Comparative Effectiveness Review Disposition of Comments Report

Research Review Title:
Effectiveness and Safety of Bronchial Thermoplasty in the Management of Asthma

Draft review available for public comment from April 26, 2017 to May 25, 2017.

Research Review citation: D'Anci KE, Lynch MP, Leas BF, Apter AJ, Bryant-Stephens T, Kaczmarek JL, Umscheid CA, Schoelles K. Effectiveness and Safety of Bronchial Thermoplasty in Management of Asthma. Comparative Effectiveness Review No. 202. (Prepared by the ECRI Institute–Penn Medicine Evidence-based Practice Center under Contract No. 290-2015-00005-I.) AHRQ Publication No. 18-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm. DOI: https://doi.org/10.23970/AHRQEPCCER202.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	General Comments	The section on bronchial thermoplasty is less problematic due to the studies being of better design, and it is clear from this section that the authors acknowledge the general lack of appropriate mock controls in the studies that have been published. Although, this reviewer again believes that the key message from this section should contain something with respect to the lack of these appropriately controlled studies in the literature.	Thank you for your comments. We have revised the evidence gaps section and key messages to reflect the need for more sham-controlled studies to guide appropriate use of bronchial thermoplasty (BT).
Peer Reviewer 1	General Comments	To my read, the major take home message is that the studies in these areas are in desperate need of new research studies that are appropriate designed and implemented (allergen reduction being the worst of the two). This seems to be the important take home message for NHLBI, but it is garbled and lost throughout the text, and appears to just suggest that individuals with asthma should undergo bronchial thermoplasty before considering allergen reduction. This is an unfortunate outcome of the writing bias (as mentioned above) and the juxtaposition of the two disparate issues together in the same report.	Thank you for your review and feedback. We have separated the document into two distinct reports for clarity and ease of use. We agree that new studies are needed that address these interventions, and we emphasize that need in both reports.
Peer Reviewer 4	General Comments	Thank you for the opportunity to review the draft of "The Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma." The manuscript is very well written and the methods used including the study inclusion and exclusion criteria and the judgment of the significance of evidence were very rigorous. The goals of the review are well stated. However, the form is very dry and quite difficult to follow. The frequent use of acronyms requires constant referral to the glossary.	Thank you for your review and feedback. We have separated the document into two distinct reports, and reduced the use of acronyms, for clarity and ease of use explained each acronym in each chapter of the report.
Peer Reviewer 4	General Comments	I did notice that you did not include a calculation of a number needed to treat value for the BT studies. This would be helpful.	We decided against conducting meta-analysis because the evidence base is small and heterogeneous in terms of study design, comparators, and included patient populations.
TEP Reviewer 1	General Comments	This is a well-written systematic review of two key question areas, the effects of allergen remediation in the home to improve asthma and the effects of bronchial Thermoplasty, BT, to improve asthma. There are a few points and clarifications that would be useful for the clinician in understanding the results of these analyses. Those are listed below.	Thank you for your review and feedback.
TEP Reviewer 2	General Comments	Overall, the manuscript is written well and is the product of a substantial amount of work and is timely.	Thank you for your review and feedback.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 3	General Comments	Combining allergen reduction and BT in a single report is not intuitive. Would suggest a statement in the report (likely in Intro) as to why these 2 unrelated therapies are being presented together.	Thank you for your review and feedback. We have separated the document into two distinct reports for clarity and ease of use.
TEP Reviewer 5	General Comments	It was unclear to me why these 2 very different questions were lumped together.	Thank you for your review and feedback. We have separated the document into two distinct reports for clarity and ease of use.
TEP Reviewer 5	General Comments	Report is clinically meaningful with regard to key question 1 and accurate. However key question 2 regarding bronchial thermoplasty seems biased and the benefits with regard to exacerbations, both at 1 year and 5 year , are underestimated. The lung function benefits are overstated.	We have noted that the AIR trial found a significant reduction in mild exacerbations, but also noted our concern that measuring exacerbations rates only during the 2 weeks when patients were instructed to stop taking maintenance medications was an indirect outcome, since we were interested in the number of exacerbations over the entire time period and while patients were taking their usual medications (LABA). We noted that the AIR 2 trial found a reduction in severe exacerbations (Low SOE) and emergency room visits (Moderate SOE) after the 12-week treatment period. The RISA study did find a statistically significant improvement in FEV1% predicted (prebronchodilator) in the BT and standard care group compared to the standard care only group at 22 weeks. However, we have clarified that the post-bronchodilator result at 22 and 52 weeks was not significant. Further, we noted that the AIR study and AIR 2 study did not find improvements in prebronchodilator FEV1% predicted.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 5	General Comments	Target populations are well defined for KQ1, but again for KQ2, there seems to be a bias against it- why the critique regarding not having subjects with more than 3 exacerbations? Key questions are appropriate and explicitly stated.	We have expanded the discussion of the patient inclusion criteria to illustrate the spectrum of asthma severity in the populations. We noted that patients in the Bicknell study who were not enrolled in RCTs were on higher doses of steroids, and were not excluded based on frequency of exacerbations at baseline than patients at that site who were enrolled in the RCTs. This small retrospective comparison suggested that these sicker patients experienced less benefit from BT, but this is only one small study. It would be helpful to have more studies exploring the patient characteristics predictive of benefit.
Public Reviewer 3 Rubin Cohen on behalf of AACP-CHEST	General Comments	The report is well done. I would suggest separating the 2 topics under 2 subheadings in the abstract and in conclusions	Thank you for your comments. We have separated the document into two distinct reports for clarity and ease of use.
Public Reviewer 4 Joe Zein	General Comments	After I thoroughly reviewed this reports, I have concerns with its accuracy. I hope AHRQ ask external reviewers to repeat the grading of the evidence. Data from Air 2 was erroneously graded as weak. Additionally, BT is also found to be cost effective as well.	Thank you for your comments. The EPC Program Methods guidance (available on the AHRQ EPC program Web site) generally discourages strong conclusions based on a single trial for a given outcome. We graded the evidence for individual outcomes based on study limitations, directness, consistency and precision. We assessed each of the outcomes of interest reported in AIR 2 separately. Additional sham-controlled studies measuring these same outcomes in similar patients would strengthen the evidence if their results are consistent with those in AIR 2.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 5 Douglas Kyle Hogarth	General Comments	Publications not included in AHRQ review: Pretolani M et al Aubier M. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: Clinical and histopathologic correlations. J Allergy Clin Immunol. 2017 Apr;139(4):1176-1185. Denner DR, Doeing DC, Hogarth, D.K., Dugan K, Naureckas ET, White SR. Airway Inflammation after Bronchial Thermoplasty for Severe Asthma. Ann Am Thorac Soc. 2015 Sep;12(9):1302-9	Thank you for your comments. We reviewed and excluded these studies because they did not fit our pre-specified criteria for inclusion, which are described in the report Methods section and in the published protocol. We excluded the Pretolani et al. and Denner et al. studies because they were uncontrolled and did not report adverse events
Public Reviewer 5 Douglas Kyle Hogarth	General Comments	Effect of BT on Healthcare utilization: -The report cites insufficient evidence in the area of Healthcare Utilization, despite multiple publications describing statistically significant reductions in such utilization measures as ED visits, hospitalizations, and days missed from work and school. This is not incorrect and your review should reflect the large amount of robust data published.	Studies were included or excluded based on criteria specified in the protocol, which was developed with input from experts in asthma management. We chose the health care utilization outcomes for our review based on recommendations for prospective clinical trials of asthma from an NHLBI-AHRQ sponsored workshop, published in J Allergy Clin Immunol. 2012 March ; 129(3 Supplement): S1–S8. We extracted data on these outcomes whenever they were reported in the included studies. We described the reduction in ED visits found in the AIR 2 trial, and judged the strength of evidence for this outcome for this comparison as moderate (due to unknown consistency).

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 5 Douglas Kyle Hogarth	General Comments	Effect of BT on Quality of life: The report cites low strength of the evidence in the area of Quality of Life improvement, despite consistent, clinically meaningful improvements to QOL being demonstrated compared to sham and statistically significant improvements to QOL compared to medical management. This has been demonstrated across AIR1 and AIR 2.	We judged the strength of evidence for each of the comparisons for this outcome separately. The RCT that compared BT and medical management to sham and medical management found improved quality of life when analyzed on a per-protocol basis, but the results were not significant when assessed in the intention-to-treat analysis. The degree of improvement did not achieve the MID for this outcome. We were asked to also consider the responder analysis, which favored the BT and standard care group, but this analysis was not prespecified. We ultimately assessed these findings as inconclusive and graded this evidence as insufficient given only a single trial of this comparison, the limitations of relying on a per-protocol analysis and analysis that was not prespecified, and the imprecision of the results. The two studies comparing BT with medical management to medical management alone did find significant improvement in quality of life, but the clinical importance was unclear, as the lower bounds of the confidence interval was less than the minimum important difference. The strength of evidence for this comparison was low because the study limitations of the two trials were medium (lack of blinding) and the results were not precise.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 5 Douglas Kyle Hogarth	General Comments	BT efficacy construed as a placebo effect is just simply wrong and the clinical and pathologic data presented in Pretolani M et al Aubier M. Efectiveness of bronchial thermoplasty in patients with severe refractory asthma: Clinical and histopathologic correlations. J Allergy Clin Immunol. 2017 Apr;139(4):1176-1185. as well as Mahajan, A.K., Hogarth, D.K. Bronchial Thermoplasty: Therapeutic Success in Severe Asthma Associated with Persistent Airflow Obstruction. Journal of Asthma 2012; Early online e-pub. 1-3. Our center treats roughly 4 BT patients per month. We have been performing BT clinically since 2010 and had been part of the AIR2 trial, the PAS-2 trial, and the AIR2 10 year follow-up trial. Our center, through careful patient selection, has noted significant improvement in quality of life, exacerbations, OCS usage (total dose, and number of Pulses), and lung function. We have had no significant complications from this procedure: and it should be noted that we have utilized this safely and effectively on patients "sicker" than described in AIR2. Of note, our first patient done in 2010 used to be on prednisone 4 to 6 times a year. 2010 was her last dose of oral steroid. She is now controlled simply by ICS. Doeing DC, Mahajan AK, White SR, Naureckas ET, Krishnan JA, Hogarth DK. Safety and feasibility of bronchial thermoplasty in asthma patients with very severe fixed airflow obstruction: a case series. Journal of Asthma. 2013. 50(2):215-8.	Studies were included or excluded based on criteria specified in the protocol, which was developed with input from experts in asthma management. We excluded the Pretolani study because it did not have a control group and did not report adverse events. The other two studies were included in our assessment of adverse effects, but did not meet the inclusion criteria for evidence of benefit. We required controlled studies for evidence of benefit.
Public Reviewer 6 Tonya Winders on behalf of the Allergy and Asthma Network	General Comments	We applaud the AHRQ on this systematic review and believe both of these issues are important updates advance asthma care.	Thank you for your comments.
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	General Comments	The American Lung Association appreciates the opportunity to submit comments with regard to the Agency for Healthcare Research and Quality (AHRQ) draft report for Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma, conducted by AHRQ's Evidence-Based Practice Center Program. The American Lung Association is the leading organization working to save lives by improving lung health and preventing lung disease through education, advocacy and research. The organization represents lung disease patients, their families, loved ones and caregivers. The Lung Association appreciates the analysis conducted with this report and provides the following comments.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	General Comments	It might be more effective to separate these two analyses on allergens and BT within the document itself, or consider making two separate documents.	We have separated the document into two distinct reports for clarity and ease of use.
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	General Comments	The Lung Association respectfully thanks the AHRQ for conducting this report. We thank you for the opportunity to submit our comments and for your consideration.	Thank you.
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	General Comments	Boston Scientific Corporation appreciates the opportunity to provide comments in response to the Agency for Healthcare Research and Quality's (AHRQ's) draft comparative effectiveness review "The Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma." Boston Scientific is one of the world's largest companies dedicated to developing, manufacturing, and marketing of less-invasive therapies. Boston Scientific manufactures the Alair™ Bronchial Thermoplasty (BT) System, the only device currently marketed for use in the bronchial thermoplasty procedure. Alair is indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting beta-agonists. Boston Scientific supports the important role that AHRQ plays in the assessment of novel therapies based on rigorous evidence requirements to provide safer, higher quality and more accessible health care. We are pleased to see that AHRQ is considering the vast body of evidence available for BT, and we applaud the generally thorough nature of the report. That said, there are several areas where we would like to offer more substantive and specific comments or suggestions, as outlined below.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 David Peden on behalf of the American Academy of Allergy, Asthma and Immunology (AAAAI)	General Comments	Established in 1943, the American Academy of Allergy, Asthma & Immunology (AAAAI) is a professional organization with more than 7,000 members in the United States, Canada and 72 other countries. This membership includes allergist/immunologists (A/I), other medical specialists, allied health and related healthcare professionals—all with a special interest in the research and treatment of patients with allergic and immunologic diseases. On behalf of this membership, please accept the following comments regarding the Draft Report, "The Effectiveness of Indoor Air Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma". Academy leadership notes that the manuscript is well written, the product of a substantial amount of work and time. Academy leadership further notes that the group explained the various choices made by analysis very effectively. Academy leadership commends the research group for a careful and organized approach in addressing these two questions, and offers these further comments for their consideration.	Thank you for your comments.
Peer Reviewer 2	Introduction	No concerns.	Thank you.
Peer Reviewer 3	Introduction	The material as it stands is appropriately introduced.	Thank you for your review and feedback.
Peer Reviewer 4	Introduction	This is very short. A little history and creative writing here would reimburse the reader to a small extent for the dry, grinding work to come.	We hope that dividing the review into two separate reports improves its readability and usefulness. We attempted to write succinct, focused introductory sections.
TEP Reviewer 3	Introduction	Succinct. As noted in General Comments: Combining allergen reduction and BT in a single report is not intuitive. Would suggest a statement in the report as to why these 2 unrelated therapies are being presented together.	We have separated the document into two distinct reports for clarity and ease of use.
TEP Reviewer 5	Introduction	Appropriate	Thank you.
TEP Reviewer 6	Introduction	Very well written and clear. The report clearly states the two key questions and the analytical framework applied. Figure 1 is quite helpful	Thank you.
Public Reviewer 2 William Busse	Introduction	Both reviews were extensive and conclusions supported by available evidence. BT inconclusive with SOE-low in most outcomes.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 4 Joe Zein	Introduction	The authors performed an extensive review of the literature of Bronchial thermoplasty, and considered published literature. Unfortunately, looking at this analysis from an expert perspective, I would like to raise few concerns.	Thank you for your comments.
Peer Reviewer 2	Methods	Study selection and inclusion/ exclusion criteria seemed appropriate.	Thank you
Peer Reviewer 2	Methods	This is a fast-moving field, and ongoing studies on both allergen reduction and BT are underway and should be published in next few years. At this point I could not find applicable studies that were missed.	Thank you.
Peer Reviewer 2	Methods	Please explicitly define the GRADE criteria approach.	We have expanded our discussion of the methods for grading the strength of evidence in the methods section.
TEP Reviewer 3	Methods	I/E criteria are appropriate and justifiable. Methodologies explained well.	Thank you.
TEP Reviewer 4	Methods	Under data synthesis (18 of 173): How was an absolute 10% difference (between groups etc) chosen for the SOE tables?	In revising the report, we were able to determine minimum important differences for outcomes from the literature. We did not use this criterion (10% absolute difference between groups) in the BT report.
TEP Reviewer 4	Methods	In the Strength of the Body of Evidence (18 of 173). I had to keep reminding myself what high strength of a negative result meant. It would have been helpful to me in this section to explain the two most common SOE assessments (high SOE, neg result, low SOE positive result).	There were no instances of high strength of evidence in the BT report. The strength of evidence assessment is intended to convey our confidence in the findings. When the strength of evidence is low for a positive finding, we believe that future research may not be able to replicate the finding, and encourage the user of the information to monitor the literature for future developments. Guideline developers are less likely to make strong recommendations based on evidence of low strength, although sometimes other considerations override the assessment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 5	Methods	For outcomes, the order seems inappropriate. Most generally consider exacerbations as a key outcome. It is reported second to asthma control and there should not be prioritization based on alphabet.	We do not disagree that exacerbations are very important. We developed the list of outcomes relevant to bronchial thermoplasty from the outcomes recommended for prospective clinical trials of asthma from an NHLBI-AHRQ sponsored workshop, published in J Allergy Clin Immunol. 2012 March ; 129(3 Supplement): S1–S8.
TEP Reviewer 5		Also, the assessment of evidence when there are few studies, even if well done, reflexes to LOW. This should not be the case.	We do maintain that more studies confirming the findings are needed to increase our confidence in the evidence base. However, the assessment of the strength of evidence involves additional factors: study limitations (considering the risk of bias of the individual studies contributing evidence to a specific outcome), directness of the population, intervention and outcome measurement to our questions, and precision of the results (reflecting the sample size and variance). The approach is described more fully in the EPC Methods Guidance, available at https://effectivehealthcare.ahrq.gov/search/?type=Methods%20Guide%20%C2%96%20Chapter|Methods%20Guide%20%E2%80%93%20Chapter&page=1&q=&audience=Professionals.
TEP Reviewer 5	Methods	Otherwise, incl/excl are appropriate and justifiable. Statistical methods are genrally appropriate but again, for KQ 2, there maybe subordination of the sham control trial to comparison with standard medical management.	Due to the differences in the control arms (sham and medical management control in one study; medical management alone in two other studies), as well as differences in populations, we thought the studies were too heterogeneous to combine statistically. The sham-controlled study is the superior design for determining differences in subjective outcomes, and is at lower risk of bias. Strength of evidence ratings were higher for some outcomes from this study..

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 6	Methods	Clear and well written. Attempts were made to include gray literature. Studies were selected according to a pre-specified framework, and this is a major strength.	Thank you.
Public Reviewer 3 Rubin Cohen on behalf of AACP-CHEST	Methods	No issues	Thank you.
Public Reviewer 4 Joe Zein	Methods	Although the authors followed standard methodology, in my opinion, they failed to accurately score the literature, and understand its historical perspective. BT studies evolved and their quality improved over time. Their analysis seems to be biased. For example, they quote Air study as a negative study, without taking into account that Air was not powered and included ~110 patients. The authors frequently mistakenly compared Air and Air 2 as if they were equivalent without taking into consideration the methodological differences between the 2 trials and that Air 2 was conducted specifically to address the weaknesses of Air study.	Thank you for your comments. We did not assess studies as "negative" or "positive" overall, but rather assessed individuals outcomes in the studies based on available data. In some instances in the AIR trial, findings favored BT; likewise, there were findings favoring BT in the AIR 2 trial. We described the study limitations of the AIR trial as medium because it was not blinded, but assessed the AIR 2 trial as having lower risk of bias because of the sham control.
Public Reviewer 11 David Peden on behalf of AAAAI	Methods	Further, Academy leadership would question at least one of the pre-specified outcomes described under, "Studies had to report on the outcomes pre-specified in our PICOTS." Academy leadership would comment regarding the statement, "Duplicate abstraction on a 10-percent random sample was used to ensure accuracy," under Data Extraction. What was the inter-rater reliability? Further, why not duplicate for all data abstraction?	It is standard practice for systematic reviews to follow a protocol specifying methods and outcomes. If a study did not report on any of the outcomes prespecified in our protocol, it would not be included. A second investigator was able to recheck the all of the extracted data for the BT report during the revision process.
Public Reviewer 11 David Peden on behalf of AAAAI	Methods	Academy leadership would also comment upon "Data Synthesis" and the statement, "In the Strength of Evidence tables, we noted any cases where a statistically significant result was not associated with an absolute difference of at least ten percent (between groups or above baseline, depending on the comparison), for the critical outcomes." How was ten percent selected for the clinically important difference? Academy leadership would suggest that this should be specific to the outcome (e.g. MID for ACQ=0.5)?	During the revision of the draft report, we obtained information on minimum important differences (MIDs) for many of the outcomes in the report. We have added a new table of MIDs to the Appendix and have referenced it in the results for each outcome, including the ACQ.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 David Peden on behalf of AAAAI	Methods	Further, related to the KQ2 Description of Included Studies, Academy leadership would comment, how did five-year single arm extensions provide efficacy outcomes without a control group?	We have added the following statement to the Methods section: "Single-arm extensions of RCTs were included to describe long-term changes in efficacy or safety in patients treated with BT." We noted whether findings in the BT groups were stable over time, but based our conclusions for effectiveness outcomes on the 12-months during which studies were controlled. We reported information on safety extracted from uncontrolled studies, including the extension studies.
Peer Reviewer 2	Results	Amount of detail and study characteristics are clearly articulated and summarized in multiple logically organized tables. Inclusion / Exclusion strategies were clear.	Thank you.
Peer Reviewer 3	Results	The key messages are clear but I have problems with some of them.	Thank you.
TEP Reviewer 3	Results	Figure 2 - would provide 2 figures here - 1 for each of the KQs. Combining these does not provide enough detail for the respective KQs.	We have separated the document into two distinct reports, one for each KQ, for clarity and ease of use.
TEP Reviewer 3	Results	For KQ2, is it worth including a comment in the 1st paragraph summarizing the total # of patients who have undergone BT in the included trials. This is likely a major source of the multitude of inconclusive findings - inadequate sample sizes	We added the total (n=432) for the three clinical trials from which the conclusions were made under the heading "Description of included studies."
TEP Reviewer 5	Results	Amount of detail is appropriate. Study characteristics are well described.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 5	Results	For BT question, Healthcare utilization in terms of ER visits and unscheduled office visits and days missed from school and work is not reported but is reported in the 1 year and 5 year data. AQLQ from AIR2 was significant but reported as no difference. The benefits of BT on lung function appear to be overstated.	The reduction in ER visits in the AIR 2 trial is reported under the heading "Exacerbations" rather than under "Health Care Utilization." The AIR 2 trial statistical plan described the Bayesian analysis planned for the trial, and the criteria for defining "success" for each outcome. The primary outcome, difference between groups in the AQLQ score change from baseline to the average of the 6-, 9-, and 12-month scores ("integrated" AQLQ), required adjustment of the definition of success due to two interim looks at the data. The posterior probability of superiority for BT in the intention-to-treat analysis was 96.0%, less than the 96.4% pre-specified success rule for this outcome; therefore, it was not statistically significant. We also report the significant results on this outcome for the per-protocol population, which was statistically significant but did not meet the minimum important difference. We were asked to also consider the responder analysis, which favored the BT and standard care group, but this analysis was not prespecified. We ultimately assessed these findings as inconclusive and graded this evidence as insufficient given only a single trial of this comparison, the limitations of relying on a per-protocol analysis and an analysis that was not prespecified, and the imprecision of the results. We have expanded our discussion of the pulmonary function measures in the studies, and clarified that the only improvement reported for FEV1 was the prebronchodilator measurement in the RISA trial at 22 weeks of followup, not at 12 months. We note that it did not improve in either AIR or AIR 2.

Public Reviewer 4 Joe Zein	Results	The authors repeatedly scored the result from Air 2 as weak using standard grading criteria. However, Air 2 is a RCT blinded study. Classically, RCTs are usually reported as "the highest grade of evidence". furthermore, Air 2 used a sham procedure to avoid bias from placebo effect. This support my suspicion that the grading of the literature may be biased. To support my concerns regarding this grading bias, I quote the FDA BT approval in 2010. The FDA approved BT because they considered the data from Air 2 is strong and unequivocal. Otherwise, the FDA would have asked for more studies. The contradiction between the FDA scientists and the authors listed in this review, raises concerns with this review including the scoring of the evidence. Finally, the authors did not accurately differentiate severe from non-severe asthma. Understanding such differences significantly impact the conclusion they made	We do not consider the AIR 2 trial to be weak, and agree that a blinded and randomized trial was appropriate for assessing impact on subjective outcome measures such as quality of life. We assessed the strength of evidence for each outcome using the methods guidance for the AHRQ EPC Program. In doing so, we noted the low risk of bias in the AIR 2 trial. The evidence supporting the findings in the study was graded based on additional factors, including directness, consistency, and precision. The FDA presentation to the Anesthesiology provided and Respiratory Therapy Devices Panel on October 28, 2009 provided additional data related to precision and clinical importance of findings. The strength of evidence for several of the outcomes reported in AIR 2 was low because consistency is unknown when there is only a single trial with a sham control, and because the results were not precise, even though the risk of bias in this study was low. The findings on reduction of ED visits in the post-treatment period did warrant an assessment of moderate strength of evidence and the assessment has been revised. The FDA has different goals (reasonable assurance that the device is safe and effective for its intended use) and therefore different methods for assessing studies. The purpose of our review is to inform developers of a clinical practice guideline. We have provided much more detail about the patient inclusion criteria for the 3 trials in an effort to clarify that although the labelled indication for the device is for adults with severe persistent asthma, the studies included a broader spectrum of patients.

Public Reviewer 6 Tonya Winders on behalf of the Allergy and Asthma Network	Results	In regard to the effect of bronchial thermoplasty: The report cites insufficient evidence in the area of Healthcare Utilization, despite multiple publications describing statistically significant reductions in such utilization measures as ED visits, hospitalizations, and days missed from work and school. The report also cites low strength of the evidence in the area of Quality of Life improvement, despite consistent, clinically meaningful improvements to QOL being demonstrated compared to sham and statistically significant improvements to QOL compared to medical management. We are concerned that the following 2017 study strengthening the evidence was not included in the review. Pretolani M et al Aubier M. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: Clinical and histopathologic correlations. J Allergy Clin Immunol. 2017 Apr;139(4):1176-1185.	Studies were included or excluded based on criteria specified in the protocol, which was developed with input from experts in asthma management. We chose the health care utilization outcomes for our review based on recommendations for prospective clinical trials of asthma from an NHLBI-AHRQ sponsored workshop, published in J Allergy Clin Immunol. 2012 March ; 129(3 Supplement): S1–S8. We extracted data on these outcomes whenever they were reported in the included studies. We described the reduction in ED visits found in the AIR 2 trial, and judged the strength of evidence for this outcome for this comparison as moderate (due to unknown consistency). We note the improved quality of life (AQLQ) with BT and standard care compared to standard care alone (the AIR and RISA studies). The results from the AIR trial did not achieve the minimum important difference for the AQLQ scale. The strength of this evidence is low because these 2 studies had a medium level of study limitations and the results were imprecise. We thought carefully about our assessment of the AQLQ outcomes in the AIR 2 study in the patients receiving BT and standard care compared to those receiving standard care and bronchoscopy without thermoplasty (sham). The result in the ITT analysis was not statistically significant, and while the per-protocol analysis found a statistically significant result, it did not meet the minimum important difference for the AQLQ scale. We further considered the responder analysis, which favored BT, but note that this analysis was not prespecified. We ultimately assessed the findings as inconclusive and graded this evidence as insufficient given only a single trial of this

Commentator & Affiliation	Section	Comment	Response

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	Results	Our first comment concerns the analysis of bronchial thermoplasty (BT). The conclusion that bronchial thermoplasty improves lung function is not supported by the evidence. In fact, the author's state, "mean FEV1 values remained unchanged in BT-treated patients through the five-year follow-up." The comment concerning "….the effect of BT on health care utilization or costs when compared with medical management without a sham control was inconclusive in two RCTs (SOE: Insufficient)" is also not accurate. AIR2 demonstrated an 84% reduction in ED visits. Additionally, hospitalizations were reduced by 74% in the post-procedure period. The increase in hospitalizations related to the procedure is offset by this reduction at one year. Subsequently, the five-year studies demonstrated a sustained reduction in hospitalizations and ED visits. To state this effect on health care utilization (HCU) was inconclusive is incorrect.	We have clarified the findings regarding pulmonary function in the final report. The only improvements at 12 months were for the peak expiratory flow in the BT and standard care group in the AIR trial. Otherwise, pulmonary functions remained stable in the extension studies. We have expanded the discussion of findings for hospitalizations, both during the treatment period and post-treatment periods. We reported the finding of no difference in post-treatment hospitalizations in the RISA trial and the AIR 2 trial. We report the reduction in ED visits found in the AIR 2 trial, and graded the strength of evidence as moderate because there is only one trial with a sham control, so the consistency is unknown. Because these outcomes were reported under the heading "Exacerbations," the only other health care utilization outcomes remaining were related to use of rescue medications. Evidence for change in rescue medication usage favored the BT and standard care over standard care alone (RISA and AIR), but the difference did not exceed the MID. The SOE was Low due to medium study limitations, inconsistency, and imprecision. The strength of evidence for the BT and standard care vs. sham and standard care comparison was low for the finding of no difference between groups in use of rescue medication (only a single trial, imprecise results).

Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	Results	Our second comment concerns the conclusion that "quality of life scores did not differ for patients assigned to BT compared to those assigned to sham treatment in one RCT (SOE: Low)" – which is not accurate as AIR2 did demonstrate a significant improvement in AQLQ (albeit small). Although the report states that "the available body of literature on BT is small, however, and the generalizability of the findings to patients with severe asthma and multiple comorbidities is limited," this is contradicted by the prior statement that 15 studies were reviewed, including a five-year follow-up. Furthermore, severe asthma patients were included in RISA (taking steroids up to 30 mg/d) and AIR2 (taking steroids up to 10 mg/d), which was even broader than most of the biologic studies performed to date (except for those specifically studying steroid dependent asthma with mepolizumab). On page 37 regarding reference 90, the five-year follow up was done only in the BT group and not the sham group and that should be clarified.	The AIR 2 trial used Bayesian statistics to assess results. The primary outcome for the trial was the quality of life scale, AQLQ. Prior to conducting the trial, the investigators chose a level of statistical significance for stating a benefit from BT compared to sham. The term for their test of significance is the "posterior probability of superiority" (PPS). They chose a level of 96.4% for this outcome instead of the usual 95%, because they were looking at the data twice before the trial was completed. When they assessed the results for all the patients in the study according to the treatment they were randomized to, the result did not meet this level of significance. This type of comparison, called intention-to-treat, is considered preferable. The investigators also analyzed the results just for those patients who actually got the treatments they were randomized to, (the per protocol analysis) and found a statistically significant effect. However, the difference did not achieve the MID for this outcome. Doing this type of analysis detracts from some of the benefit of randomizing patients in the first place, and is therefore less rigorous. We were asked to also consider the responder analysis, which favored the BT and standard care group, but this analysis was not prespecified. We ultimately assessed these findings as inconclusive and graded this evidence as insufficient given only a single trial of this comparison, the limitations of relying on a per-protocol analysis and an analysis that was not prespecified, and the imprecision of the results. We have expanded our discussion of the characteristics of the patients included in the RCTs. It would be helpful to have more information on patients' comorbid conditions. In the Applicability section of

Commentator & Affiliation	Section	Comment	Response
			the Discussion chapter, we discuss the spectrum of included patients in the RCTs and in the retrospective comparison (Bicknell et al), which described patients undergoing BT at their institution, some of whom enrolled in RCTs and some who did not. We clarified that 5-year followup was done only in the BT group in the AIR 2 trial.
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	Results	Additionally, to state that the generalizability of BT to patients with severe asthma is limited effectively provides payors with support to reject payment for this valuable treatment. BT is the only disease-modifying agent we have for smooth muscle in these patients and this document will only further limit its availability. More recent publications regarding the effect on smooth muscle reduction were not included, most notably, Pretolani M et al … Aubier M. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: Clinical and histopathologic correlations. J Allergy Clin Immunol. 2017 Apr;139(4):1176-1185).	The Pretolani et al. study was reviewed and excluded because it did not include a control group or report adverse events.
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	Results	Second, on the top of page 38 under healthcare utilization section, the authors of the document cast doubt on patients self-report of rescue medication use in general and report that consideration should be given to the known limitation that patients do not consistently use rescue medications appropriately. This editorializing does not belong in this document.	This section has been revised and the referenced statement has been removed.

Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Description of Included Studies In the draft comparative effectiveness review, AHRQ included fifteen studies to evaluate the benefits and risks of BT, including three RCTs and several case studies. Boston Scientific requests that the AHRQ report also consider the following single arm studies, recently published in peer-reviewed journals, that examine the physiological effects post-BT: *Pretolani M et al … Aubier M. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: Clinical and histopathologic correlations. J Allergy Clin Immunol. 2017 Apr;139(4):1176-1185.* *Chakir J et al. Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Collagen Deposition in Asthma. Ann Am Thorac Soc 2015 Nov. Vol12(11)1612-1618.* The results of these studies demonstrate the histopathologic effect of BT[1] on airway physiology and correlated improvements in asthma control. Moreover and pertinent to the draft comparative effectiveness review comment indicating the need for studies demonstrating evidence in more severe populations, the population evaluated in the Pretolani study is more severe than those studied within RISA, AIR, or AIR2. For example, patients in the study had a mean rate of exacerbations during the year before entry of 9.7 instead of less than 1 exacerbation per year in AIR2, a mean AQLQ score of 2.6 instead of 4.7 in AIR2, and a greater prevalence of maintenance use of OCS (67% instead of 41%). In addition, results support earlier observations found in prior studies of BT. [1]This manuscript demonstrates the correlation between severe, persistent asthma and airway smooth muscle (ASM) hypertrophy and that the reduction of this ASM helps to mitigate ASM-mediated asthma exacerbations, leading to reduced healthcare utilization. Results from this study demonstrate BT marginally but significantly decreased sub-basement membrane (SBM) thickening, without significantly modifying the density of blood and lymphatic vessels. Submucosal and ASM-associated nerve fibers were significantly reduced 3 months after BT compared with values measured before BT; submucosal	Thank you for these references. We agree that Pretolani and Chakir studies are important studies that elucidate BT's mechanism of action. We excluded these studies because they did not have control groups and did not report adverse events, and thus did not fit the pre-specified criteria for inclusion outlined in the protocol.

Commentator & Affiliation	Section	Comment	Response
		nerves amounted to 1.0% immunoreactivity and 0.3% immunoreactivity before and after BT, respectively (P < .001), and values of ASM-associated nerves were of 452.6/mm2 and 62.7/mm2 before and after BT, respectively. Additionally, with regards to healthcare utilization, BT significantly improved asthma control, as assessed by daily symptoms (ACT; 152%), rate of severe exacerbations, hospitalizations for asthma, ICU stays, and emergency department visits. These effects were accompanied by a significant reduction in maintenance doses and numbers of OCS bursts and improvements in AQLQ (162%) scores at 12 months. Clinical benefit was detectable at 3 months after BT and persisted until 12 months.	
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Additionally, the following study provides additional context for the need for BT in a patient population not indicated for and/or not responsive to other treatments for severe asthma: *Chipps B et al. Asthma Yardstick Practical recommendations for a sustained step-up in asthma therapy for poorly controlled asthma. Ann Allergy Asthma Immunol 118 (2017) 133-142.*	The Chipps et al publication was excluded at the abstract level because it is not a clinical study, clinical practice guideline or systematic review.
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	The following study demonstrates in a single-arm study, the real-world experience of more-severe patients treated with BT; the patients' mean FEV1 was 52% of predicted, and five patients with very severe asthma had a mean FEV1 of only 37% and were safely treated with BT; with incidental overnight hospitalizations for a transitory need for a bronchodilator immediately post-procedure, suggesting reasonable safety in this extremely severe asthma population. Long-term follow-up of this cohort demonstrated that no patients experienced clinical deterioration and a significant share experienced clinical improvement. *Doening DC et al. Safety and Feasibility of Bronchial Thermoplasty in Asthma Patients with Very Severe Fixed Airflow Obstruction: A Case Series. J Asthma. 2013;50(2)215-218.*	We included the case series reported by Doeing et al, 2013 in the table of adverse events in the Appendix. We did not include uncontrolled studies in our evaluation of benefit, other than to report on the longer term followup of patients in the extensions of the RCTs

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	On Wednesday, May 24, 2017, 2-year follow-up data from the FDA-mandated Post Approval Study 2 (PAS2) study was presented at the American Thoracic Society's annual meeting. The presentation for these findings is included in these comments as an addendum. The findings generated are highly consistent with findings from AIR2, yet they reflect a real world patient population whose asthma was even more severe than that of the AIR2 study population (average of 1.6 severe exacerbations per patient per year in PAS2 versus 0.4 in AIR2 treated patients) and who had more comorbidities and medication use than AIR2 patients (BMI [kg/m2] 32.2 for PAS2 versus 29.3 for AIR2, OCS use 19.4% for PAS2 versus 4.2% for AIR2). Specifically: • The results from the PAS2 study confirm the effectiveness, safety and durability of BT to 2 years; • 2 years after BT treatment, subjects experienced improved asthma control, fewer severe exacerbations, hospitalizations, and ER visits compared to the 12 months prior to treatment; • PAS2 subjects experienced a significant reduction in steroid exposure 2 years following treatment; and • BT does not significantly affect spirometric measurements including FEV1 *Chupp G et al. Post-Approval Study (PAS2) for Bronchial Thermoplasty (BT): Results to 2 Years. Presented at the 2017 American Thoracic Society Annual Meeting. Wednesday, May 24, 2017.*	Our review is limited to data included in full-length, peer-reviewed publications. Abstracts do not always reflect the final results, and often do not report sufficient information for assessing risk of bias. Additionally, the study did not meet our prespecified criteria for inclusion for evidence of benefit because it is not a controlled study. We acknowledge receipt of the online version of the publication in the European Respiratory Journal as our report was in the final stages of preparation. As you note, despite the very similar inclusion criteria for the PAS2 and AIR 2, the PAS2 patients were more likely to have had exacerbations and hospitalizations in the 12 months prior to BT than the AIR 2 patients, and had more severe exacerbations and emergency department visits during the treatment period than patients in AIR 2..
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Finally, Boston Scientific would like to advise AHRQ that additional data comparing a subset of patients in PAS2 who have completed 3 year follow-up with the 3 year follow-up data for AIR2 BT treated patients has been accepted for publication and is expected to be available by September, 2017. Prior to publication, we are unable to provide this manuscript, however we will forward it to AHRQ immediately upon release. We believe the data contained in this manuscript will further support findings from prior studies and confirm the important role of BT in the management of patients with severe, poorly controlled asthma.	We recognize that forthcoming data and future studies will continue to expand and refine the evidence base for this important intervention.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Key Points In the draft comparative effectiveness review, AHRQ reports that *"the rates of exacerbations were low, limiting our ability to draw conclusions regarding the impact of BT on exacerbation frequency."* While rates of exacerbations at baseline within the included RCTs may be perceived as lower than those observed within studies describing 'real-world' clinical practice (e.g. Bicknell et al.), the included studies were all statistically powered to be able to provide reviewers with the ability to draw conclusions of the effect of BT among the populations considered in the studies. Boston Scientific therefore requests removal of the above sentence regarding the ability to draw conclusions from the draft review.	We have revised the section on exacerbations and the referenced sentence has been removed. The evidence from the AIR trial on severe exacerbations was insufficient and inconclusive. There was a statistically significant reduction in mild exacerbations, but we considered the strength of evidence Low because of the study limitations, unknown consistency, and indirectness of measuring exacerbations only while patients were off maintenance medication. We noted that the AIR 2 trial found improvement in severe exacerbations compared to the sham control, although the clinical importance of the degree of reduction is unclear. We rated the strength of evidence as Low because of the unknown consistency and imprecision.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Key Points AHRQ also notes, *"The effect of BT on health care utilization or costs when compared with medical management without a sham control was inconclusive in two RCTs (SOE: Insufficient)."* Within the AIR2 trial, BT demonstrated a reduction in ER visits compared to sham (PPS 99.9%), and physician office visits and hospitalizations compared to baseline. Boston Scientific requests that these conclusions be included within the 'Key Points' section. In addition, while healthcare utilization was not directly measured within the AIR or RISA trials, these trials did measure and demonstrate a reduction in exacerbations, which would presumably result in some level of healthcare utilization in the real world. Finally, please note that three published, peer-reviewed cost effectiveness analyses found BT to be cost effective versus standard of care, though none of these publications were considered in the AHRQ review. The availability of these manuscripts suggests that adequate data are available to assess the effect of BT on health care utilization or costs. Citations for these manuscripts are provided below for AHRQ's review: *Cangelosi M et al. Cost–effectiveness of bronchial thermoplasty in commercially-insured patients with poorly controlled, severe, persistent asthma Expert Rev. 2015 Apr;15(2):357-64.* *Zein JG et al. Cost effectiveness of bronchial thermoplasty in patients with severe uncontrolled asthma. J Asthma. 2016;53(2):194-200.* *Zafari Z. Cost-Effectiveness of Bronchial Thermoplasty, Omalizumab, and Standard Therapy for Moderate-to-Severe Allergic Asthma. PLoS One. 2016 Jan 11;11(1):e0146003.*	The Key Points have been revised. We note the inconclusive evidence for severe exacerbations from the comparison of BT and standard care to standard care alone. We also report the finding of a statistically significant reduction in exacerbations and ED visits for patients undergoing BT compared to the group in the sham control arm of AIR 2. The prioritized outcomes in this review were taken from the recommendations for outcomes in prospective clinical trials of asthma from an NHLBI-AHRQ sponsored workshop, published in J Allergy Clin Immunol. 2012 March ; 129(3 Supplement): S1–S8. Because we covered exacerbations, ED visits and hospitalizations under the category of "Exacerbations," we only covered rescue medication use and medication dosage reductions under "Health care utilization." The cost-effectiveness study by Cangelosi et al does not meet inclusion criteria for this review because it does not report unique data from a clinical trial, since it relies on data from AIR 2. The cost-effectiveness study by Zein et al does not report unique data from a clinical trial, since it relies on data from AIR 2. The cost-effectiveness study by Zafari et al does not provide any unique data from a clinical trial, since it relies on data from AIR 2. The authors of the paper state "there is substantial uncertainty in the underlying evidence." A review of cost-effectiveness models themselves was beyond the scope of this review.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Key Points AHRQ notes, *"Pulmonary physiology measures (forced expiratory volume in 1 second [FEV1] and morning peak expiratory flow [PEF]) were improved in patients given BT compared to patients given sham treatment or medical management (SOE: Low)."* While statistically significant differences were observed in PEF in the AIR trial, and similar observations in FEV1 observed in the RISA trial (both compared to medical management), no statistically significant differences in [am] PEF or FEV1 were observed in the AIR2 trial compared to sham treatment. The intent of bronchial thermoplasty is asthma control, not improvement in pulmonary physiology as measured by FEV1. In AIR2, most patients had relatively favorable FEV1 measurements prior to treatment, yet they were experiencing exacerbations and other symptoms that characterized them as having severe asthma according to the ATS / ERS definition. FEV1 data was collected in AIR2 as a safety measure, to confirm that pulmonary physiology does not worsen after bronchial thermoplasty. Given this clarification, it would be our recommendation that 'Inconclusive' or 'Low' strength of evidence be considered for any conclusions of *improvements* to airway physiology; however, we would also recommend that the following conclusion be considered for addition: A 'High' strength of evidence that airway physiology measurements such as FEV1 remain unchanged in the long-term and thus there is no worsening pulmonary physiology.	We have revised the section on pulmonary physiology measures. We note "In 1 small trial, BT and standard care improved FEV1 at 22 weeks from baseline; the between-group difference was not significant at 52 weeks" while "In the other study, patients treated with BT and standard care had greater increases in morning and evening peak flow compared with standard care alone from baseline to 12 months. Between-group change in FEV1 was not significant." We assessed the strength of evidence as insufficient for drawing any conclusions about changes in spirometry. We provide information on the pulmonary function measures from the extension trials, but note that only one study had only partial followup of the control group.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Key Points AHRQ notes, *"Quality of life scores did not differ for patients assigned to BT compared to those assigned to sham treatment in one RCT (SOE: Low)."* As reported in the Castro 2010 AIR2 trial, there existed a 96% PPS of an *improvement* in the asthma-specific quality of life measure AQLQ (97.9% PPS per protocol). This finding is corroborated in correspondence from Elizabeth Juniper, the originator of the AQLQ instrument (attached as appendix). In this letter, dated December 18, 2008, Ms. Juniper writes, "Based on published literature to date, I am not aware of any other therapy for severe asthma that has demonstrated this degree of clinically meaningful benefit between groups (measured by the proportion of patients benefitting from the treatment) as compared to optimal standard of care." While this statement may now be considered dated due to the introduction of AQLQ data for other therapies, it nonetheless supports the conclusion that quality of life scores did differ for patients assigned to BT compared to those assigned to sham treatment in AIR2. Per the high-level of reported posterior probability of superiority as well as the statement by the developer of the AQLQ instrument, Boston Scientific requests that AHRQ revise this statement to reflect that there was an improvement in quality of life post-BT compared to sham.	We revised the statement to read " "Evidence as to whether patients receiving BT and standard care versus the sham bronchoscopic procedure and standard care had different quality of life (AQLQ) scores was inconclusive (SOE: Insufficient). Analysis of results for the intention-to-treat population found no improvement, but analysis of results for the per-protocol population found a difference that may not be clinically important, as it did not achieve the minimum important difference for this measure. A responder analysis (proportion of patients who achieved the minimum important difference) favored the BT and standard care intervention, but this outcome was not prespecified."
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Key Points AHRQ omits mention of durability of treatment effect (5-year follow-up) in the 'Key Points' section. While long-term follow-up post 1-year was not controlled, conclusions about the durability of observed treatment effect and safety can be made based on five-year follow-up from all three randomized controlled trials (RISA, AIR, and AIR2) and we would recommend that a 'High' strength of certainty regarding the absence of any delayed safety concerns be assigned in the report.	We have noted the results of the extension studies in the text of the Results chapter.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Detailed Synthesis – Asthma Control AHRQ concludes, "*Low-strength evidence from two RCTs (RISA and AIR) suggests that patients treated with BT have greater improvement in ACQ score than with patients treated with medical management (p=0.01 and p=0.001, respectively).*" Given the validation across two separate RCTs compared to medical management demonstrating benefits to ACQ scores of a very significant (p=0.01) and an extremely significant (p=0.001) nature, we disagree with AHRQ's characterization of the strength of the evidence as "low," and we recommend a 'High' strength of evidence of this finding. The confirmatory results of the body of this evidence suggest that further research of BT versus medical management is very unlikely to change the direction or magnitude of the effect.	The assessment of the strength of evidence involves several factors: study limitations (considering the risk of bias of the individual studies contributing evidence to a specific outcome), directness of the population, intervention and outcome measurement to our questions, and precision of the results (reflecting the sample size, event rates, minimum important differences, and variance). The approach is described more fully in the EPC Methods Guidance, available on the AHRQ Effective Health Care Web site (https://effectivehealthcare.ahrq.gov/). The wording of the conclusion has changed to **"Favors BT, but clinical importance unclear:** ACQ scores improved in patients who underwent BT compared to those who received standard medical management, but the upper bounds of the confidence interval was less than the MID." The strength of evidence is Low for the following reasons: Medium study limitations and imprecision (MID not met).

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Detailed Synthesis – Asthma Control AHRQ notes, "*A small trial (n=25) comparing 10 patients presenting at a clinic with 15 patients from three RCTs who were treated at the same institution, suggests patients treated with BT while enrolled in an RCT saw greater improvement in asthma control than those treated with BT outside an RCT; p=0.003).*" The 2 year follow-up data from 279 patients treated in PAS2 described earlier in these comments and presented at the American Thoracic Society on May 24, 2017, directly refutes the finding from the small trial referenced by AHRQ with a far greater strength of evidence. In addition, we advise AHRQ that forthcoming investigator-sponsored research submitted as a manuscript to a peer-reviewed journal will directly address this conclusion and will be a significantly larger sample size than the 10 patients who were treated in this clinic outside of an RCT[2]. [2] Additional patients have continued to be treated at this clinic and treated by the interventional pulmonologist authors on this manuscript continue to practice BT today.	We recognize that forthcoming data and future studies will continue to expand and refine the evidence base for this important intervention. To remain consistent with our pre-specified methodology, we have limited the current analysis to data presented in full-length, peer-reviewed publications.

Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Detailed Synthesis – Exacerbations AHRQ notes that "*one RCT comparing BT to medical management found that during the treatment period (weeks 0–6), four patients treated with BT experienced seven hospitalizations due to respiratory AEs compared with no hospitalizations in patients treated with medical management.[89] In the post-treatment period (weeks 6–52), no difference was found in hospitalizations between groups.[89] In the long-term extension, BT reduced overall respiratory-related hospitalizations by 68 percent at 5 years compared with baseline.[92] When comparing BT with sham treatment, one RCT found that respiratory-related hospitalizations were increased (10.5% vs. 5.1%; PPS sham > BT=57.2%) through 12 months.[87] One RCT extension study found no difference between BT and medical management in the frequency of emergency department (ED)visits from baseline through 5 years.[92] Compared to sham, one RCT found that BT reduced the risk of ED visits for respiratory symptoms by 84% (PPS 99.9%).[87] In the long-term extension of this RCT, in patients treated with BT, ED visits for respiratory complications were reduced by 78 percent at 5 years compared with 12 months before the procedure.[90]"* We recommend that this paragraph be moved to the 'Healthcare Utilization' section as it is relates to the healthcare required to treat asthma exacerbations, rather than the asthma exacerbations directly. Moreover, given AHRQ's focus on opportunities to make healthcare more efficient and less costly, we would recommend adding conclusions regarding hospitalizations and ER visits to the 'Key Points' section to emphasize this reduction in healthcare utilization. We would encourage consideration of a greater grade of 'High' be used to communicate the strength of the evidence related to healthcare utilization.[3] [3] Put into context with the 'Low' strength of the evidence regarding pulmonary physiology "BT compared with sham from baseline to 12 months (PPS 24.1% and 80.6%, respectively)…" readers of the report may not readily understand AHRQ's conclusions of the evidence related to healthcare utilization as 'Low', compared with more certain language used to describe the evidence related to pulmonary physiology, which was reported in the literature less-certainly – as measured by posterior probability of superiority (PPS).	The organization of the outcomes was based on recommendations for outcome measures in prospective clinical trials of asthma from an NHLBI-AHRQ sponsored workshop, published in J Allergy Clin Immunol. 2012 March ; 129(3 Supplement): S1–S8. In the recommendations, exacerbation outcomes are put into their own category. The "Healthcare utilization and costs" category repeats some of the Exacerbation outcomes, but it would be unnecessarily redundant to repeat them in the report. The only unique outcomes listed in the Healthcare Utilization and Costs" category are "asthma-specific detailed medication use" and "resource use related to the intervention (e.g., personnel time, mite eradication, equipment)." The Key Points do include findings related to emergency room visits from the AIR 2 study for the post-treatment period up to 12 months. After further consideration, we have revised the strength of evidence assessment of the reduction in ED visits in the post treatment period to moderate. The consistency is unknown because there is only a single trial of this comparison (BT and standard care compared to bronchoscopy (without thermoplasty). and standard care. The finding of "no difference" for the two groups on the pulmonary physiology measures is low-strength evidence because of the unknown consistency and imprecision of the results.

Source: https://effectivehealthcare.ahrq.gov/topics/asthma-nonpharmacologic-treatment/thermoplasty-systematic-review
Published Online: December 14, 2017

Commentator & Affiliation	Section	Comment	Response
		Given the 'Low' result describing pulmonary physiology, we would recommend AHRQ consider a 'High' grade of the evidence to describe healthcare utilization – as the PPS demonstrates that it is highly unlikely that additional research will alter this finding of BT reducing healthcare utilization.	
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Detailed Synthesis – Healthcare Utilization See above recommendations for moving healthcare utilization relevant conclusions from 'Asthma Exacerbations' to 'Healthcare Utilization' and comments related to the strength of the evidence. Moreover, the beneficial result of reduced asthma-specific healthcare utilization has informed the body of literature demonstrating the cost-effectiveness of BT in three publications, citations for which were provided earlier in this document.	All 3 of the cost-effectiveness studies rely on the results of the AIR 2 trial, so they do not provide any unique data. The low strength of evidence for the effectiveness data informing the cost-effectiveness models lowers our confidence in the findings of the analyses.
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Detailed Synthesis – Pulmonary Physiology AHRQ notes that, "*in one RCT and extension trial comparing BT to sham treatment, FEV1 (% predicted, pre-bronchodilator) and morning PEF (L/min) improved in patients treated with BT compared with sham from baseline to 12 months (PPS 24.1% and 80.6%, respectively), and no significant change in FEV1 occurred in BT-treated patients through the 5-year followup.*[87,90] *In a comparative trial, FEV1 was similar in patients treated with BT in a clinic or in an RCT.*[93]" While the incidental findings from early trials of bronchial thermoplasty compared to medical management reported the observations reflected in the draft comparative evidence review, currently Boston Scientific does not market the therapy as having a direct impact toward improving FEV1. Given the inconclusive evidence of pulmonary physiology improvement across the three trials but *no* observation of any FEV1 degradation/worsening among the RCT populations, we recommend a 'High' grade to describe the certainty of the evidence that BT does *not worsen / degrade* pulmonary physiology measures indicative of non-improving asthma control.	We have revised the text discussing the pulmonary physiology measures, clarifying that the only report of improvement in FEV_1 was in the RISA trial at the 22-week followup. We have reported the findings that FEV_1 was stable over 5 years in the extension studies.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Detailed Synthesis – Asthma-related Quality of Life AHRQ notes that, "*ITT patients were more likely to gain a clinically meaningful improvement in AQLQ than sham (PPS 99.6%).*" This high PPS result indicates that there is a low probability that additional research will alter this conclusion of clinically-meaningful improvement. Additionally, given the observations of statistically significant improvements compared to medical management observed in AIR and RISA, we would request AHRQ consider grading the strength of the evidence as 'Moderate'.	We have reconsidered our assessment of the strength of evidence. The primary outcome, the mean difference between groups on the AQLQ, did not meet the prespecified level of significance in the ITT analysis, and the difference did not meet the minimum important difference. We note that the per protocol analysis found a significant difference as judged by the PPS, but the FDA pointed out that the 95% credible interval crossed 0. We also noted that there are disadvantages to reliance on per protocol analysis since it counters some of the benefits of randomization, and again, the difference did not meet the MID. While we mention the significant difference in the proportion of patients achieving the MID on the AQLQ, we were concerned that it was not prespecified in the study protocol. Consequently, we decided that the evidence was inconclusive and graded the evidence as insufficient for this outcome.
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Detailed Synthesis – Symptoms (secondary measure) AHRQ did not include within this section pertinent secondary reported outcomes concerning to productivity improvements related to asthma control. As reported in AIR2 (Castro 2010), post procedure, BT patients experienced only ~1.3 days lost from work related to asthma; while AIR2 sham patients lost ~3.9 days from work post-procedure (99.3% PPS). This important result is indicative of improved asthma control and is potentially relevant to the working age population.	We are aware that Castro 2010 reports this difference in days lost from work, but the result is only presented for the time period after treatment. Given the number of events experienced by patients receiving BT during the treatment period, it would be more useful to see the results for the full 12-month study period in addition to the results as presented. We have included the data as presented in the Appendix.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Results	Detailed Synthesis – Adverse Events and Mortality Boston Scientific agrees with the draft comparative effectiveness report's findings that, in general, low-frequency of adverse events occur during the treatment and only minor adverse events are reported post procedure. We would recommend contextualizing these adverse events by highlighting the methods utilized to treat them, as reported in the AIR2 trial: *"All these events resolved with standard therapy, including the hemoptysis, which was managed with bronchial artery embolization".* (Castro, 2010)	We added the following to the Adverse Events and Mortality section, after listing the events for the AIR2 trial: "The investigators state that all adverse events were treated with "standard therapy" (including bronchial artery embolization for hemoptysis). While bronchial artery embolization has been described as effective in a number of case series for managing moderate and severe hemoptysis, the procedure must be performed by experienced interventional radiologists, and has resulted in rare but serious complications (e.g., paraplegia due to spinal artery embolization).

Public Reviewer 11 David Peden on behalf of AAAAI	Results	Academy leadership would comment upon the statement in "Results", "Fifteen studies, including three RCTs with 5-year follow up, examined the impact of BT on patients with moderate to severe asthma, who also had fewer than three exacerbations within the past year or who did not use high doses of oral corticosteroids." Academy leadership would note that it is very important to clarify in the summary that these are single arm follow-up, over the 5 year period; under conclusions, the authors state that "Multicomponent interventions MAY be more valuable…" and that, "BT improved FEV1 and quality of life while reducing exacerbations." Academy leadership would comment that the SOE for both is low, and would therefore recommend that both statements should have a MAY in front of them to qualify the statements for the casual reader who may be inclined to read only the summary conclusion.	The two topics have now been split into two separate reports, and the results specific to BT have been revised. The results section now begins with the following text: "Fifteen studies were included to address the benefits and harms of bronchial thermoplasty (BT). Six trials, including three randomized controlled trials (RCTs) (n=432)18-20 and their 5-year, single-arm extension studies,[21-23] provided outcomes related to safety and efficacy. One of the extension studies also reported data for the control arm through 3 years." Regarding the impact of BT on FEV1, we have revised the conclusion for the comparison of BT and standard care to standard care alone to read "**Inconclusive**: In 1 small trial, BT and standard care improved FEV1 at 22 weeks from baseline; the between-group difference was not significant at 52 weeks. In the other study, patients treated with BT and standard care had greater increases in morning and evening peak flow compared with standard care alone from baseline to 12 months. Between-group change in FEV1 was not significant." The evidence in this instance is graded as **Insufficient**. For the comparison of BT and standard care to bronchoscopy without thermoplasty (sham) and standard care, the report concludes "No difference: FEV1 and morning peak flow in patients treated with BT and standard care compared with sham and standard care from baseline to 12 months." The strength of evidence for this conclusion is **Low**. In the text we note that FEV1 remained stable in the

Commentator & Affiliation	Section	Comment	Response
			BT groups over 5 years and in the AIR study's control group (i.e. in the 24 of 49 who agreed to long-term followup) over 3 years of followup. For the AQLQ results, we note that the improvement was only statistically significant (although not clearly clinically important) in the unblinded studies and the per protocol analysis of the blinded study. We are aware that the responder analysis indicated that more patients in the BT and standard care achieved the MID on the AQLQ, but this was not a prespecified analysis. We agree that it is best to use "may improve" in describing BT's effects in some patients with asthma.
Peer Reviewer 2	Discussion	Implications and limitations were clearly considered.	Thank you.
TEP Reviewer 1	Discussion	In the discussion and results sections of the BT section of the paper, it would also be important to list what are clinically meaningful differences. For example, a statistically significant improvement in peak expiratory flow or FEV1 percent predicted might not be clinically meaningful. As with the allergen intervention sections, some discussion on the differences between statistically significant improvements and clinically meaningful improvements in the outcome parameters would be useful.	Thank you for your comment. We have added more information about clinically meaningful endpoints to the report and have included a table of minimum important differences in the Appendix.
TEP Reviewer 1	Discussion	In the discussion of BT, the authors frequently referred to the fact that most of the studies were supported by the manufacturers of the instrument used to perform BT. Whereas I agree this can be a problem, it is typically no different from any other phase 3 or postmarketing study conducted by a pharmaceutical company. Optimally, one would like to see these types of studies funded by federal agencies and not the manufacturers, but this is the reality we face currently with limited funding.	We did not intend to overstate the impact of the study funding source, but it is standard practice in EPC reports to consider the possibility that funding by a party with a financial interest in the results could impact the trial conduct, analysis, interpretation or reporting.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 1	Discussion	In the BT studies, it would also be important to determine the phenotype of the patients enrolled. It has clearly been shown that for many of the Biologics, a T2 high eosinophilic phenotype is required to show clinical efficacy. For BT, one might speculate that this would be best used in patients that either have a neutrophilic or paucigranulocytic phenotype since we currently have no specific therapies for these patients. Nonetheless, description of the patients phenotype would be helpful as well as characterization of previous asthma exacerbations as pointed out by the authors.	We addressed your comments in the evidence gaps section of the discussion. Data on the granulocyte phenotypes for BT treated patients is extremely limited. The published studies meeting inclusion criteria did not include this information.
TEP Reviewer 3	Discussion	pg 45 lines 34-38 - not sure how a statement of "absence of benefit for BT...compared to sham" is justified by data in Table 11, where there are several measures that favor BT, albeit generally of low SOE. Does low SOE equal absence of benefit?	Thank you for your comments In splitting the report into two reports and revising the text, the statement was removed. We have tried to convey that we have limited confidence in the conclusion that there is no difference between groups in the single study making the comparison on certain outcomes, and in the conclusion of benefit on others. The conclusion of "no difference" is based not on the SOE, but on the study result (e.g., calculated SMD for ACQ: -0.05, 8=95% CI: -0.29 to 0.19).: "Compared with the sham bronchoscopic procedure and standard care, the intention-to-treat analysis in a single RCT suggests that BT with standard care had no effect on asthma control (defined as improvement in ACQ from baseline), hospitalizations for respiratory symptoms, rescue medication usage, pulmonary physiologic measures, or other asthma symptom scores (Low SOE).[18]"

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 3	Discussion	pg 46, lines 25-32 - there seems to be a bias among the authors that patients studied for BT were not "the sickest". There are no compelling data to suggest those studied were not "sick enough" to warrant a trial of BT. An argument that it would have been unethical to include the very sickest of patients in these trials can easily be made. Line 28-29 stating they were not using "high doses of oral steroids" seems out of place, as this is not required in any definition of severe asthma (including ATS/ERS task force). I am concerned this review may have been a bit "biased" against this KQ and suggest the authors carefully examine these issues.	We have now provided greater detail regarding individual study inclusion criteria and noted that the studies included patients with a spectrum of asthma severity. Although oral corticosteroid (OCS) dosage is not part of the definition of severity, it is an important treatment typically reserved for patients experiencing more frequent exacerbations. OCS Dosage restrictions were mentioned by the RISA and AIR 2 studies.
TEP Reviewer 3	Discussion	pg 46, line 51 - similar to comment above about high doses of oral corticosteroids.	Thank you for your comments.

TEP Reviewer 5	Discussion	For Key question 2, regarding bronchial thermoplasty, i believe that the analysis of available data seems biased against BT. All published studies have demonstrated efficacy and very few studies go to the lengths performed to do a sham controlled trial. Both the comparisons with standard of care and the sham controlled trial were done well and all have suggested significant efficacy, including with regard to healthcare utilization. While these effects are understated, the effects on lung function are overstated. Only 1 study showed significant effect on lung function and the sham controlled study did not.	We assessed the risk of bias of the 2 studies in which BT and standard care was compared to standard care as being at medium risk of bias. Our concern was that the unblinded nature of the interventions lowered our confidence for attributing the outcomes (which are primarily subjective) to the interventions. We assessed the risk of bias of the AIR 2 trial as low because the BT component was blinded. Consequently, we graded the strength of evidence emanating from the unblinded trials lower than from the blinded trial. Each of the outcomes we deemed critical has its own strength of evidence grade for each intervention comparison. For exacerbations as an indicator of health care utilization, we were concerned that the AIR study measured exacerbations only during periods when patients were off LABAs. We concluded that the findings favored BT, but the clinical importance of the difference was unclear. We graded the evidence as Low for impact on mild exacerbations because the study had medium risk of bias, the evidence presented was indirect (not measured while patients were on standard therapy), and was only reported in one study. For severe exacerbations, the results were inconclusive given that the confidence interval crossed 0. Again, we were concerned that the studies had medium risk of bias, the evidence from AIR was indirect, and the results were imprecise. Consequently we graded the evidence in this situation as insufficient. In revising our presentation of the AIR 2 findings, we have split the grading of exacerbations, ED visits and hospitalizations for the periods during BT treatment and after completion of treatment where possible. We thought

Commentator & Affiliation	Section	Comment	Response
			this would be more helpful for shared decisionmaking, as patients need to weigh the possibility of worsening during the treatment period against possible improvements later.
TEP Reviewer 5	Discussion	Newer BT studies are omitted especially the ones related to mechanism. Pretolani M et al Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: Clinical and histopathologic correlations. J Allergy Clin Immunol. 2017 Apr;139(4):1176-1185.	The Pretolani et al. study was excluded because it does not have a concurrent control group and does not report adverse events.
TEP Reviewer 5	Discussion	Overall, the report makes BT appear to be little better than placebo- however the sham controlled study strongly suggests efficacy. Future research section is clear.	Thank you for your comments.
TEP Reviewer 6	Discussion	Well written discussion, nice review of the strength of evidence. Limitations are clear and discussed in the context of the review process as well as the evidence base. I really like the discussion of the findings in relation to other reviews.	Thank you.
Public Reviewer 4 Joe Zein	Discussion	The authors concluded that BT improved FEV1 and quality of life while reducing exacerbations. Serious adverse events were infrequent. they also concluded that the available body of literature on BT is small, however, and the generalizability of the findings to patients with severe asthma and multiple comorbidities is limited. This conclusion might need to be revised once the above concerns are addressed.	We have revised the conclusion paragraph to read: "Based on the available literature, BT may be modestly beneficial in some patients with asthma, but is not without risks in any population. The risk of adverse events is higher early in treatment while benefit is typically observed weeks to months after therapy and can last for at least 5 years, after which the duration of effect is unknown."

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Discussion	Key Findings and Strength of Evidence AHRQ notes, *"Compared to sham treatment, the evidence suggests that BT had no effect on asthma control, healthcare utilization, quality of life, or secondary measures of asthma symptoms (SOE: Low). However, improvement in pulmonary physiology measures and a reduced risk of exacerbations were suggested (SOE: Low) when BT was compared to sham treatment. Serious adverse events attributed to BT were infrequent, and no deaths were reported."* Given the above mentioned responses to the draft comparative effectiveness report, with evidence that compared to sham, BT had a statistically significant reduction in healthcare utilization and potential improvements in quality of life and secondary measures, while modest effects were observed regarding pulmonary physiology[4], we would recommend a restructuring of this section of the report as follows: "Compared to sham treatment, the evidence suggests that BT had significant reduction in healthcare utilization and improvements in secondary measures of asthma symptoms (SOE: Moderate). Moreover, a reduced risk of exacerbations was suggested (SOE: Moderate) when BT was compared to sham treatment. Serious adverse events attributed to BT were infrequent, and no deaths were reported." [4] As evidenced by lower PPS% measures relative to healthcare utilization and loss of work/school.	The quoted text has been revised: Compared with the sham bronchoscopic procedure and standard care, the intention-to-treat analysis in a single RCT suggests that BT with standard care had no effect on asthma control (defined as improvement in ACQ from baseline), hospitalizations for respiratory symptoms, rescue medication usage, pulmonary physiologic measures, or other asthma symptom scores (Low SOE). Reduced risk of severe exacerbations was suggested (Low SOE), but the clinical importance of the degree of the reduction was unclear. Rates of emergency department visits for exacerbations during the post-treatment period were significantly lower in patients receiving the BT and standard care than in those who received the sham bronchoscopic procedure and standard care (Moderate SOE).[18]Serious adverse events attributed to BT occurred during the 12-week treatment period, and no deaths were reported.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Discussion	Findings in Relation to What is Already Known AHRQ notes that, "*while some outcomes may have been influenced by knowledge of the treatment condition (only the RCT comparing BT to sham was blinded), the absence of benefit for BT on asthma-related outcomes compared to sham treatment is concerning. As treatment effects were similar between BT and sham, it is unclear whether treatment response was due to a placebo effect or whether sham treatment of the lungs had a true effect."* While the duplication of specific effects observed within the AIR trial related to pulmonary physiology were observed in the AIR2 trial, it should be noted that – as reported in Castro, 2010 AIR2 trial, researchers observed a statistically significantly (PPS 99.6%) difference in a clinically meaningful improvement in AQLQ[5] compared to sham. Moreover, this same trial notes improvements in asthma control as evidenced by reductions in days lost from work/school, and reductions in ER visits and hospitalizations. As such, the 'concern' of AHRQ related to BT versus sham comparison may be misplaced. A most likely alternative that AHRQ does not include in the final sentence is that the sham arm had a 'placebo' effect due to the non-therapeutic but highly-organized nature of the sham comparator and the subjective nature of the AQLQ metric. Research has been published since the AIR2 trial that suggests a mere bronchoscopy can influence AQLQ scores to be subjectively assessed by the patient as having improvement. (Hróbjartsson A et al. 2001; Kaptchuk TJ et al 2000.; Pastis NJ et al. 2013) However, no such subjective 'placebo' effect was observed among the more objective endpoints of days lost from work, ER visits, or hospitalizations post-procedure. [5] AQLQ score +0.5.	The primary reason we believe a sham control is necessary is the subjective nature of the majority of the outcomes, which are more susceptible to the placebo effect of undergoing an intervention. The statement quoted was removed in the revised version of the report.

Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Discussion	Evidence Gaps AHRQ notes that "*the studies for KQ 2 tended to have overall better reporting of study details, although there was lack of clarity regarding patient care, such as consistent reporting of concomitant medication use, and different trials used different measures to assess asthma control. As noted above, only one sham-controlled trial of BT has been conducted thus far. Given BT's invasive nature and the presence of a treatment effect in the sham condition, further studies using a sham comparison are needed. Studies could also be undertaken to test BT in other populations, especially patients with poor asthma control who experience high rates of exacerbations.*" AHRQ will find through review of the aforementioned Pretolani peer-reviewed publication, results that are specific to populations of asthma patients who experience higher rates of exacerbations. These data further demonstrate efficacy of BT within this more severe population. Data recently presented at the American Thoracic Society (ATS) annual meeting describes the observations and conclusions from the FDA-mandated PAS2 study (Chupp G et al. 2017), which treated 279 patients at 27 research centers in the United States and Canada. The study demonstrates a comparable treatment effect to that observed and reported in AIR2 – as measured by severe exacerbations, health care utilization, etc. Moreover, this group of 279 patients would be characterized as having more-severe asthma than the BT subjects enrolled in the AIR2 study. Differences in baseline demographics and clinical correlates in the 12 months prior to BT indicate: • The PAS2 patients had higher BMI and were older. They also had more cardiovascular and respiratory related comorbidities linked to higher BMI and age. 5 AQLQ score +0.5. • PAS2 patients were on higher doses of ICS and a higher percentage was on maintenance OCS and/or biologicals for the treatment of their asthma. • PAS2 patients had a greater frequency of history in the prior 12 months of (i) severe asthma exacerbations and (ii) hospitalizations for asthma.	The Pretolani et al. study was excluded because it does not have a concurrent control group and does not report adverse events. The PAS2 study did not meet inclusion criteria for this report because it was only available as an abstract before the report was in its final stages. The publication came out after our final searches were completed. In addition to the findings you describe, we note that the PAS2 patients also had more severe exacerbations and emergency department visits during the treatment period than patients in AIR 2. The full publication of PAS2 would have only met criteria for inclusion of the adverse events because it lacks a control group. The two narrative reviews did not meet our inclusion criteria.

		• 95.0% of PAS2 patients were severe asthmatics per the ATS/ERS definition (versus 82.1% of AIR2 patients). Therefore the PAS2 subjects may indeed resemble real world BT patients more closely. PAS2 study patients treated with BT showed procedural safety and clinical improvements during each of the two years following treatment with a 43.5 percent reduction in severe asthma exacerbations, a 51.2 percent reduction in hospitalizations and a 55.3 percent reduction in emergency room visits. Additional data showed: • The percentage of patients that had at least one severe asthma exacerbation requiring the use of systemic corticosteroids decreased from 77.8 percent in the year prior to treatment to 50.4 percent in year one and 46.4 percent in year two. • The proportion of patients who had asthma-related hospitalizations decreased from 16.1 percent in the year prior to BT to 8.0 percent and 7.3 percent in years one and two following treatment. • Patients with asthma-related ER visits reduced from 29.4 percent in the year before BT to 18.3 percent and 14.5 percent in years one and two post-BT. In the press release accompanying the presentation of these findings, Geoffrey Chupp, MD, principal investigator and director, Yale Center for Asthma and Airways Disease, Yale University School of Medicine, New Haven, Connecticut, concluded: "*The findings of the PAS2 study provide important 'real-world' evidence that patients with poorly controlled asthma on high doses of medications, including biologics, experience significant and sustained improvements in asthma control following BT. Overall, patients in PAS2 showed a marked improvement that was sustained out to two years, reinforcing previously published data from randomized controlled studies. These results suggest that for a wide range of patients with severe asthma BT is both effective and safe*." A very good and comprehensive review of all the available literature published in the high-impact journal CHEST "*Advances in Bronchial Thermoplasty*" demonstrates practitioners' learnings of BT based on the	

Source: https://effectivehealthcare.ahrq.gov/topics/asthma-nonpharmacologic-treatment/thermoplasty-systematic-review
Published Online: December 14, 2017

Commentator & Affiliation	Section	Comment	Response
		published data, and areas in which these same practitioners would like additional data. Finally, echoing the positioning of the AAAAi 'Yardstick' recommending consideration of BT (Chipps, 2017 aforementioned); research published in the extremely high-impact journal Lancet Respiratory notes that *"Bronchial thermoplasty reduces airway smooth muscle mass and exacerbations, and improves symptoms in patients with severe uncontrolled asthma on inhaled corticosteroids plus a second controller, and should be considered in patients who do not respond to or are not candidates for anti-IgE or anti-interleukin 5 treatment.*" *Trivedi A Pavord ID and Castro M. Bronchial Thermoplasty and Biological Tehrapy as Targeted Treatments for Severe Uncontrolled Asthma. Lancet Respir Med May 2016. S2213-2600(16)30018-2.*	
Public Reviewer 10 Ann Roy on behalf of Boston Scientific	Discussion	Conclusions AHRQ notes, that *"while BT appears safe in a highly select group of patients, no information is available regarding BT's safety and efficacy in a broader population of patients with multiple comorbidities or more severe asthma."* Per the comment above, data from the numerous above mentioned, peer-reviewed publications report the efficacy of BT in a more severe population and notes the safety of BT within this population.	The data reported in other studies were not eligible for inclusion in our review, due to lack of a concurrent control group and/or lack of adverse event reporting, and/or because they were not available as a full-length peer-reviewed publication.
Public Reviewer 11 David Peden on behalf of AAAAI	Discussion	Under "Finding in Relation to What is Already Known", Academy leadership would recommend that the authors reference and comment on how different conclusions were drawn than ATS/ERS Severe Asthma report which recommended BT only be used on study conditions, and would observe that this discussion could be similar to the discussion in the previous paragraph with NHLBI 2007 recommendations for indoor allergen interventions.	We have added a summary of statements from several guidelines (including the ATS/ERS guideline) regarding the role of BT in the management of asthma.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Clarity and Usability	It really isn't helpful to have these two interventions combined in a single report. As it is written it almost seems like the report is saying telling patients and physicians that allergen reduction doesn't work for asthma, but bronchial thermoplasty does. That is clearly not the intent of the AHRQ, but nonetheless that is how the report reads (and, in fact, is what the Key Messages on page 2 appear to indicate).	We have separated the document into two distinct reports for clarity and ease of use.
Peer Reviewer 2	Clarity and Usability	Very well done in terms of clarity and usability.	Thank you.
Peer Reviewer 3	Clarity and Usability	The report is very clear.	Thank you.
TEP Reviewer 1	Clarity and Usability	This is a well-written document providing some critical information to hopefully guide patient care. In addition, BT does not appear to be as effective as advertised.	Thank you for your review and feedback.
TEP Reviewer 3	Clarity and Usability	Well presented. Again, the inclusion of 2 unrelated treatment approaches makes this document a bit more difficult to read and digest than if the 2 KQ2 were presented separately.	We have separated the document into two distinct reports for clarity and ease of use.
TEP Reviewer 3	Clarity and Usability	Unfortunately, the findings do not provide much clinical guidance other than to "think twice" before recommended either of these approaches.	Thank you for your review.
TEP Reviewer 3	Clarity and Usability	Well done!	Thank you.
TEP Reviewer 5	Clarity and Usability	Report is well stuctured and organized but it is hard to follow the tables easily. Why not just summarize each outcome followed by findings with each study. Would have been helpful to have some data figures.	Thank you for your suggestion. We have attempted to revise and organize both reports to maximize their readability.
TEP Reviewer 5	Clarity and Usability	I do not believe the conclusions are relevant for either question. Reduction of allergens in the home may still be useful in a subset of patients. BT may be useful in a subset of patients. Why not state that?	We have revised our conclusions to include the possibility that some patients may benefit, but noted the current difficulty in selecting patients most likely to benefit.

TEP Reviewer 5	Clarity and Usability	For bT, the conclusion is "BT appears to be well tolerated and may provide benefit in FEV1 and quality of life." Lung function effects are modest. What is most important is the long term reduction in exacerbations. This is omitted. The comment about the limitation regarding types of subjects for whom BT is effective is inappropriate as well.	We have revised the summary of key findings in the Discussion chapter as follows: "Compared with standard care alone, the evidence from two RCTs suggests that BT with standard care improved asthma control (defined by the Asthma Control Questionnaire [ACQ], rates of mild exacerbations change from baseline to 12 months), utilization of rescue medication and quality of life (Low strength of evidence [SOE]), but the clinical importance of the findings for each of these outcomes is unclear. Rates of hospitalizations for respiratory symptoms were not different for these comparators during the post-treatment period (6 weeks after the third BT treatment through 12-month followup) (SOE: Low). The evidence base was insufficient to draw conclusions about BT's effects on severe exacerbations or pulmonary physiologic measures compared with standard care.[19,20] Compared with the sham bronchoscopic procedure and standard care, the intention-to-treat analysis in a single RCT suggests that BT with standard care had no effect on asthma control (defined as improvement in ACQ from baseline), hospitalizations for respiratory symptoms, rescue medication usage, pulmonary physiologic measures, or other asthma symptom scores (Low SOE). Reduced risk of severe exacerbations was suggested (Low SOE), but the clinical importance of the degree of the reduction was unclear. Rates of emergency department visits for exacerbations during the post-treatment period were significantly lower in patients receiving the BT and standard care than in those who received the sham bronchoscopic procedure and standard care (Moderate SOE).[18]Serious adverse events attributed to BT occurred during

Commentator & Affiliation	Section	Comment	Response
			the 12-week treatment period, and no deaths were reported."
TEP Reviewer 6	Clarity and Usability	Well written and clear. This is a very important document that will be widely read and disseminated. It also highlights the gaps and need for future research.	Thank you.