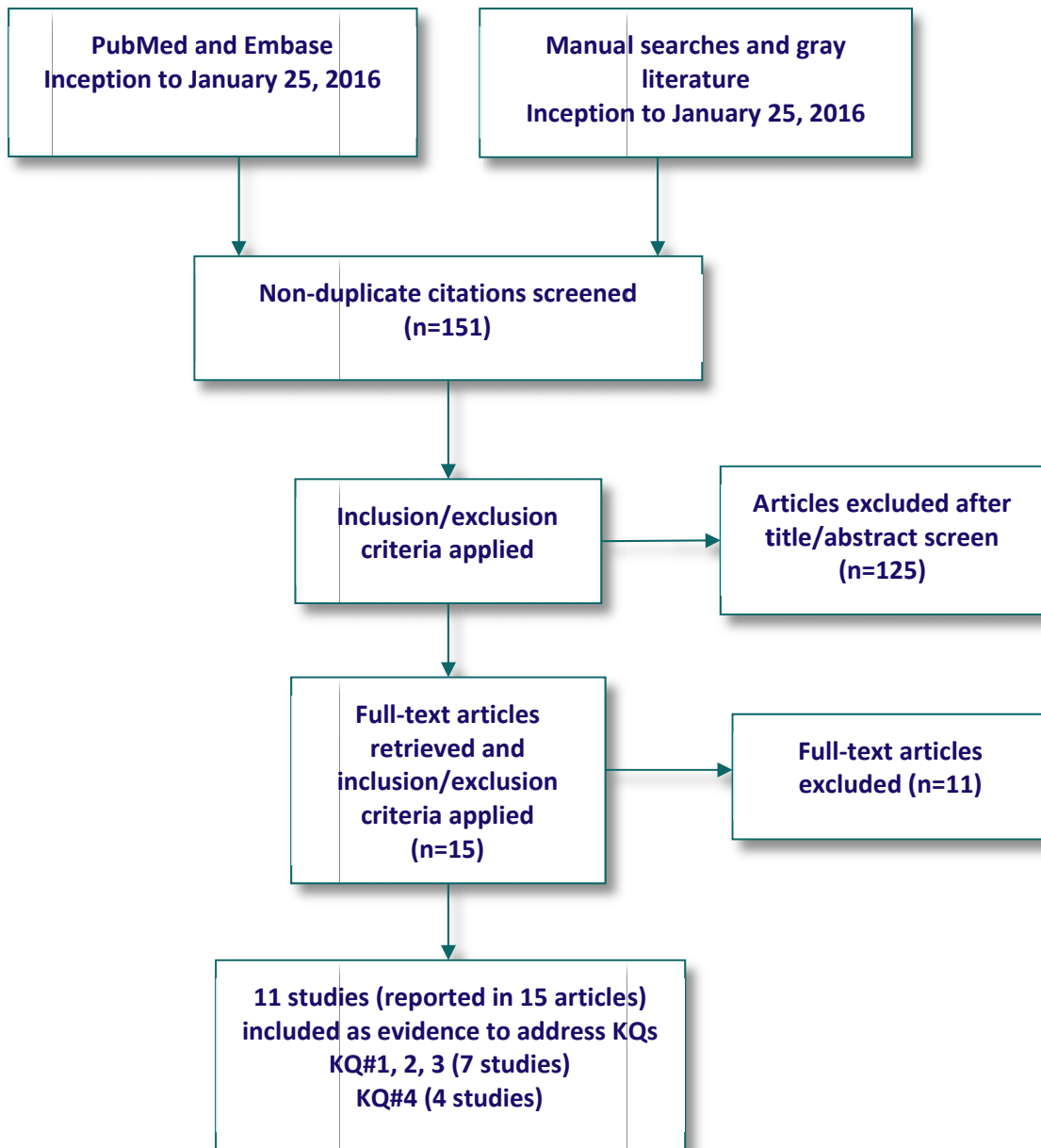
Eleven studies reported in 15 publications were selected for detailed analysis as evidence pertaining to the Key Questions. [Figure 1](#) summarizes the systematic identification and selection of these studies. No unique studies were identified for Key Question #2 (safety) or Key Question #3 (differential effectiveness). Four studies were identified for Key Question #4 (cost-effectiveness).

### *Excluded Studies*

See [Appendix III](#) for a listing of the 11 studies that were excluded from analysis after full-text review.



Figure 1. Summary of Search Results



## Literature Review

### Key Question #1

**Key Question #1: What is the clinical effectiveness of bronchial thermoplasty for treatment of asthma? #1a: Is there clinically meaningful improvement for patients with severe asthma?**

#### *Clinical Effectiveness of Bronchial Thermoplasty for Asthma (Key Question #1)*

The searches identified a total of 7 studies (reported in 11 articles) that evaluated the effectiveness of bronchial thermoplasty treatment in patients with asthma (Cox et al., 2006; Cox et al., 2007; Pavord et al., 2007; Castro et al., 2010; Castro et al., 2011; Thomson et al., 2011; Doeing et al., 2013; Pavord et al., 2013; Wechsler et al., 2013; Bicknell et al., 2015; Chakir et al., 2015). The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3 very-poor-quality case series. Outcome measures included laboratory-collected respiratory parameters (e.g., forced expiratory volume in 1 second [FEV<sub>1</sub>]; provocation challenge causing 20% decrease in FEV<sub>1</sub> [PC<sub>20</sub>]), quality-of-life (QOL) assessments (Asthma Quality of Life Questionnaire [AQLQ]; Asthma Control Questionnaire [ACQ]), patient self-report data collected in daily diaries (e.g., peak expiratory flow, asthma symptoms, asthma exacerbations, rescue medication use), changes in medication requirements, and hospitalizations and ED visits.

See [Appendix IV](#) for details regarding selected studies. The following sections are organized by study design.

**RCTs:** The literature search identified 3 RCTs that evaluated the Alair Bronchial Thermoplasty System for treatment of moderate or severe asthma (Cox et al., 2007; Pavord et al., 2007; Castro et al., 2010). One trial used sham bronchial thermoplasty in the control group (Castro et al., 2010) and 2 studies used asthma maintenance medication in the control group (Cox et al., 2007; Pavord et al., 2007). Although all of these studies were RCTs, 1 study enrolled less than 50 patients (Pavord et al., 2007) and 2 studies did not involve blinding or placebo controls (Cox et al., 2007; Pavord et al., 2007). Two RCTs enrolled patients with severe asthma (Pavord et al., 2007; Castro et al., 2010), and 1 RCT enrolled patients with moderate or severe asthma (Cox et al., 2007). All of the RCTs evaluated thermoplasty as an adjunct to continued drug therapy. Detailed descriptions of the QOL measures can be found in [Appendix VI](#). The initial reports of the RCTs involved only 1 year of follow-up; however, subsequent reports for the RCTs extended this follow-up to 5 years for patients who underwent thermoplasty (Castro et al., 2011; Thomson et al., 2011; Pavord et al., 2013; Wechsler et al., 2013) and 1 of these extensions included a subset of control group patients with 3 years follow-up (Thomson et al., 2011). All of the RCTs were supported by the device manufacturer and

#### **KQ#1, Asthma:**

RCTs: Cox 2007, Pavord 2007, Castro 2010  
RCT follow-up studies: Castro 2011, Thomson 2011, Pavord 2013, Wechsler 2013

Nonrandomized studies: Cox 2006, Doeing 2013, Bicknell 2015, Chakir 2015

performed, in part, by investigators who had financial relationships with the device manufacturer (Cox et al., 2007; Pavord et al., 2007; Castro et al., 2010). Industry-supported funding of clinical trials does not introduce automatic bias into the results of the study, and was not considered a limitation when evaluating the quality of the evidence; however, this information may be of interest to the reader.

Patient selection criteria varied across studies:

- Castro et al. (2010) enrolled patients with severe asthma. For study inclusion, patients must require daily treatment with high-dose inhaled corticosteroids ( $\geq 1000$   $\mu\text{g}/\text{day}$  beclomethasone or equivalent), LABA ( $\geq 100$   $\mu\text{g}/\text{day}$  salmeterol or equivalent), and have been on stable maintenance asthma medication for  $\geq 4$  weeks. Oral corticosteroids were acceptable in doses  $< 10$  mg per day. In addition, patients must have a low AQLQ score ( $\leq 6.25$ ),  $\geq 2$  days of asthma symptoms per week, and have pre-bronchodilator  $\text{FEV}_1 \geq 60\%$  of the predicted value; 86% of the bronchial thermoplasty group (163 patients) and 88% of the sham control group (86 patients) met ATS criteria for severe refractory asthma.
- Pavord et al. (2007) enrolled patients with severe asthma. All patients met the Global Initiative for Asthma (GINA) criteria for severe persistent asthma. All but 1 patient met ATS criteria for refractory asthma. For inclusion in the study, patients must require high-dose inhaled glucocorticoids ( $\geq 750$   $\mu\text{g}$  fluticasone propionate per day or equivalent) and LABA ( $\geq 100$   $\mu\text{g}$  of salmeterol or the equivalent). In addition, patients must also have pre-bronchodilator  $\text{FEV}_1 \geq 50\%$  of the predicted value and post-bronchodilator  $\text{FEV}_1 < 55\%$  of the predicted value.
- Cox et al. (2007) enrolled patients with moderate or severe stable asthma. For study inclusion, patients must have an absence of unscheduled physician visits for asthma care, unchanged use of asthma medication for maintenance treatment, and stable use of rescue medication ( $\leq 4$  puffs in a 24-hour period of a short-acting bronchodilator). In addition, patients must require daily treatment with inhaled corticosteroids equivalent to a dose of  $\geq 200$   $\mu\text{g}$  of beclomethasone and LABA at a dose of  $\geq 100$   $\mu\text{g}$  of salmeterol or equivalent, to maintain reasonable asthma control. Patients must also have a mean pre-bronchodilator  $\text{FEV}_1$  60% to 85% of the predicted value.

The largest available controlled study of thermoplasty for severe asthma was a double-blind, sham-controlled good-quality RCT that randomized 190 patients to thermoplasty and 98 patients to placebo treatment (Castro et al., 2010). This pivotal trial was the primary basis for FDA premarket approval (PMA) of bronchial thermoplasty. Placebo treatment involved 3 sessions of sham bronchial thermoplasty performed under conscious sedation, similar to the treatment received in the active bronchial thermoplasty group. However, in the placebo group, no radiofrequency energy was delivered. Outcomes of this study were evaluated using Bayesian methods rather than traditional statistical tools, thus the term “posterior probability of superiority (PPS)” must be used instead of the term “statistically significant.” A meaningful improvement was defined as  $\text{PPS} > 0.95$ . The authors did not provide rationale for using

Bayesian methods. It is unclear whether significant between-group differences would be observed using traditional statistical tools. The primary outcome measure for this study was mean change from baseline in AQLQ. Throughout the study, all patients continued drug therapy with no intentional or directed changes in medication use. Limitations of this study include that 3% of patients were lost to follow-up (primarily from thermoplasty group), mild exacerbations were not reported, some outcome measures were self-reported in daily diaries (i.e., rescue medication use, asthma symptoms, peak expiratory flow), lack of daily diary compliance data although daily diaries were electronic, and lack of controlled follow-up after 1 year. In addition, the peer reviewed publication did not provide information on the source of the prior distribution data used in the Bayesian model making it difficult to determine if the prior distribution data was appropriate for the purpose of the study.

At 1 year follow-up, the thermoplasty group had meaningful improvements compared with the control group for the following measures (Castro et al., 2010):

- Severe exacerbations (0.48 versus 0.70 per patient annually; PPS=0.96)
- ED visits (0.07 versus 0.43 per patient annually; PPS > 0.99)
- Days lost from work, school, or other activities due to asthma (1.3 versus 3.9 per year; PPS=0.993)
- Significantly more patients in the bronchial thermoplasty group showed a clinically meaningful improvement of 0.5 or greater in AQLQ scores compared with the sham group (78.9% versus 64.3%; PPS=0.996).

Despite these improvements, no meaningful improvements were noted between the thermoplasty group and the control group for the following measures at 1-year follow-up (Castro et al., 2010):

- The primary outcome measure of the study was improvement from baseline in AQLQ scores. Scores (mean  $\pm$  SD) were greater in the bronchial thermoplasty group than the sham group ( $1.35 \pm 1.10$  versus  $1.16 \pm 1.23$ ; PPS=0.96). However, this difference did not reach the PPS planned of 96.4%. The AQLQ is designed to measure the within-subject change in quality of life over time, and the results demonstrated meaningful improvements (i.e. within-subject change of  $\geq 0.5$ ) in 78.9% of patients in the bronchial thermoplasty group and in 64.3% of subjects in the sham group with a PPS of 0.996. The likelihood of improvement was therefore found to be greater for subjects having undergone bronchial thermoplasty. There was a higher than expected improvement in the sham group (0.5 anticipated vs. 1.16 observed), which was likely due, as noted by the study authors, to a higher than expected placebo effect in patients undergoing the sham procedure. It is important to note that mean change in AQLQ scores were averaged over the 6 to 12 months follow-up; all other outcomes were reported as mean at 12 months follow-up.

- Morning peak expiratory flow
- Total symptom scores
- Symptom-free days
- Rescue medication use
- Unscheduled physician visits
- Hospitalizations
- ACQ

An additional year of uncontrolled follow-up for 166 thermoplasty group patients (87%) evaluated with traditional statistical tools showed no statistically significant increases or decreases within this group from 1 to 2 years follow-up in severe exacerbations, asthma symptoms, ED visits, or hospitalizations (Castro et al., 2011). Uncontrolled follow-up of the thermoplasty group was extended to 5 years and found no significant increase in respiratory adverse events or need for hospitalization, and computed tomography (CT) findings were unchanged except for development of bronchiectasis in 3 (2%) patients (Wechsler et al., 2013).

A fair-quality RCT that enrolled 109 patients who had moderate to severe, persistent asthma found improvements similar to those reported above despite differences in study design (Cox et al., 2007). This trial was not blinded or placebo controlled and most of the outcomes were measured after attempted withdrawal of patients from LABA use. The primary outcome measure of this study was frequency of mild exacerbations during 2-week periods of LABA abstinence and a power analysis indicated that the study was sufficiently powered to detect between-group differences for this measure. Data on exacerbations were self-report data collected using daily diaries. Exacerbations were defined as either a reduction in the morning peak expiratory flow of at least 20% below the average value at baseline, need for at least 3 additional puffs of rescue medication exceeding the average use during baseline, or nocturnal awakening caused by asthma symptoms. The authors did not note whether the study was sufficiently powered to detect between-group differences for any secondary outcomes. Limitations of this study included a lack of blinding, a lack of sham treatment in the control group, 5% of patients lost to follow-up, most outcomes with the use of LABA were not reported, follow-up was only 1 year, and several outcome measures were self-report data collected in daily diaries (i.e., exacerbations, peak expiratory flow, asthma symptoms).

A 1-year follow-up, compared with the control group, thermoplasty was associated with statistically significant improvements in mean change in the following measures (Cox et al., 2007):

- Mild exacerbations without LABA (−0.16 versus +0.04;  $P<0.01$ )
- Mild exacerbations with LABA (−0.17 versus +0.03;  $P<0.05$ )
- AQLQ (higher score better) (+1.3 versus +0.6;  $P<0.005$ )

- ACQ (lower score better) (–1.2 versus –0.5;  $P<0.005$ )
- Symptom-free days (+41% versus +17%;  $P<0.01$ )
- Symptom scores (lower score better) (–1.9 versus –0.7;  $P<0.05$ )
- Rescue bronchodilator use (–8.9 versus –1.2 puffs per week;  $P<0.05$ )
- Morning peak expiratory flow (+39 versus +9 L/min;  $P<0.005$ )

In contrast, at 1-year follow-up, no significant differences were seen between the thermoplasty group and the control group on the following measures (Cox et al., 2007):

- Severe exacerbations
- Airway responsiveness
- FEV<sub>1</sub>

A second report of this study extended follow-up to 5 years for 45 (82%) thermoplasty group patients and to 3 years for 24 (44%) control group patients (Thomson et al., 2011). Thermoplasty was not associated with any serious long-term adverse events and at 3 years follow-up, airway responsiveness (measured based on doublings of methacholine dose giving a 20% decrease in FEV<sub>1</sub>) increased 1.3 doublings for the thermoplasty group versus a decrease of 0.4 doublings for the control group ( $P<0.05$ ). However, at 3 years follow-up, there were no significant differences between the thermoplasty group and the control group in other respiratory parameters, oral glucocorticoid use, worsening of asthma, ED visits, or hospitalizations (Thomson et al., 2011). The apparent loss of benefits of thermoplasty during longer follow-up may indicate loss of effectiveness over time or may be an artifact of selective dropping out of control group patients who had the most poorly controlled asthma.

A fair-quality RCT that enrolled 32 patients who had severe asthma also reported that thermoplasty provided benefits despite differences in study design relative to the other available RCTs (Pavord et al., 2007). This trial was not blinded or placebo controlled and patients underwent attempted weaning from oral and inhaled glucocorticoids during weeks 22 to 36 of the study followed by maintenance of reduced steroid use during weeks 37 to 52 of the study. The primary outcome measure of the study was occurrence of adverse events, which were collected by during study visits and by telephone (12 office visits and 9 telephone contacts throughout the year). It was unclear whether complications were strictly self-reported in the patients' daily diaries, or if data were supplemented using more objective data from medical charts. The authors did not state if a power analysis was conducted. Outcomes from safety data are discussed in the results for Key Question #2 (safety). The study did not appear to be sufficiently powered to detect between-group differences for efficacy outcomes. Limitations of this study included a lack of blinding, a lack of sham treatment in the control group, small sample size, no power analysis was reported, 12% of thermoplasty patients (n=2) withdrew from the study before undergoing bronchial thermoplasty (2 patients were not candidates for thermoplasty due to possible Churg-Strauss syndrome in 1 patient and post-bronchodilator

FEV<sub>1</sub> < 55% predicted in 1 patient), only 1 year of controlled follow-up, and several outcome measures were self-report data collected using daily diaries (i.e., medication use, peak expiratory flow, asthma symptoms). Compared with the control group at 22 weeks follow-up (before steroid weaning), thermoplasty was associated with statistically significant improvements in the following measures (Pavord et al., 2007):

- FEV<sub>1</sub> (+15% versus -1%;  $P < 0.05$ )
- AQLQ (higher score better) (+1.2 versus +0.2;  $P < 0.05$ )
- ACQ (lower score better) (-1.0 versus -0.1;  $P < 0.05$ )
- Rescue bronchodilator use (-27% versus -2%;  $P < 0.05$ ).

The following measures were not statistically significant:

- Morning or evening peak expiratory flow
- Symptom-free days
- Symptom scores
- Airway responsiveness (PC<sub>20</sub>)

Except for FEV<sub>1</sub>, improvements in these measures remained statistically significant at 52 weeks follow-up, after reduction of steroid dosages. Compared with the control group at 52 weeks, thermoplasty was associated with statistically significant improvements in the following measures (Pavord et al., 2007):

- AQLQ (higher score better) (+1.5 versus +0.4;  $P < 0.05$ )
- ACQ (lower score better) (-1.0 versus -0.2;  $P < 0.05$ )
- Mean rescue bronchodilator use (-26% versus -6%;  $P < 0.05$ )

Uncontrolled follow-up of 14 (93%) thermoplasty group patients found that in years 2 through 5, respiratory adverse events, hospitalizations, ED visits, asthma maintenance medication usage, and respiratory parameters were essentially unchanged compared with the first year after thermoplasty treatment (Pavord et al., 2013). Outcomes during follow-up years 2 to 5 were collected once per year and may be subject to recall bias.

Study details for RCTs investigating the use of bronchial thermoplasty in asthma patients are presented in [Appendix IVa](#).

*Nonrandomized Studies:* Four very-poor-quality nonrandomized studies assessed efficacy outcomes in patients following bronchial thermoplasty. Two of these studies suggested that there were some favorable outcomes in patients following bronchial thermoplasty. However,

caution should be exercised in interpreting results of these studies, as they do not include a control or comparison group, and are subject to several additional limitations.

One very-poor-quality retrospective cohort study compared the effect of bronchial thermoplasty in 10 clinic patients with severe asthma to a cohort of 15 patients that had undergone bronchial thermoplasty in previous clinical trials at the same center (Bicknell et al., 2015). These data were derived from 15 patients recruited to clinical trials at the same center (5 patients from Cox et al. [2007], 3 patients from Pavord et al. [2007]; 7 patients from Castro et al. [2010]). Unlike the RCT patients, patients were not excluded if they used certain asthma medications (e.g., omalizumab and high-dose oral prednisolone) or had a high frequency of exacerbations. The authors reported that at least 7 of the 10 clinic patients would have failed screening for the sham-controlled RCT (Castro et al., 2010). Demographics and clinical outcomes were compared between the clinic patients and the RCT patients. Methods for choosing the RCT patients were not reported. At baseline, clinic patients had a relatively high mean pre-bronchodilator FEV<sub>1</sub> (72%), the majority of patients required a mean inhaled glucocorticoids dose of 2580 µg /day, and 60% of patients required oral corticosteroids. Clinic patients were taking significantly lower doses of inhaled corticosteroids, had a higher percentage of patients taking Step 5 medication, and had a lower ACQ score than RCT patients. Clinical improvement was defined as achieving at least 1 of the following outcomes during the post-treatment period: (1) Reduction by ≥1 severe exacerbation (requirement for high-dose oral corticosteroids) or hospital admissions for asthma; (2) Improvement in ACQ or AQLQ score by the MCID, without worsening of the other (ACQ score decrease by ≥0.5, AQLQ score increase by ≥0.5); (3) stepdown in treatment: half the maintenance oral prednisolone dose or stop omalizumab without a loss of asthma control (no increase in hospitalization or asthma exacerbations by ≥ 1 or worsening of ACQ/AQLQ scores by the MCID. At 1 year follow-up, 5 of the 10 clinic patients (50%) met the criteria for clinical improvement. In comparison, 73% of RCT patients achieved the criteria for clinical improvement. AQLQ scores improved in 10 of 14 RCT patients that had AQLQ data (71%) and ACQ scores improved in 11 of 14 patients (79%). Asthma medications were reduced in 3 clinic patients (2 patients discontinued omalizumab and 1 patient discontinued prednisolone); changes in asthma medications were not reported in RCT patients. The number of severe exacerbations and hospitalizations was reduced in 3 of 10 clinic patients. Severe exacerbations decreased in 5 of 15 (33%) RCT patients and hospital admissions decreased in 2 of 15 (13%) RCT patients. The authors concluded that patients that may best be suited for bronchial thermoplasty are patients with moderate to severe asthma who are symptomatic despite maximal asthma therapy, with an FEV<sub>1</sub> > 60% predicted (the authors do not note if this is pre- or post-bronchodilator value) and no contraindication to bronchoscopy. Furthermore, an earlier publication from the same center recommends caution in treating patients with bronchial thermoplasty that fall outside the selection criteria of the RCTs (i.e., post-bronchodilator FEV<sub>1</sub> < 65% predicted, use of oral corticosteroids > 10 mg/day, or > 4 asthma exacerbations in the previous year (Bicknell et al., 2014). Limitations of the Bicknell et al. (2015) study include small sample size, lack of a true control or comparator group, and a lack of reporting methods for choosing the RCT patients (i.e., these patients may not have been representative of the entire population of RCT patients that underwent bronchial thermoplasty).



One very-poor-quality case series assessed the effect of bronchial thermoplasty in 16 patients with mild to moderate asthma (Cox et al., 2006). At baseline, mean pre-bronchodilator FEV<sub>1</sub> was relatively high (82%), the majority of patients required low to medium doses of inhaled glucocorticoids (< 500 µg/day), and only 31% of patients required LABA. At 12-week follow-up, mean pre-bronchodilator FEV<sub>1</sub> was significantly increased (82% versus 88%;  $P=0.03$ ) and mean airway responsiveness increased (PC<sub>20</sub> increased by 2.37,  $P<0.001$ ; number of methacholine PC<sub>20</sub> doublings increased by 2.4,  $P<0.001$ ). Patient-reported outcomes of number of symptom-free days increased from baseline to 12-week follow-up (47% versus 73%;  $P=0.015$ ), as well as morning peak expiratory flow (427.1 versus 465.9 L/min;  $P=0.010$ ) and evening peak expiratory flow (435.3 versus 476.4 L/min;  $P=0.007$ ). At 1-year follow-up, the increase in pre-bronchodilator FEV<sub>1</sub> was maintained (88.6%;  $P=0.043$ ); however, this increase was not maintained at the 2-year follow-up (85.7%; not significant). The increase in airway responsiveness was maintained at the 1- and 2-year follow-up (PC<sub>20</sub> increased by 2.77 at 1 year and 2.64 at 2 years,  $P<0.01$ ; number of methacholine PC<sub>20</sub> doublings increased by 3.0 at 1 year and 2.3 at 2 years,  $P<0.001$ ). Limitations of this study include small sample size, lack of control or comparator group, patients were included that had mild to moderate stable asthma (i.e., population is not generalizable to patients that may be indicated for bronchial thermoplasty), and the bronchial thermoplasty and methodological procedures varied somewhat between clinic sites.

A second very-poor-quality case series assessed the effect of bronchial thermoplasty in 8 patients with severe asthma that had severe airflow obstruction (Doeing et al., 2013). At baseline, mean pre-bronchodilator FEV<sub>1</sub> was relatively low (52%), mean dose of inhaled glucocorticoids was 1000 µg/day, all patients required LABA  $\geq$  100 µg/day, and 50% of patients required oral glucocorticoids. At 1-year follow-up, there was no change in mean pre-bronchodilator FEV<sub>1</sub> (52%) or mean hospitalizations for asthma (2.88 in last year at baseline versus 0.50 during the median follow-up of 31 weeks following thermoplasty). Limitations of this study include small sample size, lack of control or comparator group, patients had a low FEV<sub>1</sub> (i.e., population is not generalizable to patients enrolled in the RCTs), and efficacy outcomes other than FEV<sub>1</sub> were not assessed.

A third very-poor-quality case series assessed the effect of bronchial thermoplasty in 17 patients with severe asthma (Chakir et al., 2015). At baseline, mean pre-bronchodilator FEV<sub>1</sub> was 64%, mean dose of inhaled glucocorticoids was 1281 µg/day, mean LABA dose was 123 µg/day, 29% of patients required oral glucocorticoids, 29% of patients were using omalizumab, and 47% of patients were using montelukast. At 1-year follow-up, the mean inhaled corticosteroid (ICS) dose was significantly decreased (937.5 µg/day;  $P=0.002$ ) and mean prednisone dose was decreased (5.0 µg/day; significant NR). There was no effect on doses required of omalizumab or montelukast. Self-reported number of exacerbations in prior year decreased from 1.5 to 0 ( $P=0.005$ ), and the Asthma Control Scoring System increased from 72 to 84 ( $P=0.02$ ). However, there was no significant change in mean pre-bronchodilator FEV<sub>1</sub> (77%). Limitations of this study include small sample size, lack of control or comparator group, and the study was designed to assess effects of bronchial thermoplasty on airway smooth muscle (i.e., efficacy outcomes were secondary).

Study details are presented in [Appendix IVb](#).

*Is there clinically meaningful improvement for patients with severe asthma (Key Question #1a)?*

Three RCTs and 1 retrospective cohort study addressed whether improvements in outcome measures were clinically meaningful. All 4 studies included the AQLQ in their assessments. A *within-group* change of 0.5 in scores on the AQLQ is considered to be the MCID, with higher scores indicating improved asthma-related QOL (Juniper et al., 1994). The study authors applied this MCID to *between-group* differences. Cox et al. (2007) found a between-group difference of 0.69 (+1.3 thermoplasty group versus +0.6 control group;  $P < 0.005$ ) at 12 months, which suggests that the increase in AQLQ is clinically meaningful. Likewise, Pavord et al. (2007) found a clinically meaningful between-group difference of 1.1 in AQLQ (+1.5 thermoplasty group versus +0.4 control group). The most recent sham-controlled trial found that the AQLQ score improved from baseline to 1 year by 1.16 in the sham group and by 1.35 in the thermoplasty group, with a difference in AQLQ scores between the 2 groups of only 0.19 (PPS=0.96). The PPS did not reach the PPS planned of 0.964 (Castro et al., 2010). However, more thermoplasty patients (78.9%) met the MCID than sham patients (64.3%; PPS=0.996).

One very-poor-quality retrospective cohort study assessed clinically meaningful improvement in asthma-related outcomes (Bicknell et al., 2015). Clinical improvement was defined as achieving at least 1 of the following outcomes during the posttreatment period: (1) Reduction by  $\geq 1$  severe exacerbation (requirement for high-dose oral corticosteroids) or hospital admissions for asthma; (2) Improvement in ACQ or AQLQ score by the MCID, without worsening of the other (ACQ score decrease by  $\geq 0.5$ , AQLQ score increase by  $\geq 0.5$ ); (3) stepdown in treatment: half the maintenance oral prednisolone dose or stop omalizumab without a loss of asthma control (no increase in hospitalization or asthma exacerbations by  $\geq 1$  or worsening of ACQ/AQLQ scores by the MCID). At the 1 year of follow-up, 5 of the 10 clinic patients (50%) met the criteria for clinical improvement. In comparison, 73% of RCT patients achieved the criteria for clinical improvement. AQLQ scores improved in 10 of 14 RCT patients that had AQLQ data (71%) and ACQ scores improved in 11 of 14 patients (79%). Asthma medications were reduced in 3 clinic patients (2 patients discontinued omalizumab and 1 patient discontinued prednisolone); changes in asthma medications were not reported in RCT patients. The number of severe exacerbations and hospitalizations was reduced in 3 of 10 clinic patients. Severe exacerbations decreased in 5 of 15 (33%) RCT patients and hospital admissions decreased in 2 of 15 RCT patients (13%).

The reviewed studies did not provide definitions for clinically meaningful changes for any outcome measures other than AQLQ.

**Summary of Clinical Effectiveness of Bronchial Thermoplasty for Asthma (Key Question #1):**

The body of evidence for the clinical effectiveness of bronchial thermoplasty for asthma identified a total of 7 studies (reported in 11 articles) that evaluated the effectiveness of bronchial thermoplasty treatment in patients with asthma. The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3

very-poor-quality case series. The best available evidence consisted of an RCT of 32 patients, an RCT of 109 patients, and an RCT of 288 patients. The primary outcome measures varied across studies, and included AQLQ (Castro et al., 2010), frequency of mild exacerbations during LABA abstinence (Cox et al., 2007), safety (Cox et al., 2006; Pavord et al., 2007; Doeing et al., 2013), clinical improvement (Bicknell et al., 2015), and airway smooth muscle mass (Chakir et al., 2015; outcome measures of interest for this report included FEV<sub>1</sub>, changes in medication use, asthma exacerbations, and hospitalizations).

Overall, the body of evidence suggests that during the first year after thermoplasty, benefits were observed, including improved QOL, symptom relief, reduced medication use, and reductions in ED visits; however, the benefits varied somewhat across studies and outcomes. These differences in benefits may have resulted from differences in study protocols since the 2 smaller RCTs involved partial discontinuation of certain asthma medications. Although observation of benefits of thermoplasty after medication reduction may give a more accurate representation of the clinical situation and a desire to minimize medication usage and associated side effects of medications, reduction of medication for the control group may have exaggerated symptoms and led to an overestimation of the benefits of thermoplasty.

Only one of the RCTs reported results of controlled follow-up for longer than 1 year. This study found that, at 3 years follow-up, the only statistically significant benefit of thermoplasty was an improvement in airway responsiveness. However, this follow-up may have been flawed since it involved only 69 patients and the dropout rate was much higher for the control group than for the thermoplasty group. The apparent loss of benefits of thermoplasty during longer follow-up may indicate loss of effectiveness over time or may be an artifact of selective dropping out of control group patients who have the most poorly controlled asthma.

Limitations of individual studies included a lack of control or comparator group, lack of sham control, small sample size, moderate-to-high loss to follow-up, use of self-report data collected in daily diaries that may be subject to recall bias (e.g., rescue medication use, asthma symptoms and exacerbations, peak expiratory flow), and lack of controlled follow-up after 1 year.

#### *Quality of the Evidence:*

The quality of the evidence was assessed taking into consideration the quality of the individual studies; the precision, directness, and consistency of data; and the applicability of the data to the relevant patient population in clinical practice. The evidence for the effectiveness of bronchial thermoplasty for treating asthma was considered to be of low quality because of some positive but inconsistent results regarding short-term benefits of bronchial thermoplasty, varied patient selection criteria across studies, small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long-term efficacy of bronchial thermoplasty.

**Key Question #2****Key Question #2: What are the harms associated with bronchial thermoplasty?**

*Complications during treatment period.* Seven studies reported on adverse events and/or rates of hospitalizations that occurred during the treatment period (i.e., treatment period plus 6-week follow-up) (Cox et al., 2006; Cox et al., 2007; Pavord et al., 2007; Castro et al., 2010; Doeing et al., 2013; Bicknell et al., 2015; Chakir et al., 2015). The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3 very-poor-quality case series.

Three studies reported on the rate of specific adverse events occurring during the bronchial thermoplasty treatment period. These studies included 2 fair-quality RCTs (Cox et al., 2007; Pavord et al., 2007) and 1 very-poor-quality case series (Cox et al., 2006). Bronchial thermoplasty was associated with statistically significant increases in dyspnea (60% to 71% of thermoplasty patients), wheezing (50% to 73%), chest discomfort (40% to 56%), night awakenings (40%), sputum discoloration (11% to 33%), cough (53% to 94%), productive cough (40% to 53%), bronchial irritation (9% to 13%), and nasal congestion (13% to 20%). Most of these complications were mild or moderate in severity. Other potential adverse events that may occur during the treatment period are headache, fever, chest infection, upper respiratory infections, pleurisy, bronchitis, hoarseness, throat irritation, bronchospasm, mucus production, retention of mucus, hypoxemia, pneumothorax, atelectasis, and exacerbation of asthma (Cox et al., 2006; Cox et al., 2007; Pavord et al., 2007; Castro et al., 2010; Bicknell et al., 2015).

*Hospitalizations during treatment period.* Seven studies reported on an increased need for hospitalization during the treatment period (Cox et al., 2006; Cox et al., 2007; Pavord et al., 2007; Castro et al., 2010; Doeing et al., 2013; Bicknell et al., 2015; Chakir et al., 2015). Two of the 3 RCTs found that 5% to 27% of thermoplasty patients compared with 0% to 4% of control patients required hospitalization during the treatment period (Cox et al., 2007; Pavord et al., 2007; Castro et al., 2010). However, only 1 fair-quality small RCT found that the between-group difference was significant (Pavord et al., 2007). The rate of hospitalization in thermoplasty patients among the nonrandomized studies ranged from 0% to 62.5% (Cox et al., 2006; Doeing et al., 2013; Bicknell et al., 2015; Chakir et al., 2015). The rate of hospitalization appeared to be higher in studies that enrolled patients with more severe asthma. The percentage of patients hospitalized ranged from 0% to 5.5% in patients that included patients with mild and/or moderate asthma (Cox et al., 2006; Cox et al., 2007). The percentage of patients hospitalized ranged from 5% to 62.5% in patients that included patients with only severe asthma (Castro et al., 2010; Doeing et al., 2013; Bicknell et al., 2015; Chakir et al., 2015). The study with 0% hospitalizations enrolled only patients with stable mild to moderate asthma (Cox et al., 2006). The study with 62.5% of patients hospitalized during the treatment period enrolled patients with severe asthma with obstructed airflow ( $FEV_1 < 50\%$ ) (Doeing et al., 2013).

*Complications during long-term follow-up.* Thomson et al. (2011) reported controlled follow-up data on complications occurring during 1 to 5 years following bronchial thermoplasty for 69 of 109 patients (63%) that were enrolled in Cox et al. (2007). Control patients were followed for only 3 years. Greater mean number of events of worsening of asthma occurred during year 1 (4.5 events in the thermoplasty group, 3.1 events in the control group) than in subsequent years (1.1 to 1.3 events in the thermoplasty group, 1.2 to 1.3 in the control group). In the thermoplasty group, hospitalizations occurred in 7% of patients during years 1 and 2, and 2% of patients in years 3 through 5. Hospitalizations occurred in 0% of control patients in years 1 and 2, and 5% of patients in year 3. ED visits occurred in 4% of patients during year 1, and 2% to 7% of patients during years 2 through 5. ED visits occurred in 0% of control patients during year 1, and 5% to 13% of patients in years 2 and 3. Between-group differences in worsening of asthma, hospitalizations, and ED visits were not statistically significant. During the 5 years of follow-up, no patients had pneumothorax or cardiac arrhythmias, were intubated or mechanically ventilated, or died due to thermoplasty.

Pavord et al. (2007) reported that at 1-year follow-up, between-group differences in complications were not significant. Five hospitalizations occurred in 3 bronchial thermoplasty patients and 4 hospitalizations occurred in a single patient in the control group. Uncontrolled follow-up of 14 thermoplasty patients (93%) found that in years 2 to 5, rates of respiratory adverse events (1.4, 2.4, 1.7, and 2.4 events per patient), respiratory-related hospitalizations (21% of patients in year 1, 29% of patients in year 2, 14% of patients in year 3, 7% of patients in years 4 and 5), and ED visits (mean 0.36 ED visits per patient per year before thermoplasty versus mean 0.12 ED visits per patient per year for 5 years of follow-up) were essentially unchanged (Pavord et al., 2013). There were no deaths during the study. There were no incidences of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias, or deaths as a result of bronchial thermoplasty.

An additional year of uncontrolled follow-up of thermoplasty patients enrolled in Castro et al. (2010) showed no statistically significant differences within this group from 1 and 2 years follow-up in ED visits or hospitalizations (Castro et al., 2011). Uncontrolled follow-up of the thermoplasty group was extended to 5 years and found no significant increase in respiratory adverse events or need for hospitalization, and bronchiectasis developed in 3 (2%) patients (Wechsler et al., 2013).

Three of the nonrandomized studies reported on adverse events occurring during 1 to 2 years follow-up. Cox et al. (2006) reported that over a 2-year follow-up period, 312 adverse events occurred. Over half of these (155 events) were directly related to the procedure. Of these events, 230 (74%) were mild, 79 (25%) were moderate, and 3 (1%) were severe. All 3 severe adverse events (allergic reaction to peanuts, ovarian cyst and fibroid removal, and partial mastectomy) involved hospitalization and were considered to be not related to the procedure. No ED visits related to thermoplasty or asthma exacerbation occurred. Doeing et al. (2013) reported that no patients had an increase in hospitalization rate up to 1-year follow-up. Mean hospitalizations for asthma in the year prior to bronchial thermoplasty was 2.88, compared to 0.50 hospitalizations during the median follow-up of 31 weeks following thermoplasty (Doeing

et al., 2013). Bicknell et al. (2015) reported that 1 patient was hospitalized during the 1-year follow-up period. No deaths occurred during the study period in any of the nonrandomized studies.

In addition to the complications listed above, labeling information approved by the FDA warns that pneumothorax and respiratory failure requiring intubation are potential complications (CDRH, 2010) and the NICE has stated that bronchial stenosis is a potential long-term complication (NICE, 2012).

According to labeling information approved by the FDA, bronchial thermoplasty is contraindicated under any of the following circumstances (Asthmatx Inc., 2010):

- Presence of a pacemaker, internal defibrillator, or similar implanted electronic device
- Known sensitivity to the drugs employed during bronchoscopy such as lidocaine, atropine, or benzodiazepines
- Prior bronchial thermoplasty procedure
- Active respiratory infection
- An asthma attack or alteration of the dose of systemic glucocorticoids in the preceding 14 days
- Known bleeding disorder
- Need for aspirin, anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory drugs that cannot be interrupted

The latter 4 contraindications listed here are relative rather than absolute and, in some cases, may only require delay of bronchial thermoplasty (CDRH, 2010).

*Quality of the Evidence:*

The quality of the evidence was assessed taking into consideration the quality of the individual studies; the precision, directness, and consistency of data; and the applicability of the data to the relevant patient population in clinical practice. The evidence for the safety of bronchial thermoplasty for treating asthma was considered to be of low quality because of the small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long-term safety of bronchial thermoplasty.

**Key Question #3****Key Question #3: Does the effectiveness of bronchial thermoplasty or incidence of adverse events vary by clinical history or patient characteristics (e.g., age, sex, prior treatments)?**

The literature search found no studies that were specifically designed to assess differential effects of bronchial thermoplasty. The analyzed studies varied considerably in patient selection criteria, which may have had an impact on study outcomes. In addition, several studies conducted post-hoc analyses investigating the impact of various patient characteristics and other prognostic factors on clinical outcomes. These data were of very poor quality; therefore, all findings should be considered preliminary in nature.

Patient selection criteria varied considerably between studies, and the RCTs were selective in the patients that were enrolled in the study. Because the body of literature concerning safety and efficacy of bronchial thermoplasty for asthma is small, it is difficult to determine whether efficacy or safety or thermoplasty varied by baseline variables such as asthma severity, medication use, pulmonary function, or other characteristics.

- A good-quality sham-controlled RCT assessing thermoplasty in patients with severe asthma (Castro et al., 2010). For study inclusion, patients had to require daily treatment with high-dose inhaled corticosteroids ( $\geq 1000$   $\mu\text{g}/\text{day}$  beclomethasone or equivalent) and LABA ( $\geq 100$   $\mu\text{g}/\text{day}$  salmeterol or equivalent), and have been on stable maintenance asthma medication for  $\geq 4$  weeks. Oral corticosteroids were acceptable in doses  $< 10$  mg per day. Patients had to require  $< 8$  puffs/day of short-acting bronchodilator,  $< 4$  puffs/day of long-acting rescue bronchodilator, and  $< 2$  nebulizer treatments per day. In addition, patients had to have a low AQLQ score ( $\leq 6.25$ ), low percentage of symptom-free days ( $\geq 2$  days of asthma symptoms per week), and have pre-bronchodilator  $\text{FEV}_1 \geq 60\%$  of the predicted value; 86% of the bronchial thermoplasty group (163 patients) and 88% of the sham control group (86 patients) met ATS criteria for severe refractory asthma. Bronchial thermoplasty patients had a mean pre-bronchodilator  $\text{FEV}_1$  of 78% of the predicted value.
- A fair-quality small RCT enrolled patients with severe asthma (Pavord et al., 2007). All patients met the GINA criteria for severe persistent asthma. All but 1 patient met ATS criteria for refractory asthma. For inclusion in the study, patients had to require high-dose inhaled glucocorticoids ( $\geq 750$   $\mu\text{g}$  fluticasone propionate per day or equivalent) and LABA ( $\geq 100$   $\mu\text{g}$  of salmeterol or the equivalent). In addition, patients were required to have a pre-bronchodilator  $\text{FEV}_1 \geq 50\%$  of the predicted value. Bronchial thermoplasty patients had a mean pre-bronchodilator  $\text{FEV}_1$  of 63% of the predicted value.
- A fair-quality RCT enrolled patients with moderate or severe stable asthma (Cox et al., 2007). Data were not reported separately according to asthma severity. For study inclusion, patients were required to have an absence of unscheduled physician visits for asthma care, unchanged use of asthma medication for maintenance treatment, and

stable use of rescue medication ( $\leq 4$  puffs in a 24-hour period of a short-acting bronchodilator). In addition, patients were required to need daily treatment with inhaled corticosteroids equivalent to a dose of  $\geq 200 \mu\text{g}$  of beclomethasone and LABA at a dose of  $\geq 100 \mu\text{g}$  of salmeterol or equivalent, to maintain reasonable asthma control. Patients were required to have a mean pre-bronchodilator FEV<sub>1</sub> 60% to 85% of the predicted value. Bronchial thermoplasty patients had a mean pre-bronchodilator FEV<sub>1</sub> of 73% of the predicted value.

- A very-poor-quality case series enrolled patients with stable mild to moderate stable asthma (Cox et al., 2006). Patients were excluded if they used more than 4 puffs in a 24-hour period of a short-acting  $\beta_2$ -adrenergic agonist (e.g., albuterol 100  $\mu\text{g}$ /puff or equivalent) except for exercise. Patients had a mean pre-bronchodilator FEV<sub>1</sub> of 82% of the predicted value.
- A very-poor-quality case series enrolled patients with severe asthma that had severe airflow obstruction (Doeing et al., 2013). For inclusion in the study, patients were required to use high-dose inhaled glucocorticoids ( $\geq 1000 \mu\text{g}/\text{day}$  fluticasone or equivalent) and LABA  $\geq 100 \mu\text{g}/\text{day}$ . Patients had a mean pre-bronchodilator FEV<sub>1</sub> of 52% of the predicted value.
- A small very-poor-quality retrospective cohort study enrolled patients with severe asthma requiring high-dose inhaled glucocorticoids ( $\geq 1000 \mu\text{g}/\text{day}$  beclomethasone equivalent daily) plus additional preventer medications (Bicknell et al., 2015). Patients had a mean pre-bronchodilator FEV<sub>1</sub> of 72% of the predicted value.
- A very-poor-quality case series enrolled patients with severe asthma requiring  $\geq 500 \mu\text{g}/\text{day}$  fluticasone plus salmeterol 100  $\mu\text{g}$  daily or equivalent (Chakir et al., 2015). Patients were required to have a pre-bronchodilator FEV<sub>1</sub>  $\geq 50\%$ , and were allowed to have a previous smoking history under certain conditions. Patients had a mean pre-bronchodilator FEV<sub>1</sub> of 64% of the predicted value.

Cox et al. (2007) conducted a post hoc analysis on 32 patients (16 thermoplasty, 16 control) who required  $> 1000 \mu\text{g}$  beclomethasone per day or equivalent at baseline. At 12 months follow-up, there were greater improvements observed relative to the between-group differences observed in the entire cohort for several outcome measures. Statistically significant improvements in the thermoplasty group compared with the control group were observed in morning peak expiratory flow (+63.6 versus +24.3 L/min;  $P=0.05$ ), airway hyperresponsiveness (PC<sub>20</sub> +1.38 versus +0.15; number of methacholine PC<sub>20</sub> doublings +2.39 versus -0.57;  $P=0.03$ ), AQLQ (+1.72 versus +0.26;  $P=0.002$ ) and ACQ (-1.54 versus -0.21;  $P=0.004$ ). Changes in FEV<sub>1</sub>, use of rescue medication, percentage of symptom-free days, and total symptom score were not statistically significant at 12-month follow-up in this more severe cohort. Cox et al. (2007) also noted that although there were variations among the study centers in the size of treatment effect and number of adverse events, there appeared to be no relation between the investigators' experience with bronchial thermoplasty or the numbers of patients treated and efficacy or safety. No details were reported on how differential effect of treatment site or previous experience with thermoplasty was determined.



Pavord et al. (2007) conducted a post hoc analysis of covariance to investigate whether nonsignificant differences in baseline values of rescue medication use, AQLQ, and ACQ affected outcomes. Baseline ACQ score was found to have a statistically significant relationship to ACQ at 22 weeks, resulting in a loss of statistical significance for this single measure.

Castro et al. (2010) conducted a univariate logistic regression within the bronchial thermoplasty group to investigate whether baseline characteristics were statistically significant predictors of AQLQ response (responders versus nonresponders). Responders were defined as those patients that had a change in AQLQ score of 0.5 or greater. A total of 150 patients responded to treatment, and 40 patients did not respond to treatment. Responders were found to have lower (less favorable) baseline AQLQ scores than nonresponders (4.1 versus 5.1;  $P < 0.001$ ) and higher (less favorable) ACQ scores than nonresponders (2.2 versus 1.9;  $P = 0.041$ ). Long-term follow-up data suggests that responders have fewer asthma-related adverse events and healthcare utilization than nonresponders (Wechsler et al., 2013). Average severe exacerbations (0.72 versus 0.39), respiratory adverse events (1.5 versus 1.0), asthma multiple symptoms (0.75 versus 0.4), ED visits for respiratory symptoms (0.21 versus 0.07), and hospitalizations for respiratory symptoms (0.08 versus 0.05) over years 2 through 5 follow-up were higher in nonresponders than in responders. Wechsler et al. (2013) also investigated the impact of reported seasonal allergy status and found that there was no difference in severe exacerbations over 5 years between those patients with seasonal allergy (29.3%) and those with no allergies (29.5%). In addition, both patients with FEV<sub>1</sub> values of 60% to 70% of predicted value and those with FEV<sub>1</sub> values of > 70% of predicted value had sustained improvements in exacerbations over the 5-year period.

Although no formal post hoc analyses were conducted, 2 of the nonrandomized studies commented on effects of baseline and procedural characteristics on study outcomes. Cox et al. (2006) reported that there was no relationship between rate or severity of adverse events and the anesthesia used, baseline medication use, or baseline airway hyperresponsiveness. Chakir et al. (2015) noted that patients with greater ASM mass ( $\geq 15\%$ ) had greater absolute reduction in ASM following bronchial thermoplasty. The ASM of the entire cohort of 17 patients decreased from 12.9% at baseline to 4.6% after thermoplasty (decrease of 8.3%). Five patients with ASM area of 15% or greater at baseline had a mean absolute reduction of 16.2% following bronchial thermoplasty.

#### *Quality of the Evidence:*

The quality of the evidence was assessed taking into consideration the quality of the individual studies; the precision, directness, and consistency of data; and the applicability of the data to the relevant patient population in clinical practice. The evidence for differential effectiveness of bronchial thermoplasty for treating asthma was considered to be of very low quality because of the lack of studies specifically designed to assess differential effects of bronchial thermoplasty.

**Key Question #4****Key Question #4: What are the cost implications and cost-effectiveness of bronchial thermoplasty?**

Four studies were found that compared the cost of usual care with bronchial thermoplasty or assessed the cost effectiveness of bronchial thermoplasty (Menzella et al., 2014; Cangelosi et al., 2015; Zein et al., 2015; Zafari et al., 2016). One of these studies was conducted in Italy; the other 3 studies were conducted in the United States.

**Cost of Bronchial Thermoplasty Procedure**

Menzella et al. (2014) assumed a cost of €6550 (USD \$7864.18, year 2015\*) for the bronchial thermoplasty procedure, which was estimated from data provided by a single hospital in Italy, which included costs of physicians and staff, bronchial thermoplasty procedure, and hospital admission.

Cangelosi et al. (2015) calculated the costs of bronchial thermoplasty to be \$50,470 (\$52,346.23, year 2015\*) based on private, commercial payer data and included both physician payments and procedure costs over a 5-year period. This is compared with \$49,510 (\$51350.54, year 2015\*) for standard care. Thus, bronchial thermoplasty increased costs by \$960 (\$996.69, year 2015\*) over the 5-year period.

Zein et al. (2015) calculated the costs of bronchial thermoplasty to be \$6690 (\$6938.70, year 2015\*) based on average Medicare reimbursement rates.

Zafari et al. (2016) calculated the costs of bronchial thermoplasty to be \$14,900 (\$15,453.91, year 2015\*) based on data from a published trial, to estimate the average cost of 3 catheters, facility, and professional fee.

\*NOTE: The above conversions represent an approximate translation of the procedural cost and/or product price values to current U.S. values. These conversions do NOT provide an estimate of the current cost; they are based on January 30, 2016, use of the CCEMG - EPPI-Centre web-based cost converter with the International Monetary Fund (IMF) dataset for Purchasing Power Parity (PPP) values, available at: [click here](#) [last updated on January 27, 2014] (Shemilt et al., 2010).

**Cost of Usual Care Compared with Bronchial Thermoplasty****Menzella et al. (2014) – Cost of adding bronchial thermoplasty for patients with severe asthma receiving standard care with or without omalizumab from a payer perspective:**

Menzella et al. (2014) performed a budget impact analysis to project the costs of a hypothetical cohort of adult patients with severe asthma. In one scenario, hypothetical patients received standard care with or without omalizumab. In the second scenario, patients had bronchial thermoplasty made available in addition to standard care with or without omalizumab. Costs

were estimated based on the established literature or were estimates provided by an expert clinical panel. During the first year of treatment, the bronchial thermoplasty procedure adds approximately €20,000 (USD \$24,012.77, year 2015\*) to standard care. However, since bronchial thermoplasty is a 1-time procedure, the cumulative costs decreased strongly in the following years, generating net savings. In terms of healthcare utilization, savings were clear  $\geq 3$  years post-procedure. Bronchial thermoplasty reduced the rate of ED visits by 83.3% and reduced the rate of hospitalization by 74.2%. In terms of costs to the regional healthcare system, the cost of introducing bronchial thermoplasty would be approximately €17.7 million (USD \$21.25 million, year 2015\*) during the first year, but these costs would be offset by savings from avoided adverse events. Bronchial thermoplasty would produce savings of approximately €1 million (USD \$1.2 million, year 2015\*) after year 3, €10.5 million (USD \$12.6 million, year 2015\*) after year 4, and up to €19.2 million (USD \$23.1 million, year 2015\*) after year 5.

The study had several limitations. Imputed data were derived from multiple sources, which may have resulted in selection bias. Although several of the imputed data points were based on data from Castro et al. (2010), the population of patients chosen to be hypothetically treated with bronchial thermoplasty ( $FEV_1 < 60\%$ ) differed from those included in the Castro et al. study ( $FEV_1 \geq 60\%$ ). Proportion of patients that would respond to each level of treatments, use and adherence to maintenance medications, and risk of serious adverse events from bronchial thermoplasty were based on single studies and the results may not be applicable to all U.S. healthcare settings. In addition, medication costs were based on average dosage and retail cost in Italy and may not reflect usage and cost in the U.S. The processing charge for this article was paid by the device manufacturer (Boston Scientific Corp.).

\*NOTE: The above conversions represent an approximate translation of the procedural cost and/or product price values to current U.S. values. These conversions do NOT provide an estimate of the current cost; they are based on January 30, 2016, use of the CCEMG - EPPI-Centre web-based cost converter with the International Monetary Fund (IMF) dataset for Purchasing Power Parity (PPP) values, available at: [click here](#) [last updated on January 27, 2014] (Shemilt et al., 2010).

### ***Cost-Effectiveness***

The literature search identified 3 cost-effectiveness assessments for bronchial thermoplasty for asthma (Cangelosi et al., 2015; Zein et al., 2015; Zafari et al., 2016). These studies provided a cost-effectiveness analysis for the use of bronchial thermoplasty from a payer perspective. In these studies, although bronchial thermoplasty increased costs in the short term, it was found to increase quality-adjusted life-years (QALYs) in the longer term. The studies are summarized in the following paragraphs.

Cangelosi et al. (2015) applied a Markov model to estimate the costs and QOL impact of bronchial thermoplasty compared with high-dose combination therapy among severe persistent asthma patients (i.e., those patients requiring high-dose combination therapy and required  $\geq 1$  asthma exacerbation-related ED visit in the past year). Over a 5-year period,

bronchial thermoplasty increased quality-adjusted life expectancy by approximately 0.18 QALYs (3.14 versus 2.96), driven primarily by the decrease in exacerbations. Bronchial thermoplasty increased costs by \$960 (\$995.69, year 2015\*) when considering both the procedural costs and costs of treating periprocedural exacerbations. These findings resulted in an incremental cost-effectiveness ratio (ICER) of \$5495 (\$5699.28, year 2015\*) per QALY. This economic evaluation was funded by the device manufacturer.

Zein et al. (2015) applied a Markov model to estimate the costs and QOL impact of bronchial thermoplasty compared with usual care among severe persistent asthma patients whose asthma is not well controlled with combination therapy of ICS and LABA. Compared with Cangelosi et al. (2015), this study used a less severe patient population and estimated a lesser healthcare utilization without bronchial thermoplasty. Use of bronchial thermoplasty increased costs by \$5458 (\$5660.90, year 2015\*) compared with usual care at baseline. Treatment with bronchial thermoplasty resulted in 6.40 QALYs and \$7512 (\$7791.26, year 2015\*) in cost compared to 6.21 QALYs and \$2054 (\$2130.36, year 2015\*) for usual care. These findings resulted in an ICER of \$45,300 (\$46,984.04, year 2015\*) per QALY at 5 years and an ICER of \$29,821 (\$30,929.60, year 2015\*) per QALY at 10 years.

Zafari et al. (2016) applied a Markov model to estimate the costs and QOL impact of bronchial thermoplasty compared with usual care and omalizumab treatment for moderate-to-severe allergic asthma patients whose asthma is not well controlled despite therapy with ICS, with or without LABA. This study was conducted from the healthcare system perspective. Treatment with bronchial thermoplasty resulted in 3.24 QALYs and \$28,100 (\$29,144.62, year 2015\*) in cost compared to 3.08 QALYs and \$15,400 (\$15,972.50, year 2015\*) for usual care and 3.26 QALYs and \$117,000 (\$121,349.50, year 2015\*) for omalizumab. In the lifetime analysis that assumed an exponentially declining effect for bronchial thermoplasty after the fifth year, the ICER of bronchial thermoplasty compared with usual care, omalizumab compared with bronchial thermoplasty, and omalizumab compared with usual care was \$12,500/QALY (\$12,964.69/QALY, year 2015\*), \$3.15 million/QALY (\$3.27 million/QALY, year 2015\*), and \$529,000/QALY (\$548,665.67/QALY, year 2015\*), respectively.

\*NOTE: The above conversions represent an approximate translation of the procedural cost and/or product price values to current U.S. values. These conversions do NOT provide an estimate of the current cost; they are based on January 30, 2016, use of the CCEMG - EPPI-Centre web-based cost converter with the International Monetary Fund (IMF) dataset for Purchasing Power Parity (PPP) values, available at: [click here](#) [last updated on January 27, 2014] (Shemilt et al., 2010).

## Overall Summary and Discussion

### *Evidence-Based Summary Statement*

The Alair Bronchial Thermoplasty System (Boston Scientific Corp.) is regulated via the premarket approval (PMA) process as a Class III (high risk) device and is subject to the most

stringent regulations enforced by the FDA. The FDA approved the bronchial thermoplasty system on April 27, 2010, for the treatment of severe persistent asthma in adults whose asthma is not well controlled with ICS and LABAs (CRDH, 2010). FDA PMA was primarily based on a pivotal double-blind sham-controlled RCT (Castro et al., 2010). The FDA concluded that bronchial thermoplasty had an acceptable safety profile, as adverse events were reversible and most were common in both active and control groups. Serious adverse events included hemoptysis, respiratory infections, atelectasis, pneumonia, and asthma symptoms. With the exceptions of atelectasis and hemoptysis, these serious complications occurred in both active and sham treatment groups. However, these are expected events in the patient population and may be related to bronchoscopic procedures rather than the thermoplasty treatment; thus, it did not raise major concerns. The primary efficacy measure of AQLQ scores between treatment and sham groups did not meet prespecified success criteria. However, the FDA considered severe asthma exacerbations to be an important measure of clinical performance; there was a clinically important difference in favor of the thermoplasty group for this endpoint. In addition, several other clinically important endpoints that may be related to severe asthma exacerbations also showed differences in favor of the thermoplasty group (e.g., ED visits; hospitalizations; rescue medication use; asthma symptoms; days lost from work, school, or other activities; unscheduled physician office visits for respiratory symptoms).

The overall body of evidence concerning thermoplasty for treatment of asthma was small in size and low in quality. The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3 very-poor-quality case series. The evidence for the effectiveness of bronchial thermoplasty for treating asthma was considered to be of low quality because of some positive but inconsistent results regarding short-term benefits of bronchial thermoplasty, varied patient selection criteria across studies, small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long-term efficacy of bronchial thermoplasty.

Overall, the body of evidence suggests that during the first year after thermoplasty, some benefits were observed, including improved QOL, symptom relief, reduced medication use, and reductions in ED visits; however, the benefits varied somewhat across studies. These differences in benefits may have resulted from differences in study protocols (e.g., different primary outcome measures in all 3 RCTs, 2 RCTs involved partial discontinuation of certain asthma medications). Only one of the RCTs reported results of controlled follow-up for longer than 1 year. This study found that, at 3 years follow-up, the only statistically significant benefit of thermoplasty was an improvement in airway responsiveness. However, this follow-up may have been flawed since it involved only 69 patients and the dropout rate was much higher for the control group than for the thermoplasty group. The apparent loss of benefits of thermoplasty during longer follow-up may indicate loss of effectiveness over time or may be an artifact of selective dropping out of control group patients who have the most poorly controlled asthma.

Results from 4 very-poor-quality nonrandomized studies report some positive but mixed outcomes. In a single retrospective cohort study in patients with severe asthma, 5 of 10 clinic

patients (50%) met criteria for clinical improvement at 1-year follow-up. Asthma medications were reduced in 3 of 10 (30%) patients and the number of severe exacerbations and hospitalizations was reduced in 3 of 10 (30%) patients. A case series of 16 patients with mild to moderate asthma found that mean pre-bronchodilator FEV<sub>1</sub> and airway responsiveness was significantly increased from baseline at 1 year post-thermoplasty; however, this increase in FEV<sub>1</sub> was not maintained at 2 years. A second case series assessed the effect of bronchial thermoplasty in 8 patients with severe asthma that had severe airflow obstruction and found that at 1-year follow-up, there were no changes in mean pre bronchodilator FEV<sub>1</sub> or mean hospitalizations for asthma. A third case series assessed the effect of bronchial thermoplasty in 17 patients with severe asthma and found that at 1-year follow-up, some medications were reduced relative to baseline, self-reported number of exacerbations decreased, and the Asthma Control Scoring System improved. However, there was no significant change in mean pre-bronchodilator FEV<sub>1</sub>.

The majority of complications associated with bronchial thermoplasty occurred within the treatment period. Bronchial thermoplasty was associated with statistically significant increases in dyspnea, wheezing, chest discomfort, night awakenings, sputum discoloration, cough, productive cough, bronchial irritation, and nasal congestion. Most of these complications were mild or moderate in severity. The 3 RCTs found that 5% to 27% of thermoplasty patients compared with 0% to 4% of control patients required hospitalization during the treatment period. However, only 1 fair-quality small RCT found that the between-group difference was significant. Uncontrolled follow-up of patients who underwent thermoplasty treatment found that, in years 2 to 5 versus the first year after treatment, there were no significant changes in respiratory adverse events, ED visits, need for hospitalization, maintenance asthma medication usage, respiratory parameters, or most computed tomography (CT) findings. One study reported that bronchiectasis occurred in 3 (2%) patients.

Labeling information approved by the FDA warns that pneumothorax and respiratory failure requiring intubation are potential complications. In addition, bronchial thermoplasty is contraindicated under any of the following circumstances: presence of a pacemaker, internal defibrillator or similar implanted electronic device; known sensitivity to the drugs employed during bronchoscopy such as lidocaine, atropine, or benzodiazepines; prior bronchial thermoplasty procedure; active respiratory infection; an asthma attack or alteration of the dose of systemic glucocorticoids in the preceding 14 days; known bleeding disorder; need for aspirin, anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory drugs that cannot be interrupted. The UK NICE has stated that bronchial stenosis is a potential long-term complication. In the available literature, no deaths were reported that were related to bronchial thermoplasty for treatment of asthma.

Patient selection criteria varied considerably between studies, and the RCTs were selective in the patients that were enrolled in the study. Although bronchial thermoplasty is indicated in patients with severe asthma, one RCT included patients with moderate and severe asthma. Because we did not want to exclude this important study, studies that included patients with moderate or severe asthma were eligible for inclusion in this report. Because the body of

literature concerning safety and efficacy of bronchial thermoplasty for asthma is small, it is difficult to determine whether efficacy or safety or thermoplasty varied by baseline variables such as asthma severity, medication use, pulmonary function, or other characteristics. More data on differential effects of baseline characteristics are needed to better define patient selection criteria for bronchial thermoplasty.

### **Gaps in the Evidence**

The following evidence is needed to better answer the Key Questions of this report:

- RCTs and long-term cohort studies of sufficient size, design and length to further investigate the safety and efficacy of bronchial thermoplasty in patients with severe asthma.
- Studies designed to systematically investigate differential effectiveness and safety according to patient characteristics (e.g., severity of asthma, baseline respiratory function and medication needs, and previous treatment history).
- Additional studies investigating the impact of bronchial thermoplasty on QOL and functional status.

### **Practice Guidelines**

Four practice guidelines with relevant recommendations were identified addressing bronchial thermoplasty for treatment of asthma. [Appendix V](#) presents the recommendations of each guideline.

### **Selected Payer Policies**

The following payer sites were searched on January 27, 2016, using the keywords *thermoplasty*, *bronchial thermoplasty*, *alair*, or *asthmatx*.

#### ***Aetna***

Aetna considers bronchial thermoplasty experimental and investigational for the treatment of asthma because its effectiveness has not been established.

See Bronchial Thermoplasty: Aetna Clinical Policy Bulletin No. 0744: [click here](#).

#### ***Centers for Medicare & Medicaid Services (CMS)***

No CMS National Coverage Determination (NCD) was identified for bronchial thermoplasty on January 27, 2016 (search National Coverage Documents in National Coverage Determinations and Medicare Coverage Documents at: [click here](#)). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**GroupHealth**

GroupHealth states that the use of bronchial thermoplasty does not meet the GroupHealth Medical Technology Assessment Criteria.

See Bronchial Thermoplasty for Treatment of Severe Bronchial Asthma: [click here](#).

**Oregon Health Evidence Review Commission (HERC)**

No coverage policy bronchial thermoplasty was identified on the Oregon HERC website (HERC Coverage Guidances: [click here](#)).

**Regence Group**

Regence Group considers bronchial thermoplasty investigational for the treatment of asthma.

See Bronchial Thermoplasty: Regence Group Medical Policy No. 178: [click here](#).

**Systematic Reviews**

Three systematic reviews and meta-analyses were found on the efficacy and safety of bronchial thermoplasty for asthma. All 3 studies analyzed data from the 3 RCTs that were analyzed in the current report. Two of the trials analyzed data from 1-year follow-up of bronchial thermoplasty. One trial analyzed results from uncontrolled long-term follow-up 1 to 5 years following thermoplasty. In general, the systematic reviews resulted in some positive but inconsistent results across outcome measures.

Zhou et al. (2015) conducted a meta-analysis on the long-term safety and effectiveness data from the 3 RCTs analyzed in this report. Follow-up data for bronchial thermoplasty patients at 1 year (249 patients) and 5 years (216 patients) were analyzed. Follow-up data from the control groups were not assessed. No evidence of significant decline was found in pre-bronchodilator FEV<sub>1</sub> (percentage predicted) from years 1 to 5 (weighted mean difference [WMD] 0.75; 95% CI, 3.4 to 1.9;  $P=0.57$ ). There was a statistically significant decrease in the incidence of respiratory adverse events from years 1 to 5 (relative risk [RR], 3.4; 95% CI, 3.0 to 3.9;  $P<0.00001$ ). However, there were no changes in frequency of ED visits (RR, 1.1; 95% CI, 0.8 to 1.5;  $P=0.71$ ) or hospitalizations (RR, 1.5; 95% CI, 0.7 to 3.1;  $P=0.32$ ) from years 1 to 5.

A Cochrane review analyzed the data from the 3 RCTs analyzed in the current report at the primary endpoint of 12 months post-thermoplasty (Torrego et al., 2014). A pooled analysis of the 3 RCTs found a clinically small but statistically significant mean difference in QOL (AQLQ score, 0.28; 95% CI, 0.07 to 0.5). The authors noted that the risk for bias was high, as 2 of the 3 RCTs did not have a sham intervention for the control group. No significant difference was found with symptom control (ACQ score, -0.15; 95% CI, -0.4 to 0.1). Hospitalization for respiratory complications increased during bronchial thermoplasty treatment (RR, 3.5; 95% CI, 1.26 to 9.68); however, there was no significant difference compared with control groups after



the treatment period. Furthermore, there was no improvement across studies in pulmonary function at 12 months (except for morning peak expiratory flow), or use of rescue medication.

A meta-analysis analyzed data from the 3 RCTs included in the current report at 12 months follow-up (Wu et al., 2011). The study found that compared with either medical management or sham control, bronchial thermoplasty significantly improved AQLQ scores (WMD, 0.64; 95% CI, 0.10 to 1.15;  $P=0.02$ ). Morning peak expiratory flow was found to significantly improve (WMD, 21.78 L/min; 95% CI, 8.1 to 35.5;  $P=0.002$ ); however, no other efficacy or pulmonary function outcomes were presented. Hospitalization for respiratory complications increased during the treatment period (RR, 3.8; 95% CI, 1.39 to 10.24); however, there was no significant difference compared with control groups after the treatment period (RR, 1.15; 95% CI, 0.47 to 2.79).

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## APPENDICES

### APPENDIX I. Search Strategy

#### INITIAL SEARCH, SYSTEMATIC REVIEWS AND PRACTICE GUIDELINES (conducted October 2, 2015)

Initially, evidence for this report was obtained by searching for systematic reviews, meta-analyses, practice guidelines, and economic evaluations that had been published in the past 10 years. Searches were conducted in the following databases using the terms *thermoplasty* or *Alair* or *Asthmatx*: Agency for Healthcare Research and Quality (AHRQ), Blue Cross Blue Shield TEC Assessments, Canadian Agency for Drugs and Technology in Health (CADTH), Centre for Reviews and Dissemination (CRD) (York University), Hayes Knowledge Center, Institute for Clinical Systems Improvement (ICSI), National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (UK), U.S. Preventive Services Task Force (USPSTF), National Guidelines Clearinghouse (NGC), National Institute for Health and Care Excellence (NICE), and Veterans Affairs Technology Assessment Program (VA TAP). (NOTE: The CRD search strategy includes a search for Cochrane Reviews.)

The websites for Global Strategy for Asthma Management and Prevention (GINA) and American Thoracic Society (ATS) were also searched.

Additional systematic reviews were sought from a search of the PubMed database using filters for Practice Guidelines, Guidelines, Meta-analyses, and Systematic Reviews, according to this search:

1. thermoplasty or Alair or Asthmatx

Filters: Meta-Analysis; Systematic Reviews; Publication date from 2005/01/01 to 2015/12/31; English

#### SEARCH FOR PRIMARY CLINICAL STUDIES AND ECONOMIC EVALUATIONS

Because the body of literature regarding bronchial thermoplasty was so small, the main literature search was designed to identify all relevant primary studies.

#### *PubMed search on October 2, 2015*

##### ***Combined using “or”***

1. thermoplasty
2. Alair
3. Asthmatx

Filters: English

***OVID-Embase search on October 2, 2014***

The following search was run in both the Embase and MEDLINE databases. Only search results in Embase were reviewed.

1. thermoplasty
2. Alair
3. Asthmatx
4. 1 or 2 or 3
5. remove duplicates from 4
6. limit 5 to human
7. limit 6 to humans

***Update Searches***

Update searches were conducted on December 15, 2015, and January 25, 2016.

## APPENDIX II. Overview of Evidence Quality Assessment Methods

### Clinical Studies

Tools used include internally developed Quality Checklists for evaluating the quality (internal validity) of different types of studies, a checklist for judging the adequacy of systematic reviews used instead of de novo analysis, and Hayes Evidence-Grading Guides for evaluating bodies of evidence for different types of technologies. Hayes methodology is in alignment with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, which was developed by the GRADE Working Group, an international collaborative body.

<b>Step 1</b>	<p><u>Individual study appraisal:</u></p> <p>a. Initial rating according to study design</p> <p style="padding-left: 20px;"><i>Good:</i> Randomized Controlled Trials</p> <p style="padding-left: 20px;"><i>Fair:</i> Nonrandomized Trial (controlled, parallel-group, quasi-randomized)</p> <p style="padding-left: 20px;"><i>Poor:</i> Observational Analytic Studies (prospective or retrospective trials involving historical controls, pretest-posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group)</p> <p style="padding-left: 20px;"><i>Very Poor:</i> Descriptive Uncontrolled Studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data])</p> <p>b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist</p> <p>c. Repeat for each study</p>
<b>Step 2</b>	<p><u>Evaluation of each body of evidence by outcome, key question, or application:</u></p> <p>a. Initial quality designation according to best study design in a body of evidence</p> <p>b. Downgrade/upgrade</p> <p style="padding-left: 20px;"><i>Downgrade factors:</i> Study weaknesses (Quality Checklists), small quantity of evidence, lack of applicability, inconsistency of results, publication bias</p> <p style="padding-left: 20px;"><i>Possible upgrade factors:</i> Strong association, dose-response effect, bias favoring no effect</p> <p>c. Assign final rating: High-Moderate-Low-Insufficient</p> <p>d. Repeat for each outcome/question/application</p>
<b>Step 3</b>	<p><u>Evaluation of overall evidence:</u></p> <p>a. Rank outcomes by clinical importance</p> <p>b. Consider overall quality of evidence for each critical outcome</p> <p>c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Insufficient</p>
<b>Step 4</b>	<p><u>Evidence-based conclusion:</u></p> <p>Overall quality of evidence plus balance of benefits and harms</p>

**Practice Guidelines (checklist taken from [AGREE Tool](#) and approach to scoring used in this report)**

Rank each item on a scale of 1 to 7.

Decide on overall quality (1 = lowest to 7 = highest), giving strongest weight to items 7 to 14 (Rigor of Development Domain) and items 22 to 23 (Editorial Independence).

For qualitative labels:

Very poor = 1

Poor = 2-3

Fair = 4-5

Good = 6-7

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
18. The guideline describes facilitators and barriers to its application.



19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/or auditing criteria.
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

### APPENDIX III. Excluded Studies

The following 11 studies were excluded during full-text review.

#### Conducted in patients with diagnoses other than asthma

Miller JD, Cox G, Vincic L, Lombard CM, Loomas BE, Danek CJ. A prospective feasibility study of bronchial thermoplasty in the human airway. *Chest*. 2005;127(6):1999-2006. PMID: [15947312](#).

#### Outcome measures not useful in answering Key Questions

Denner DR, Doeing DC, Hogarth DK, Dugan K, Naureckas ET, White SR. Airway inflammation after bronchial thermoplasty for severe asthma. *Ann Am Thorac Soc*. 2015;12(9):1302-1309. PMID: 26230374.

Pretolani M, Dombret M-C, Thabut G, et al. Reduction of airway smooth muscle mass by bronchial thermoplasty in patients with severe asthma. *Am J Respir Crit Care Med*. 2014;190(12):1452-1454. PMID: 25496106.

Thomen RP, Sheshadri A, Quirk JD, et al. Regional ventilation changes in severe asthma after bronchial thermoplasty with (3)He MR imaging and CT. *Radiology*. 2015;274(1):250-259. PMID: 25144646.

#### Case reports

Doeing DC, Husain AN, Naureckas ET, White SR, Hogarth DK. Bronchial thermoplasty failure in severe persistent asthma: a case report. *J Asthma*. 2013;50(7):799-801. PMID: 23651158.

Kirby M, Ohtani K, Lopez Lisbona RM, et al. Bronchial thermoplasty in asthma: 2-year follow-up using optical coherence tomography. *Eur Respir J*. 2015;46(3):859-862. PMID: 26022958.

Lee JA, Rowen DW, Rose DD. Bronchial thermoplasty: a novel treatment for severe asthma requiring monitored anesthesia care. *AANA J*. 2011;79(6):480-483. PMID: 22400414.

Lim HY, Puah SH, Ang LJ, et al. Subconjunctival haemorrhage from bronchoscopy: a case report. *Respir Med Case Rep*. 2015;16:97-100. PMID: 26744668.

Mahajan AK, Hogarth DK. Bronchial thermoplasty: therapeutic success in severe asthma associated with persistent airflow obstruction. *J Asthma*. 2012;49(5):527-529. PMID: 22515527.

#### Conference abstract

Bogart M, Roberts A, Wheeler S. Cost-effectiveness of refractory asthma treatment strategies: a decision tree analysis. Presented at ISPOR 20th Annual International Meeting. Philadelphia, PA. May 2015. Available at: <http://www.ispor.org/ScientificPresentationsDatabase/Presentation/56172>. Accessed March 26, 2016.

Koh MS, Ang SY, Lam SW, Zhang J, Nguyen HV. Cost-effectiveness of bronchial thermoplasty (BT) treatment relative to no BT treatment option for patients with severe asthma. Presented at 22nd Annual Congress, Munich, Germany. Munich, Germany. September 2014. Available at: [http://erj.ersjournals.com/content/44/Suppl\\_58/P917](http://erj.ersjournals.com/content/44/Suppl_58/P917). Accessed March 26, 2016.

**APPENDIX IV. Evidence Tables**

**Appendix IVa. Randomized Controlled Trials Assessing the Clinical Performance of Bronchial Thermoplasty for Asthma**

**Key:** ACQ, Asthma Control Questionnaire; AE(s), adverse event(s); AQLQ, Asthma Quality of Life Questionnaire; ATC, American Thoracic Society; BD, bronchodilator; BL, baseline; BT, bronchial thermoplasty; btwn, between; CFBL, change from baseline; CT, computed tomography; ED, emergency department; FEV<sub>1</sub>, forced expiratory volume in 1 second; f/u, follow-up; GINA, Global Initiative for Asthma; grp(s), group(s); hx, history; ICS, inhaled corticosteroid(s); ITT, intention to treat; LABA, long-acting β<sub>2</sub>-agonist; LOCF, last observation carried forward; NR, not reported; NS, not statistically significant; PC<sub>20</sub>, provocation challenge causing 20% decrease in FEV<sub>1</sub>; PEF, peak expiratory flow; posttx, posttreatment; PPS, posterior probability of superiority; pt(s), patient(s); QOL, quality of life; RCT, randomized controlled trial; RTI, respiratory tract infection; SD, standard deviation; sx, symptom(s); tx, treatment (or therapy)

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p><b>Cox et al. (2007)*</b></p> <p><b>Study design:</b> Unblinded multicenter RCT</p> <p><b>Control/comparator:</b> Pts underwent continued drug tx</p> <p><b>BT tx:</b> Pts underwent 3 BT procedures performed w/ the Alair system at intervals of ~3 wks. During the procedure, they were under either general anesthesia or conscious sedation. Tx sessions were scheduled ≥3 wks apart.</p> <p><b>Study protocol:</b> During the 4-wk BL period, pts continued to receive maintenance tx w/ ICS and LABA for the first 2 wks, and LABA were then w/hold for the next 2 wks. Pts continued w/ ICS and LABA for the tx period, which lasted for ~6-9 wks. Pts were asked to refrain from LABA at the 3-mo f/u visit, unless they had a severe exacerbation or had</p>	<p>n=109 pts w/ moderate or severe stable asthma</p> <p>Thermoplasty grp: n=55 Control grp: n=54</p> <p><b>Definition of stable asthma:</b> Absence of unscheduled physician visits for asthma care, unchanged use of asthma medication for maintenance tx, and stable use of rescue medication (≤4 puffs in a 24-hr period of a short-acting bronchodilator (e.g., albuterol 100 µg/puff or equivalent)</p> <p><b>Definition of moderate to severe asthma:</b> Requiring daily tx w/ ICS equivalent to a dose of ≥200 µg of beclomethasone and LABA at a dose of ≥100 µg of salmeterol or the equivalent, to maintain reasonable asthma control</p> <p><b>Pt hx/characteristics (thermoplasty grp; control grp):</b> % men: 44; 43 Mean age (yrs): 39; 42 % white ethnicity: 93%; 93%</p>	<p>1 (2%) thermoplasty grp pt and 4 (7%) control grp pts were lost to f/u.</p> <p><b>Mean change vs BL at 1-yr f/u (no use of LABA unless specified otherwise) (thermoplasty grp; control grp):</b> Mild exacerbations per wk (+LABA): -0.17; +0.03 (P&lt;0.05) Mild exacerbations per wk: -0.16; +0.04 (P&lt;0.01) Morning PEF (L/min): +39; +9 (P&lt;0.005) AQLQ (higher score better): +1.3; +0.6 (P&lt;0.005) ACQ (lower score better): -1.2; -0.5 (P&lt;0.005) Sx-free days: +41%; +17% (P&lt;0.01) Sx scores (lower score better): -1.9; -0.7 (P&lt;0.05) Rescue BD use (puffs/wk): -8.9; -1.2 (P&lt;0.05)</p> <p>Differences between the thermoplasty and control grps in severe exacerbations, airway responsiveness (PC<sub>20</sub>), and FEV<sub>1</sub> at 1-yr f/u w/o LABA were NS.</p> <p><b>Complications during tx period (tx through 6-wk f/u) (thermoplasty grp; control grp) (% pts):</b> Dyspnea: 71%; 33% (P&lt;0.001) Wheezing: 62%; 13% (P&lt;0.001) Cough: 53%; 19% (P&lt;0.001) Chest discomfort: 47%; 20% (P&lt;0.005)</p>	<p>Fair. Downgraded from good due to lack of blinding, lack of sham/placebo control grp, and f/u of only 1 yr.</p> <p>No blinding; no placebo grp; 5% pts lost to f/u; most outcomes w/ use of LABA NR; only 1 yr f/u; several outcome measures were self-report data collected in daily diaries (e.g., exacerbations, PEF, asthma sx).</p>

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p>poor asthma control. A severe exacerbation was defined as an event requiring tx w/ oral corticosteroids, or a decrease in the morning PEF for <math>\geq 1</math> day of &gt;30% below the average BL morning PEF recorded during the wk immediately preceding w/drawal from LABA. All pts underwent attempted w/drawal from LABA for 2 wks at 3, 6, and 12 mos and assessment of respiratory function at each of these time points.</p> <p><b>Primary outcome measure:</b> Frequency of mild exacerbations (data on exacerbations were collected via daily diaries; defined as reduction in the morning PEF of <math>\geq 20\%</math> below the average value at BL, need for &gt;3 additional puffs of rescue medication exceeding the average use during BL, or nocturnal awakening caused by asthma sx)</p> <p><b>Other outcome measures:</b> Asthma sx and number of symptom free days (collected via daily diary); PEF (collected by pt and reported in daily diary); FEV<sub>1</sub>; ACQ; AQLQ; PC<sub>20</sub></p> <p><b>Data analysis:</b> All analyses were ITT w/ no imputation of missing data. Frequencies of AEs were compared w/ the use of Fisher's exact test. For continuous variables, statistical significance was determined w/ use of Student's <i>t</i>-test. For categorical variables, the Cochran-Mantel-Haenszel test was used.</p> <p><b>Power analysis:</b> The primary outcome was the frequency of mild exacerbations, calculated during 3 scheduled 2-wk periods of abstinence from LABA at 3, 6,</p>	<p>% black ethnicity: 5%; 4%                      % Asian ethnicity: 2%; 4%                      % w/ moderate asthma: 38%; 48%                      % w/ severe asthma: 62%; 52%                      % w/ seasonal allergies: 62%; 65%                      Mean PC<sub>20</sub> (mg/mL): 0.25; 0.35                      Mean pre-BD FEV<sub>1</sub> (% of predicted value): 73; 76                      Mean inhaled steroid use (mg/day): 1.4; 1.3                      Mean LABA use (mg/day): 0.11; 0.11                      % pts w/ ACQ increase <math>\geq 0.5</math> after 2 wks w/ no LABA: 31%; 22%                      % pts w/ <math>\geq 5\%</math> PEF decrease after 2 wks w/ no LABA: 27%; 26%                      Mean # mild exacerbations per wk: 0.35; 0.28                      # ED visits in prior yr: NR                      # hospitalizations in prior yr: NR                      Between-grp differences at BL were NS.</p> <p><b>Inclusion criteria:</b> Age 18-65 yrs; moderate or severe persistent asthma as defined by the GINA; daily need for high-dose inhaled glucocorticoids and LABA; pre-BD FEV<sub>1</sub> 60% to 85% of predicted value; airway hyperresponsive to methacholine challenge; stable asthma w/ no significant changes in medication use or unscheduled visits to physician during the 6 wks before enrollment in study</p> <p><b>Exclusion criteria:</b> <math>\geq 3</math> lower RTI requiring antibiotics during the last 12 mos or a RTI w/in 6 wks</p> <p><b>Setting:</b> McMaster University (Hamilton, Ontario, Canada) and 10 other institutions in the UK, Brazil, Denmark, and Canada</p> <p><b>Concurrent tx:</b> During the 4-wk BL period, pts continued to receive maintenance tx w/ inhaled corticosteroids and LABA for the first 2 wks, and LABA were then w/held for the next 2 wks. Pts continued w/ inhaled corticosteroids and LABA for the tx period, which lasted for ~6 to 9</p>	<p>Night awakenings: 40%; 9% (<math>P &lt; 0.001</math>)                      Productive cough: 40%; 11% (<math>P &lt; 0.001</math>)                      Discolored sputum: 11%; 0% (<math>P &lt; 0.05</math>)                      Nasal congestion: 13%; 11% (<math>P = NS</math>)                      Upper RTI: 13%; 4% (<math>P = NS</math>)                      Bronchial irritation: 9%; 0% (<math>P = NS</math>)                      Bronchospasm: 7%; 0% (<math>P = NS</math>)                      Abnormal chest sound: 6%; 0% (<math>P = NS</math>)                      Dry mouth: 4%; 0% (<math>P = NS</math>)                      # hospitalizations: 6; 1 (<math>P = NS</math>)</p> <p><b>Complications during posttx period:</b> Differences between grps in complications during posttx period were NS. The rate of hospitalization during the posttx period btwn grps was NS: 3 thermoplasty pts required hospitalization (1 for chest infection and 2 for asthma exacerbation) and 2 control pts required a total of 3 hospitalizations for increased asthma sx.</p> <p><b>Mortality:</b> There were no deaths during the study.</p>	

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p>and 12 mos. The study was designed w/ &gt;90% power to detect a difference of 8 mild exacerbations per pt per yr btwn the 2 grps w/ a 2-tailed t-test. The study was powered to detect differences btwn the 2 grps in the CFBL to f/u.</p> <p><b>F/u period:</b> 1 yr</p> <p><b>Funding source:</b> Ashthmatx Inc.</p> <p><b>Conflict of interest:</b> Several investigators had financial relationships w/ device manufacturer and drug manufacturers. Study funded by device manufacturer.</p>	<p>wks. Pts were asked to refrain from LABA at the 3-mo f/u visit, unless they had a severe exacerbation or had poor asthma control. A severe exacerbation was defined as an event requiring tx w/ oral corticosteroids, or a decrease in the morning PEF for ≥1 day of &gt;30% below the average BL morning PEF recorded during the wk immediately preceding w/drawal from LABA.</p>		
<p><b>Pavord et al. (2007); Pavord et al. (2013)</b></p> <p><b>Study design:</b> Unblinded multicenter RCT</p> <p><b>Control/comparator:</b> Pts underwent continued drug tx</p> <p><b>BT tx:</b> Pts underwent 3 sessions of thermoplasty tx at ≥3-wk intervals and continued drug tx.</p> <p><b>Study protocol:</b> All pts underwent attempted weaning from oral and inhaled glucocorticoids during wks 22-36 of study and maintenance of reduced steroid use during wks 37-52. Respiratory function and pt QOL were assessed at wk 22 and wk 52. In yr 1, AEs were identified during 12 office visits and 9 telephone contacts. During the longer-term f/u, AEs were solicited at the annual evaluation.</p> <p><b>Primary outcome measure:</b> Complications (pts were asked by a researcher at every visit and by phone call about potential AEs, and their diaries were examined by study personnel to</p>	<p>n=32 pts w/ severe asthma</p> <p>Thermoplasty grp: n=15 Control grp: n=17</p> <p><b>Definition of severe asthma:</b> All pts met the GINA criteria for severe persistent asthma. All but 1 pt met the ATS criteria for refractory asthma. Pts require daily tx w/ medium to high dose ICS and LABA.</p> <p><b>Pt hx/characteristics (thermoplasty grp; control grp):</b> % men: 40%; 59% Mean age (yrs): 39; 42 Mean PC20 (mg/mL): 0.19; 0.31 Mean pre-BD FEV<sub>1</sub> (% of predicted value): 63; 66 % using oral steroids: 53%; 41% Mean inhaled steroid use (mg/day): 1.2; 1.1 Mean LABA use (mg/day): 0.13; 0.14 Median rescue BD use (puffs/wk): 62; 30 Mean morning PEF (L/min): 356; 350 Mean ACQ score: 2.8; 2.2 Mean AQLQ score: 4.0; 4.7 % symptomatic days: 95%; 86% Mean # night awakenings per wk: 3.3; 1.9 Mean sx score: 5.6; 3.4</p>	<p>2 (12%) pts w/drew from thermoplasty grp before tx; 2 pts were not candidates for BT due to possible Churg-Strauss syndrome (1 pt) and post-bronchodilator FEV<sub>1</sub> &lt;55% predicted (1 pt).</p> <p><b>Mean change vs BL (thermoplasty grp; control grp):</b> Rescue BD use (22 wks) (% change): -27%; -2% (P&lt;0.05) Pre-BD FEV<sub>1</sub> (22 wks) (% change): +15%; -1% (P&lt;0.05) ACQ (22 wks) (lower score better): -1.0; -0.1 (P&lt;0.05) AQLQ (22 wks) (higher score better): +1.2; +0.2 (P&lt;0.05) Rescue BD use (52 wks) (% change): -26%; -6% (P&lt;0.05) Pre-BD FEV<sub>1</sub> (52 wks) (% change): +7%; +2% (P=NS) ACQ (52 wks) (lower score better): -1.0; -0.2 (P&lt;0.05) AQLQ (52 wks) (higher score better): +1.5; +0.4 (P&lt;0.05)</p> <p>There were no significant differences in morning or evening PEF, sx-free days, sx scores, or PC<sub>20</sub>. Between-grp differences in steroid reduction during wks 36-52 were NS.</p> <p><b>Complications during tx period (tx through 6-wk f/u) (thermoplasty grp; control grp) (% pts):</b> Wheezing: 73%; 24% (P&lt;0.05) Cough: 73%; 35% (P&lt;0.05) Chest discomfort: 40%; 6% (P&lt;0.05) Dyspnea: 60%; 41% (P=NS) Productive cough: 53%; 29% (P=NS) Discolored sputum: 33%; 0% (P&lt;0.05) Nasal congestion: 20%; 18% (P=NS)</p>	<p>Fair. Downgraded from good due to lack of blinding, lack of sham/placebo control grp, small sample size, w/drawal of 12% pts from thermoplasty tx grp before tx, and f/u of only 1 yr.</p> <p>No blinding; small sample size; no power analysis conducted; 12% thermoplasty grp pts w/drew from study before tx; only 1 yr of controlled f/u; several outcome measures were self-report data collected in daily diaries (e.g., medication use, PEF, asthma sx); outcomes during yrs 2-5 were collected once per yr and may be subject to recall bias.</p>

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p>ensure complete event reporting)</p> <p><b>Secondary outcome measures:</b> Rescue medication use (recorded by pt in daily diary); sx (recorded by pt in daily diary); PEF (recorded by pt in daily diary); FEV<sub>1</sub>; ACQ; AQLQ</p> <p><b>Data analysis:</b> Frequencies of AEs were compared w/ the use of Fisher's exact test. For continuous variables, statistical significance was determined w/ the use of Student's <i>t</i>-test or Wilcoxon rank sum test. For categorical variables, the Cochran-Mantel-Haenszel test was used.</p> <p><b>Power analysis:</b> NR</p> <p><b>F/u period:</b> 1 yr for all pts; 5 yrs for thermoplasty grp</p> <p><b>Funding source:</b> Ashthmatx Inc.</p> <p><b>Conflict of interest:</b> Several investigators had financial relationships w/ device manufacturer and drug manufacturers. Study funded by device manufacturer.</p>	<p>% w/ seasonal allergies: 67%; 53%</p> <p>% hospitalized for asthma in yr before study: 40%; 12%</p> <p># ED visits in prior yr: NR</p> <p>Differences between grps at BL were NS except for sx score.</p> <p><b>Inclusion criteria:</b> Age 18-65 yrs; need for high-dose inhaled glucocorticoids (≥750 µg fluticasone propionate per day or equivalent) and LABA (≥100 µg salmeterol per day or equivalent); pre-BD FEV<sub>1</sub> ≥50% of predicted value; airway hyperresponsive to methacholine challenge or reversible bronchoconstriction demonstrated in response to LABA during prior 12 mos; uncontrolled sx despite use of rescue medication; no smoking in prior yr; smoking hx &lt;10 pack-yrs</p> <p><b>Exclusion criteria:</b> use of immunosuppressant tx other than ICS and OCS; current lower RTI or a hx of a lower RTI w/in 6 wks; &gt;3 lower RTIs requiring antibiotics in last 3 mos; other respiratory diseases; diffusing capacity &lt;70% predicted; uncontrolled sinus disease; uncontrolled gastroesophageal reflux disease; use of implanted electronic device or external pacemaker; a variety of co-morbid illnesses; post-BD FEV<sub>1</sub> of &lt;55% predicted.</p> <p><b>Setting:</b> Glenfield General Hospital, Leicester, UK, and 7 other institutions in the UK, Canada, and Brazil</p> <p><b>Concurrent tx:</b> All pts underwent attempted weaning from oral and inhaled glucocorticoids during wks 22-36 of study and maintenance of reduced steroid use during wks 37-52. During the reduced steroid phase, pts continued those medications prescribed at the end of the steroid wean phase for as long as possible.</p>	<p>Pharyngolaryngeal pain: 20%; 6% (<i>P</i>=NS)</p> <p>Atelectasis; 7%; 0% (<i>P</i>=NS)</p> <p>Bronchial irritation: 13%; 0% (<i>P</i>=NS)</p> <p>Lower RTI: 13%; 29% (<i>P</i>=NS)</p> <p>Upper RTI: 7%; 18% (<i>P</i>=NS)</p> <p>Hospitalization: 47%; 0% (<i>P</i>&lt;0.05)</p> <p><b>Hospitalizations during tx period:</b> There were 7 hospitalizations for respiratory AEs involving 4 pts in the BT grp and 0 in the control grp. 5 of the 7 hospitalizations were for exacerbations of asthma and 2 were for partial collapse of a lower lobe of the lung.</p> <p><b>Complications during posttx period:</b> Between-grp differences in complications during posttx period were NS; 5 hospitalizations occurred in 3 pts in the BT grp and 4 hospitalizations in 1 pt in the control grp.</p> <p>Uncontrolled f/u of 14 (93%) pts in the BT grp found that in yrs 2-5, respiratory AEs, hospitalizations, ED visits, asthma maintenance medication usage, pre-BD FEV<sub>1</sub>, and post-BD FEV<sub>1</sub> were essentially unchanged.</p> <p><b>Mortality:</b> There were no deaths during the study.</p>	
<p><b>Castro et al. (2010); Castro et al. (2011); Wechsler et al. (2013)</b></p>	<p>n=288 pts w/ severe asthma</p>	<p>9 (5%) thermoplasty grp pts and 1 (1%) control grp pts were lost to f/u.</p>	<p>Good</p>

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p><b>Study design:</b> Double-blind, sham-controlled, multicenter RCT</p> <p><b>Control/comparator:</b> Pts underwent 3 sessions of placebo thermoplasty and continued drug tx</p> <p><b>BT tx:</b> Pts underwent 3 BT procedures performed w/ the Alair system at intervals of ~3 wks. Tx sessions were scheduled ≥3 wks apart.</p> <p><b>Study protocol:</b> Study protocol did not involve any intentional or directed changes in medication use. Pts were assessed at 3, 6, 9, and 12 mos after tx. Pt ability to comply w/ the use of a peak flow meter and completion of the electronic daily diary was assessed in the first wk. Compliant pts used the diary to collect BL data over 4 wks.</p> <p><b>Primary outcome measure:</b> AQLQ</p> <p><b>Secondary outcome measures:</b> Severe exacerbations (those requiring systemic corticosteroids or doubling of ICS dose); rescue medication use (recorded by pt in daily diary); sx (recorded by pt in daily diary); PEF (recorded by pt in daily diary); FEV<sub>1</sub>; ACQ; AQLQ; complications</p> <p><b>Data analysis:</b> All analyses were ITT w/ missing data imputed using LOCF. Outcomes were compared using Bayesian methodology, w/ PPS &gt;0.95 indicating a meaningful between-grp difference.</p> <p><b>Power analysis:</b> NR</p>	<p>Thermoplasty grp: n=190 Control grp: n=98</p> <p><b>Definition of severe asthma:</b> Requiring daily tx w/ high-dose ICS and LABA, a low AQLQ score and percentage of symptom-free days. 86% of the BT grp (163 pts) and 88% of the sham control grp (86 pts) met ATS criteria for severe refractory asthma.</p> <p><b>Pt hx/characteristics (thermoplasty grp; control grp):</b> % men: 43%; 39% Mean age (yrs): 41; 41 % white ethnicity: 80%; 74% % black ethnicity: 10%; 15% % other ethnicity: 11%; 11% Mean PC<sub>20</sub> (mg/mL): 0.27; 0.31 Mean pre-BD FEV<sub>1</sub> (% of predicted value): 78; 80 Mean ICS use (mg/day): 2.0; 1.8 Mean LABA use (mg/day): 0.12; 0.11 % using other asthma drugs: 31%; 26% Mean AQLQ score: 4.3; 4.3 % sx-free days: 16%; 17% # ED visits in prior yr: NR # hospitalizations in prior yr: NR NR whether between-grp differences at BL were NS.</p> <p><b>Inclusion criteria:</b> Age 18-65 yrs; ≥1000 µg/day ICS and ≥100 µg/day inhaled LABA needed for asthma; stable maintenance asthma medication for ≥4 wks before enrollment; AQLQ score ≤6.25; pre-BD FEV<sub>1</sub> ≥60% of predicted value; airway hyperresponsive to methacholine challenge; ≥2 days of asthma sx during 4-wk BL period; nonsmoker for ≥1 yr; smoking hx &lt;10 pack-yrs</p> <p><b>Exclusion criteria:</b> Life-threatening asthma; chronic sinus disease; emphysema or other respiratory disease; immunosuppressant, anticoagulant, or β-adrenergic blocking agent use; &gt;2 hospitalizations, &gt;2 lower RTIs, or &gt;3 pulses of oral steroid use for</p>	<p>Mean ± SD increase from BL in AQLQ scores from 6-12 mos was 1.4±1.1 for the thermoplasty grp vs 1.2±1.2 for the control grp (higher score better) (PPS=0.96).</p> <p><b>Mean outcomes at 12 mos (thermoplasty grp; control grp):</b> Days lost from work/school/activities due to asthma (days/yr): 1.3; 3.9 (PPS=0.993) Severe exacerbations (#/[pt × yr]): 0.48; 0.70 (PPS=0.96) ED visits (#/[pt × yr]): 0.07; 0.43 (PPS=0.999)</p> <p>No meaningful differences were seen between the thermoplasty and control grps in ACQ, FEV<sub>1</sub>, total sx score, sx-free days, rescue medication use, unscheduled physician visits, or hospitalizations (PPS &lt;0.95).</p> <p>In an uncontrolled extension of f/u for 166 (87%) thermoplasty grp pts at 1 vs 2 yrs, differences w/in the thermoplasty grp in severe exacerbations, asthma sx ED visits, and hospitalizations were NS (Castro et al., 2011).</p> <p><b>Outcomes for 5 yrs uncontrolled f/u of 162 (85%) thermoplasty grp pts (12 mos before tx or BL; first yr after tx; fifth yr after tx):</b> Severe exacerbations (% pts): 52%; 31%; 22% (P=NR) ED visits (% pts): 28%; 6%; 7% (P=NR) Pre-BD FEV<sub>1</sub> (% predicted): 86%; 84%; 82% (P=NR) Post-BD FEV<sub>1</sub> (% predicted): 78%; 77%; 77% (P=NR) (For thermoplasty grp in yrs 2-5, respiratory AEs, hospitalizations, and CT findings were unchanged except for 3 cases of bronchiectasis and a mean steroid dose decrease of 18%.)</p> <p><b>Complications during tx period (thermoplasty grp; control grp) (% pts):</b> Mild: 44%; 59% (P&lt;0.05) Moderate: 53%; 40% (P&lt;0.05) Severe: 3%; 1% (P=NS)</p> <p>Complications included wheezing, chest discomfort, cough, chest pain, and upper respiratory infections.</p> <p>Between-grp differences in posttx complications were NS.</p>	<p>Invasive placebo tx; AQLQ averaged over 6-12 mos f/u reported but AQLQ at 12 mos NR; some outcome measures reported in daily diaries; although daily diaries were electronic, no compliance data were reported; mild exacerbations NR; 3% pts lost to f/u, primarily from thermoplasty grp; after 1 yr, all f/u uncontrolled..</p>



Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p><b>F/u period:</b> 1 yr for all pts; 5 yrs for thermoplasty grp</p> <p><b>Funding source:</b> Ashthmatx Inc.; Boston Scientific Corp.</p> <p><b>Conflict of interest:</b> Several investigators had financial relationships w/ device manufacturer and drug manufacturers. Study funded by device manufacturer.</p>	<p>asthma in prior yr</p> <p><b>Setting:</b> Washington University School of Medicine, St. Louis, MO and 29 other institutions in the U.S., Australia, Canada, the Netherlands, UK, and Brazil</p> <p><b>Concurrent tx:</b> Pts continued w/ their usual medication.</p>	<p><b>Complications during posttx period:</b> Differences between grps in complications during posttx period were NS; 5 pts (2.6%) in BT grp had 6 hospitalizations for respiratory sx compared w/ 12 hospitalizations in 4 pts (4.1%) in sham grp (1 pt had 9 hospitalizations)</p> <p><b>Mortality:</b> None related to study tx; 1 BT pt died in motor vehicle accident during 5-yr f/u.</p>	
<p><b>Thomson et al. (2011)*</b></p> <p><b>Study design:</b> Long-term f/u of unblinded multicenter RCT (Cox et al., 2007)</p> <p><b>Control/comparator:</b> Pts underwent continued drug tx</p> <p><b>BT tx:</b> Pts underwent 3 sessions of thermoplasty tx at ≥3-wk intervals and continued drug tx</p> <p><b>Study protocol:</b> At 1 yr f/u in the Cox et al. (2007) study, pts were invited to participate in this extension phase of the study. All pts underwent assessment of respiratory function, drug use, and hospitalizations at 2 and 3 yrs after study entry. BT grp pts underwent additional assessments at 4 and 5 yrs after tx. During yr 1, AEs were solicited during 12 office visits and 9 telephone contacts, as well as medical chart review. During yrs 2 to 5, AEs were collected once during annual evaluation, and medical chart review. Respiratory function was assessed w/ pts off LABA and oral steroids. Signs of worsening of asthma included dyspnea, cough, wheezing, RTI, chest discomfort, discolored sputum, pharyngitis, pleuritic pain, bronchitis, and pneumonia.</p>	<p>n=69 of 109 pts w/ moderate or severe persistent asthma were randomized to the following tx grps by Cox et al. (2007):</p> <p>Thermoplasty grp: n=45 Control grp: n=24</p> <p><b>Clinical hx/pt characteristics at entry into extension phase of trial (thermoplasty grp; control grp):</b>                      % men: 42%; 38%                      Mean age (yrs): 40; 41                      % white ethnicity: 91%; 92%                      % black ethnicity: 7%; 8%                      % Asian ethnicity: 2%; 0%                      Mean PC<sub>20</sub> (mg/mL): 0.25; 0.28                      Mean pre-BD FEV<sub>1</sub> (% predicted value): 73%; 75%                      Mean inhaled steroid use (mg/day): 1.3; 1.1                      Mean LABA use (mg/day): 0.11; 0.10                      % days sx free: 33%; 46%                      Mean ACQ score: 1.3; 1.2                      Mean AQLQ score: 5.6; 5.6                      Mean rescue BD use (puffs/wk): 10.6; 5.5                      # ED visits in prior yr: 3; 0                      # hospitalizations in prior yr: 3; 2</p> <p>Between-grp differences at entry into extension phase of trial were NS.</p> <p><b>Inclusion criteria:</b> Age 18-65 yrs; moderate or severe persistent asthma as defined by the GINA; daily need for high-dose inhaled glucocorticoids</p>	<p>1 (2%) thermoplasty grp pt and 2 (8%) control grp pts were lost to f/u.</p> <p><b>Methacholine PC<sub>20</sub> doubling (thermoplasty grp; control grp) (mean # doublings):</b>                      Yr 1: +1.5; +1.0 (P=NS)                      Yr 2: +1.2; -0.5 (P&lt;0.05)                      Yr 3: +1.3; -0.4 (P&lt;0.05)</p> <p>During 1-3 yrs f/u, between-grp differences in FEV<sub>1</sub>, functional vital capacity, and asthma medication use were NS.</p> <p><b>Worsening of asthma (yr 1; 2; 3; 4; 5) (mean # events per pt):</b>                      Thermoplasty grp: 4.5; 1.2; 1.3; 1.2; 1.1                      Control grp: 3.1; 1.2; 1.3; NR; NR                      Between-grp differences were NS.</p> <p><b>Hospitalizations (yr 1; 2; 3; 4; 5) (% pts):</b>                      Thermoplasty grp: 7%; 7%; 2%; 2%; 2%                      Control grp: 0%; 0%; 5%; NR; NR                      Between-grp differences were NS.</p> <p><b>ED visits (yr 1; 2; 3; 4; 5) (% pts):</b>                      Thermoplasty grp: 4%; 7%; 5%; 5%; 2%                      Control grp: 0%; 13%; 5%; NR; NR                      Between-grp differences were NS.</p> <p><b>Oral glucocorticoid pulses (yr 1; 2; 3; 4; 5) (mean # events per pt):</b>                      Thermoplasty grp: 0.6; 0.5; 0.3; 0.6; 0.6                      Control grp: 0.4; 0.5; 0.5; NR; NR                      Between-grp differences were NS.</p>	<p>This is an f/u study and is not rated separately from Cox et al. (2007).</p> <p>No blinding; 18% thermoplasty pts and 56% control grp pts lost to f/u for this study vs original study; control grp pts w/ worse asthma more likely to drop out of study; respiratory function assessed w/ pts off LABA and oral steroids; unequal duration of f/u; safety outcomes only assessed once per yr and may be subject to recall bias in yrs 2-5.</p>

Authors/Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p><b>Outcome measures:</b> Hospitalizations; ED visits; respiratory AEs; need for oral steroids; respiratory function</p> <p><b>Data analysis:</b> Grp means were compared using Student's <i>t</i>-test. Fisher's Exact test was used to compare proportion of pts w/ respiratory hospitalizations and ED visits in the BT and control grps during yrs 1, 2, and 3. Trends in the % of pts w/ hospitalizations or ED visits for respiratory sx across yrs 1-5 were investigated using a repeated measures logistic regression, modeling the % of pts reporting the event. CFBL to each f/u yr in ICS dose was analyzed w/ signed rank test.</p> <p><b>F/u period:</b> 3 yrs for control grp; 5 yrs for thermoplasty grp</p> <p><b>Funding source:</b> Ashthmatx Inc.</p> <p><b>Conflict of interest:</b> Several investigators had financial relationships w/ device manufacturer and drug manufacturers. Study funded by device manufacturer.</p>	<p>and LABA; pre-BD FEV<sub>1</sub> 60% to 85% of predicted value; airway hyperresponsive to methacholine challenge; stable asthma w/ no significant changes in medication use or unscheduled visits to physician during the 6 wks before enrollment in study</p> <p><b>Exclusion criteria:</b> Participation in another clinical trial</p> <p><b>Setting:</b> McMaster University (Hamilton, Ontario, Canada) and 10 other institutions in the UK, Brazil, Denmark, and Canada</p>	<p><b>Complications during tx period:</b> Reported above by Cox et al. (2007)</p> <p>During 5 yrs f/u, no pts had pneumothorax or cardiac arrhythmias, were intubated or mechanically ventilated, or died due to thermoplasty.</p>	

**Appendix IVb. Nonrandomized Studies Assessing the Clinical Performance of Bronchial Thermoplasty for Asthma**

**Key:** AE(s), adverse event(s); BD, bronchodilator; BL, baseline; BT, bronchial thermoplasty; BTS, British Thoracic Society; btwn, between; dx, diagnosis; ED, emergency department; FEV<sub>1</sub>, forced expiratory volume in 1 second; f/u, follow-up; GINA, Global Initiative for Asthma; grp(s), group(s); hx, history; ICS, inhaled corticosteroid(s); LABA, long-acting β<sub>2</sub>-agonist; MCID, minimum clinical important difference; NR, not reported; NS, not statistically significant; PC<sub>20</sub>, provocation challenge causing 20% decrease in FEV<sub>1</sub>; PEF, peak expiratory flow; posttx, posttreatment; pt(s), patient(s); RTI, respiratory tract infection; sx, symptom(s); tx, treatment (or therapy); tx'd, treated

Authors/ Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p><b>Cox et al. (2006)</b></p> <p><b>Study design:</b> Case series</p> <p><b>Control/comparator:</b> None</p> <p><b>BT tx:</b> Systemic steroids were given prior to tx (Site A received 50 mg oral prednisone the day before tx and 40 mg methylprednisolone IV on the day of tx; Site B received 30 mg prednisone the day before, the day of, and the day after tx). BT was performed during bronchoscopy w/ general anesthesia (Site A) or local anesthesia w/ conscious sedation (Site B). Airways were tx'd under bronchoscopic vision moving from distal to proximal. 1 tx session each was required for each lower lobe, and both upper lobes were tx'd at another session. The right middle lobe was not tx'd. Tx sessions were scheduled ≥3 wks apart. After the first tx session, previously tx'd airways were evaluated by bronchoscopy before proceeding w/ further tx.</p> <p><b>Study protocol:</b> Safety was evaluated by assessment of AEs after each study tx and by objective measurements made at f/u visits at 1 wk, 1 yr, and 2 yrs. F/u visits included physical</p>	<p>n=16 pts w/ stable mild to moderate asthma</p> <p><b>Definition of stable asthma:</b> No change in asthma condition or medication needs in last 6 wks; inclusion/exclusion criteria include medication need criterion use of ≤4 puffs in a 24-hr period of a short-acting β<sub>2</sub>-adrenergic agonist (e.g., albuterol 100 µg/puff or equivalent) except for exercise</p> <p><b>Definition of mild to moderate asthma:</b> NR</p> <p><b>Pt hx/characteristics:</b>                      Mean (range) age (yrs): 39 (24-58)                      % men: 37.5%                      % white ethnicity: 94%                      % east Indian ethnicity: 6%                      Mean (95% CI) PC<sub>20</sub> (mg/mL): 0.92 (CI, 0.42-1.99)                      Mean (SD) pre-BD FEV<sub>1</sub> (% of predicted value): 82% (14%)                      Morning PEF (L/min): 427.1                      Evening PEF (L/min): 435.3                      % sx-free days: 47%                      No inhaled steroid use (# pts) (% pts): 1 (6.3%)                      Low dose (&lt;250 µg/day) inhaled steroid use (# pts) (% pts): 1 (6.3%)                      Medium dose (250-500 µg/day) inhaled steroid use (# pts) (% pts): 13 (81.3%)                      High-dose (&gt;500 µg/day) inhaled steroid use (# pts) (% pts): 1 (6.3%)                      LABA use (# pts) (% pts): 5 (31.3%)                      Mean (SD) rescue BD use (puffs/day): 1.0 (1.1)                      # ED visits in prior yr: NR                      # hospitalizations in prior yr: NR</p>	<p><b>BT tx:</b> All txs were completed in ≤30 mins. Tx was completed in 3 sessions in 13 pts and in 4 sessions in 2 pts; 1 pt received 2 txs but did not undergo a third based on the investigator's concern about the need for 2 courses of antibiotics for management of respiratory sx after the second tx.</p> <p><b>Efficacy outcomes at 12-wk f/u (unless otherwise noted):</b>                      Pre-BD FEV<sub>1</sub> (2 yrs): 85.7 (NS)                      Pre-BD FEV<sub>1</sub> (1 yr): 88.6 (P=0.043)                      Pre-BD FEV<sub>1</sub> (12 wks): 88.3 (P=0.030)                      Morning PEF (L/min): 465.9 (P=0.010)                      Evening PEF (L/min): 476.4 (P=0.007)                      % sx-free days: 73% (P=0.015)                      Mean PC<sub>20</sub> (mg/mL) (12 wks): 4.75                      Mean PC<sub>20</sub> (mg/mL) (1 yr): 5.45                      Mean PC<sub>20</sub> (mg/mL) (2 yrs): 3.40                      Mean # methacholine PC<sub>20</sub> doubling (12 wks): 2.4                      Mean # methacholine PC<sub>20</sub> doubling (1 yr): 3.0                      Mean # methacholine PC<sub>20</sub> doubling (2 yrs): 2.3                      Rescue BD use: Unchanged (9 pts), less use (5 pts), increased use (1 pt) (NS)</p> <p><b>Device-related complications during tx period (tx through 6-wk f/u) (% pts):</b>                      Cough: 94%                      Dyspnea: 69%                      Bronchospasm: 63%                      Chest discomfort: 56%                      Wheezing: 50%                      Productive cough: 50%                      Fever: 44%                      Throat irritation: 25%                      Headache: 25%</p>	<p>Very poor</p> <p>Small sample size. No control or comparator grp. Pts had mild to moderate stable asthma (not generalizable to typical pts undergoing BT). No power analysis conducted. BT and methodological procedures varied somewhat btwn sites.</p>

Authors/ Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p>examination; review of sx, exacerbations, and AEs, review of daily diary, spirometry, and pulse oximetry. Pts recorded PEF and asthma sx twice daily in a diary out to 12 wks posttx.</p> <p><b>Outcome measures:</b> PEF (collected by pt and reported in daily diary); sx-free days (daily diaries); FEV<sub>1</sub></p> <p><b>Data analysis:</b> Pt BL values were compared w/ tx f/u data using a paired t- test</p> <p><b>F/u period:</b> 1 yr, 2 yrs</p> <p><b>Funding source:</b> Ashthmatx Inc.</p> <p><b>Conflict of interest:</b> Study authors have received research funding from Ashthmatx Inc.</p>	<p><b>Inclusion criteria:</b> Age ≥18 yrs; had stable mild or moderate asthma</p> <p><b>Exclusion criteria:</b> RTI w/in 6 wks; hx of ≥2 RTIs per yr requiring antibiotic tx; and the use of more than 4 puffs in a 24-hr period of a short-acting β<sub>2</sub>-adrenergic agonist (e.g., albuterol 100 µg/puff or equivalent) except for exercise</p> <p><b>Setting:</b> Respiratory health clinic in Ontario (Site A) and general hospital in British Columbia (Site B)</p> <p><b>Concurrent tx:</b> Pts continued w/ their asthma management medications throughout the study.</p>	<p>Coughing up blood: 19%                      Nasal congestion: 13%                      Retained mucus: 13%                      Bronchitis: 13%                      Hypoxemia: 6%                      Hoarseness: 6%                      Lower back pain: 6%                      Localized heat: 6%                      # hospitalizations: 0</p> <p><b>Complications during 2-yr f/u:</b> 312 AEs were reported over the 2-yr f/u period; 155 were considered to be procedure related. All procedure-related AEs presented w/in 1 wk of BT, and 90 of 155 (58%) resolved spontaneously; 65 of 155 (42%) were managed w/ medication; 230 (74%) were mild, 79 (25%) were moderate, and 3 (1%) were severe. All 3 severe AEs (allergic reaction to peanuts, ovarian cyst and fibroid removal, and partial mastectomy) involved hospitalization and were considered not related to the procedure. No ED visits related to tx or asthma exacerbation occurred.</p> <p><b>Mortality:</b> None</p> <p><b>Change in medication (# pts) (% pts):</b>                      Added LABA: 3 (19%)                      Increased ICS: 1 (6%)                      Increased ICS and LABA: 2 (12.5%)                      Decreased ICS: 2 (12.5%)                      Decreased ICS and LABA: 2 (12.5%)                      No change: 6 (37.5%)</p> <p><b>Changes in CT scans from BL to 1-yr and 2-yr f/u:</b> No clinically significant findings were observed as a result of BT, including no evidence of bronchiectasis or bronchial wall thickening or parenchymal changes.</p>	
<p><b>Doeing et al. (2013)</b></p> <p><b>Study design:</b> Case series</p> <p><b>Control/comparator:</b> None</p>	<p>n=8 pts w/ severe asthma w/ FEV<sub>1</sub> &lt;50%</p> <p><b>Definition of severe asthma:</b> All pts met criteria for a dx of severe asthma as defined by the National Asthma Education and Prevention Program’s Expert Panel Report 3 guidelines</p>	<p><b>Device-related complications during tx period (tx through 6-wk f/u) (# pts):</b>                      # hospitalizations: 11                      # w/ hospitalizations: 5                      Cause of hospitalization: Increased BD use (5 hospitalizations); wheezing (2 hospitalizations); lower RTI (2 hospitalizations);</p>	<p>Very poor</p> <p>Small sample size. No control or comparator grp. Pts had low BL FEV<sub>1</sub> (results may not be generalizable). Efficacy</p>

Authors/ Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p><b>BT tx:</b> Pts underwent 3 sessions of thermoplasty tx under conscious sedation or general anesthesia and continued drug tx</p> <p><b>Outcome measures:</b> Complications; FEV<sub>1</sub></p> <p><b>Data analysis:</b> NR</p> <p><b>F/u period:</b> Up to 1 yr</p> <p><b>Funding source:</b> National Institutes of Health grant T32 HL07605</p> <p><b>Conflict of interest:</b> Study authors have received research funding from Ashthmatx Inc.</p>	<p><b>Pt hx/characteristics:</b>                      Mean (SEM) age (yrs): 47 (4.3)                      # women: 4                      # white: 5                      # black: 1                      # other: 2                      Mean (SEM) pre-BD FEV1 (% of predicted value): 52% (19%)                      Average night awakenings per wk: 4.5                      Mean ICS dose (µg/day): 1000                      # pts using LABA ≥1000 µg/day: 8                      # pts using oral corticosteroids: 4                      Mean (SEM) rescue BD use (puffs/day): 6 (0.8)                      # hospitalizations in prior yr: 23</p> <p><b>Inclusion criteria:</b> Poorly controlled severe asthma; requiring high-dose ICS (≥1000 µg/day fluticasone or equivalent) and LABA (≥100 µg salmeterol or equivalent)</p> <p><b>Exclusion criteria:</b> NR</p> <p><b>Setting:</b> University of Chicago, IL, U.S.</p> <p><b>Concurrent tx:</b> Pts continued w/ their asthma management medications.</p>	<p>atelectasis (1 hospitalization); hemoptysis (1 hospitalization)</p> <p><b>Outcomes during 1-yr f/u:</b> There was no change in percent predicted pre-BD FEV<sub>1</sub> noted &gt;15 wks after BT (pre-BT FEV<sub>1</sub> 51.8% vs post-BT tx FEV<sub>1</sub> 52.1% (P=0.40). Not pts had an increase in hospitalization rate following the tx period. Mean hospitalizations for asthma in the yr prior to BT was 2.88, compared to 0.50 hospitalizations during the median f/u of 31 wks following BT.</p> <p><b>Mortality:</b> None</p>	<p>outcomes other than FEV<sub>1</sub> not assessed.</p>
<p><b>Bicknell et al. (2015)</b></p> <p><b>Study design:</b> Retrospective cohort study</p> <p><b>Control/comparator:</b> RCT pts (derived from 15 pts recruited to clinical trials of BT)</p> <p><b>BT tx:</b> Pts underwent 3 sessions of thermoplasty tx under conscious sedation or general anesthesia and continued drug tx</p>	<p>n=10 pts w/ severe asthma</p> <p>RCT pt data were derived from 15 pts recruited to clinical trials of BT at the same center (5 pts from Cox et al. [2007], 3 pts from Pavord et al. [2007]; 7 pts from Castro et al. [2010]).</p> <p>Unlike clinical trials on BT, pts were not excluded if they used certain asthma medications (e.g., omalizumab and high-dose oral prednisolone) or had a high frequency of exacerbations.</p> <p><b>Definition of severe asthma:</b> On Step 4 or 5 of BTS guidelines (ICS ≥1000 µg beclomethasone equivalent</p>	<p>1 of the clinical pts had only 2 tx sessions, due to stenosis of the lower lobe bronchus. ACQ and AQLQ scores at 1 yr not available in 1 RCT pt.</p> <p><b>Complications:</b> AEs were similar to those in the historical clinical trials. Most pts reported mild worsening of asthma sx for a few days after each procedure. During the tx period, hospital admissions occurred in 3 pts (2 for asthma; 1 for a partial lung atelectasis that responded to routine medical tx).</p> <p><b>Outcomes during 1-yr f/u:</b>                      Mean (SD) FEV<sub>1</sub>:                      Clinical pts: 70% (16%); NS                      RCT pts: 80% (19%); NS</p>	<p>Very poor. Downgraded from poor due to small sample size, lack of details in how RCT pts were selected and data were collected.</p> <p>Small sample size. No true control or comparator grp. Methods for choosing RCT grp pts NR (i.e., the RCT patients may not have been representative of the clinical trial data population).</p>

Authors/ Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p><b>Outcome measures:</b> ACQ, ACLQ, FEV<sub>1</sub>; exacerbations; hospital admissions; medication changes</p> <p><b>Data analysis:</b> Clinical improvement was defined as achieving ≥1 of the following outcomes during the posttx period: (1) Reduction by ≥1 severe exacerbation (requirement for high-dose oral corticosteroids) or hospital admissions for asthma; (2) improvement in ACQ or AQLQ scores by the minimum clinical important difference MCID, w/o a worsening of the other (ACQ score decrease by ≥0.5, AQLQ score increase by ≥0.5); (3) stepdown in tx: half the maintenance oral prednisolone dose or stop omalizumab w/o loss of asthma control (no increase in hospitalization or asthma exacerbations by ≥1 or worsening of ACQ/AQLQ scores by the MCID). Comparison of demographic and outcome variables btwn and w/in clinical and research pts was by Student's <i>t</i>-test, Mann-Whitney U test, Wilcoxon's signed rank test or χ<sup>2</sup> test (depending on data distribution).</p> <p><b>F/u period:</b> 1 yr</p> <p><b>Funding source:</b> None</p> <p><b>Conflict of interest:</b> Study authors have received research funding from Boston Scientific Corp.</p>	<p>daily; plus additional preventer medications)</p> <p><b>Pt hx/characteristics (clinic pts; RCT pts):</b>                      Mean (SD) age (yrs): 48 (10), 43(12)                      % pts men: 70%, 67%                      Mean (SD) pre-BD FEV<sub>1</sub> (% of predicted value): 72% (16%), 74% (12%)                      Mean ICS dose (µg/day): 2580 (1425), 2980 (1000)                      % pts using BTS step 5: 60%, 13%                      % pts using BTS step 4: 40%, 67%                      Mean (SD) ACQ: 3.3 (1.0), 2.0 (0.9)                      Mean (SD) AQLQ: 3.9 (0.8), 4.8 (1.4)                      Mean (SD) # exacerbations in prior yr: 3 (3), 1 (1)                      Mean (SD) # hospitalizations in prior yr: 1 (2), 0 (0)</p> <p>Btwn-grp differences for ICS dose, # pts taking step 5 medication and ACQ score at BL significant.</p> <p><b>Inclusion criteria:</b> Severe asthma; requiring high-dose ICS (≥1000 µg/day beclomethasone equivalent daily) plus additional preventer medications</p> <p><b>Exclusion criteria:</b> Contraindications to BT</p> <p><b>Setting:</b> Difficult Asthma service, Glasgow, UK</p> <p><b>Concurrent tx:</b> Pts continued w/ their asthma management medications.</p>	<p>Difference btwn grps NS.</p> <p><b>Mean (SD) ACQ:</b>                      Clinical pts: 4.6 (1.5), 5 pts (50%) achieved MCID; NS                      RCT pts: 6.1 (1.1), 10 (79%) pts achieved MCID; <i>P</i>=0.035                      Difference btwn grps significant (<i>P</i>=0.003).</p> <p><b>Mean (SD) AQLQ:</b>                      Clinical pts: 2.9 (1.4), 4 (40%) pts achieved MCID; NS                      RCT pts: 1.2 (1.2), 10 (71%) pts achieved MCID; <i>P</i>=0.003                      Difference btwn grps NS.</p> <p><b>Mean (SD) # exacerbations in prior yr:</b>                      Clinical pts: 2(2), 3 (30%) pts achieved MCID; NS                      RCT pts: 0 (1), 11 (33%) pts achieved MCID; NS                      Difference btwn grps NS.</p> <p><b>Mean (SD) # hospitalizations in prior yr:</b>                      Clinical pts: 1 (1), 3 (30%) pts achieved MCID; NS                      RCT pts: 0 (0), 2 (13%) pts achieved MCID; NS                      Difference btwn grps NS.</p> <p>5 of the 10 clinic pts (50%) met the criteria for clinical improvement at 12 mos. Asthma medications were reduced in 3 pts (2 pts discontinued omalizumab and 1 pt discontinued prednisolone).</p> <p><b>Mortality:</b> None</p>	
<p><b>Chakir et al. (2015)</b></p> <p><b>Study design:</b> Case series</p> <p><b>Control/comparator:</b> None</p>	<p>n=17 pts w/ severe asthma w/ FEV<sub>1</sub> ≥50%</p> <p><b>Definition of severe asthma:</b> NR</p> <p><b>Pt hx/characteristics:</b></p>	<p>1 pt was lost to f/u.</p> <p><b>Device-related complications during tx period (tx through 6-wk f/u) (# pts):</b>                      Pts w/ hospitalizations: 2</p>	<p>Very poor</p> <p>Small sample size. No control or comparator grp. Study designed to assess effect of BT on airway</p>

Authors/ Study Design/ Protocol	Patient Characteristics	Main Findings	Quality/Comments
<p><b>BT tx:</b> Pts underwent 3 sessions at ≥3-wk intervals of BT under sedation</p> <p><b>Outcome measures:</b> Asthma Control Scoring System; medication dosage, FEV<sub>1</sub>; severe exacerbations (self-report; requiring tx w/ systemic corticosteroids for ≥3 days)</p> <p><b>Data analysis:</b> Repeated-measures factor w/ the use of an unstructured covariance matrix.</p> <p><b>F/u period:</b> 1 yr</p> <p><b>Funding source:</b> Québec Pulmonary research unit</p> <p><b>Conflict of interest:</b> Study authors have received research funding/lecture or consulting fees from pharmaceutical companies and Boston Scientific Corp.</p>	<p>Mean (SEM) age (yrs): 48 (12)                      # pts men: 9                      # pts white: 17                      Mean (SEM) pre-BD FEV<sub>1</sub> (% of predicted value): 64% (5%)                      Mean (SEM) Asthma Control Scoring System: 72 (4)                      Mean ICS dose (µg/day): 1281                      Mean LABA dose (µg/day): 123                      Mean prednisone dose (µg/day): 14.5                      # pts using oral corticosteroids: 5                      # pts using omalizumab: 5                      # pts using montelukast: 8                      Mean (range) severe exacerbations prior yr: 1.5 (0-1)</p> <p>Compared w/ pts in the Asthma Intervention Research 2 (AIR 2) study (Castro et al., 2010), these pts had a higher mean ICS dose and a lower pre-BD FEV<sub>1</sub> (77.8% vs 62%), and more pts taking oral prednisone (3.7% vs 23.5%) and omalizumab (1.1% vs. 28.7%).</p> <p><b>Inclusion criteria:</b> Pts w/ suboptimal asthma control despite a fluticasone dose ≥500 mg plus salmeterol 100 mg daily or their equivalents; optimal nonpharmacological tx; tx of asthma comorbidities; FEV<sub>1</sub> ≥50%; accepted previous smoking hx (&gt;10 pack-yrs) if lung volume and diffusing carbon monoxide capacity were w/in normal range, computed tomographic scans did not show signs of emphysema or other lung diseases, and had stopped smoking for &gt;2 yrs; consent to undergo bronchial biopsies during BT procedures</p> <p><b>Exclusion criteria:</b> NR</p> <p><b>Setting:</b> Institute of Cardiology and Pneumology, Quebec Asthma Clinic, Quebec, Canada</p> <p><b>Concurrent tx:</b> Pts continued w/ their asthma management medications.</p>	<p><b>Outcomes during 1-yr f/u:</b>                      Mean (SEM) pre-BD FEV<sub>1</sub>: 77% (15%); NS                      Mean (SEM) ICS dose (µg/day): 937.5 (609); P=0.002                      Mean prednisone dose (µg/day): 5.0 (significance NR)                      Mean (range) severe exacerbations prior yr: 0 (0-2); P=0.005                      Mean (SEM) Asthma Control Scoring System (higher score better): 84 (18); P=0.02</p> <p><b>Mortality:</b> None</p>	<p>smooth muscle.</p>

## APPENDIX V. Summary of Practice Guidelines

**Key:** AE(s), adverse event(s); ATS, American Thoracic Society; BT, bronchial thermoplasty; BTS, British Thoracic Society; ERS, European Respiratory Society; FEV<sub>1</sub>, forced expiratory volume in 1 second; f/u, follow-up; GINA, Global Initiative for Asthma; LABA, long-acting  $\beta_2$ -agonist; NICE, National Institute for Health and Clinical Excellence; pt(s), patient(s); RCT, randomized controlled trial; QOL, quality of life; tx, treatment (or therapy); tx'd, treated

Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
<p><b>British Thoracic Society (BTS)</b> (Du Rand et al., 2011)</p> <p><i>British Thoracic Society Guideline for Advanced Diagnostic and Therapeutic Flexible Bronchoscopy in Adults</i></p>	<p>Pt selection: Pts w/ severe persistent asthma receiving high-dose combination inhalers (&gt;1000 <math>\mu</math>g beclomethasone equivalent) plus long-acting bronchodilators or long-term oral corticosteroids. The FEV<sub>1</sub> should be &gt;50% predicted.</p> <p>Available Evidence: 3 RCTs have consistently demonstrated a transient increase in asthma-related AEs in the short term during BT, but are associated w/ a significant reduction in AEs, asthma-related symptoms, and hospitalizations in the longer term. However, the studies are selective and the outcomes are only positive in some aspects. (Evidence level 1).</p> <p>Recommendation: BT is a possible tx option in selected pts w/ severe persistent asthma already on maximal tx, although its place in the tx of asthma remains to be established (Grade A). Long-term safety and efficacy of BT remain unclear. Because of this, tx should be limited to a few specialist centers in carefully selected pts. Longer-term f/u of tx'd pts is recommended.</p>	<p>6 – Good (keywords and search strings not specified, funding source not stated, some members have potential conflicts of interest)</p>
<p><b>European Respiratory Society (ERS); American Thoracic Society (ATS)</b> (Chung et al., 2014)</p> <p><i>International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma.</i></p>	<p>Pt selection: Pts w/ severe asthma. Severe asthma is defined as asthma which requires tx w/ guidelines suggested medications for GINA steps 4-5 asthma (high-dose inhaled corticosteroid and LABA or leukotriene modifier/theophylline) for the previous yr or systemic corticosteroids for <math>\geq</math>50% of the previous yr to prevent it from becoming “uncontrolled” or which remains uncontrolled despite this tx.</p> <p>Available Evidence: The available evidence concerning this procedure is considered to be of very low quality. The ERS/ATS have very low confidence in the reported efficacy of BT. Both potential benefits and harms may be large and the long-term consequences of this new approach to asthma tx utilizing an invasive physical intervention is unknown. Additional studies are needed to assess its long-term benefits and safety, including asthma exacerbation rates and lung function, determining the phenotypes of pts who respond to BT, and evaluating its effects on pts who require systemic steroid tx or who have severe obstructive asthma.</p> <p>Recommendation: ERS and ATS strongly recommend that BT be performed only in adults w/ severe asthma and only in the context of a clinical trial or systematic registry (strong recommendation). Further research is likely to have an important impact on this recommendation.</p>	<p>5 – Fair (strengths and limitations of body of evidence not clearly described, whether guideline reviewed by external experts not stated, funding source not reported)</p>



Sponsor, Title	Relevant Recommendations	Quality*/Main Limitations
<p><b>Global Initiative for Asthma (GINA)</b> (GINA, 2015)</p> <p><i>Global Strategy for Asthma Management and Prevention</i></p>	<p>Pt selection: Caution should be used in selecting pts for this procedure, as the number of published clinical trials assessing this procedure is small, and excluded pts w/ chronic sinus disease, frequent chest infections, and FEV<sub>1</sub> &lt;60% predicted (Evidence D).</p> <p>Recommendation: BT is a potential option for highly selected adult pts who have uncontrolled asthma despite use of recommended therapeutic regimens and referral to an asthma specialty center (Evidence B). The long-term safety and efficacy of BT are unknown. Carefully controlled trials are important as a large placebo effect has been seen in studies to date.</p>	<p>4 – Fair (strengths and limitations of body of evidence not clearly described, guideline not reviewed by external experts, funding source and conflict of interest not stated)</p>
<p><b>National Institute for Health and Care Excellence (NICE)</b> (NICE, 2012)</p> <p><i>Bronchial thermoplasty for severe asthma</i></p>	<p>For pts w/ severe asthma, BT has been shown to provide some improvements in symptoms and QOL and reductions in exacerbations and hospitalizations. Although evidence of safety is adequate in the short and medium term, more evidence of long-term safety is needed; therefore, BT should only be used after establishment of special arrangements for clinical governance, including pt consent and research or audit. The NICE encourages additional research to evaluate the long-term safety and efficacy of BT.</p>	<p>4 –Fair (methods for formulating the recommendations not clearly described, guideline not reviewed by external experts, procedure for updating guideline not stated, funding source and conflict of interests not stated)</p>

\*According to the Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors. Guidelines were scored on scale of 1 to 7 and judged to be good (6-7), fair (4-5), or poor (1-3).

## APPENDIX VI. Quality of Life Measures

### Asthma Control Questionnaire (ACQ)

The ACQ score is a mean based on responses to the following 7 questions. This questionnaire is self-administered for adults and completed by an assistant for children (Juniper et al., 2000).

### Asthma Control Questionnaire (ACQ)

Questions	Responses
1) On average, during the past week, how often were you woken by your asthma during the night?	0: Never 1: Hardly ever 2: A few times 3: Several times 4: Many times 5: A great many times 6: Unable to sleep because of asthma
2) On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?	0: No symptoms 1: Very mild symptoms 2: Mild symptoms 3: Moderate symptoms 4: Quite severe symptoms 5: Severe symptoms 6: Very severe symptoms
3) In general, during the past week, how limited were you in your activities because of your asthma?	0: Not limited at all 1: Very slightly limited 2: Slightly limited 3: Moderately limited 4: Very limited 5: Extremely limited 6: Totally limited
4) In general, during the past week, how much shortness of breath did you experience because of your asthma?	0: None 1: A very little 2: A little 3: A moderate amount 4: Quite a lot 5: A great deal 6: A very great deal
5) In general, during the past week, how much of the time did you wheeze?	0: Not at all 1: Hardly any of the time 2: A little of the time 3: A moderate amount of the time

Questions	Responses
	4: A lot of the time 5: Most of the time 6: All the time
6) On average, during the past week, how many puffs of short-acting bronchodilator (e.g., Ventolin) have you used each day?	0: None 1: 1-2 puffs most days 2: 3-4 puffs most days 3: 5-8 puffs most days 4: 9-12 puffs most days 5: 13-16 puffs most days 6: More than 16 puffs most days
To be completed by a member of the clinic staff: 7) FEV <sub>1</sub> pre-bronchodilator: ..... FEV <sub>1</sub> % predicted: ..... FEV <sub>1</sub> % of predicted value: ..... (Record actual values on the dotted lines and score the FEV <sub>1</sub> % of predicted value in the next column.)	0: 95% of predicted value 1: 95%-90% of predicted value 2: 89%-80% of predicted value 3: 79%-70% of predicted value 4: 69%-60% of predicted value 5: 59%-50% of predicted value 6: 50% of predicted value

**Asthma Quality of Life Questionnaire (AQLQ)**

The AQLQ score is a mean based on responses to 32 questions in 4 domains and includes participation in 5 individualized activities selected by the patient. Each question is scored on a scale with 1 = maximal impairment and 7 = no impairment (Juniper et al., 1999).

Questions	
1)	Individualized activity 1
2)	Individualized activity 2
3)	Individualized activity 3
4)	Individualized activity 4
5)	Individualized activity 5
6)	Chest tightness
7)	Concerned regarding asthma
8)	Short of breath
9)	Exposure to cigarette smoke
10)	Wheeze
11)	Avoid cigarette smoke
12)	Cough
13)	Frustrated
14)	Chest heaviness
15)	Concerned regarding medications
16)	Clear throat
17)	Exposure to dust
18)	Difficulty breathing out
19)	Avoid dust
20)	Wake in a.m. with symptoms
21)	Afraid of not having medications
22)	Heavy breathing
23)	Exposure to weather/air pollution
24)	Woken at night by asthma
25)	Avoid weather/air pollution
26)	Exposure to strong smells
27)	Afraid of getting out of breath
28)	Avoid strong smells
29)	Lack of a good night's sleep
30)	Fighting for air
31)	Range of activities
32)	Activities in general