Washington State Health Care Authority
Health Technology Assessment

Bronchial Thermoplasty for Asthma

Draft Evidence Report: Public Comment & Response

April 15, 2016

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Bronchial Thermoplasty for Asthma
Response to Public Comments on Draft Report

April 15, 2016

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Response to Public Comments, Draft Report

Bronchial Thermoplasty for Asthma

Hayes, Inc. is an independent vendor contracted to produce evidence assessment reports for the WA HTA program. For transparency, all comments received during the comments process are included in this response document.

Comments related to program decisions, processes, or other matters not pertaining to the evidence report are acknowledged through inclusion only. When comments cite evidence, the information is forwarded to the vendor for consideration in the evidence report.

This document responds to comments from the following parties:

- Maria B. Stewart (Director, Health Economics & Reimbursement, Boston Scientific Corporation)
- Navdeep S. Rai, MD, FACP, FCCP (Pulmonary/Critical Care Physician, Tacoma, WA)
- Seth Hartung, MD, PhD (Pulmonary and Critical Care Medicine, Western Washington Medical Group and Providence Everett Hospital, Everett, WA)

Table 1 provides a summary of the comments with corresponding responses.

Table 1. Public Comments on Draft Report, Imaging for Rhinosinusitis

Key: AAO, American Academy of Otolaryngology; HNS, Head and Neck Surgery; RPS, Rhinology and Paranasal Sinus

Comment and Source	Response
March 18, 2016 e-mail from Maria B. Stewart (Boston Scientific Corporation)	
Comment: "The Draft Evidence Report inaccurately states in at least four places (pages 6, 23, 36 and 53) that FDA approval of the AlairTM Bronchial Thermoplasty System was based on a single, double-blind sham-controlled RCT (AIR2). Such statements reflect a fundamental lack of understanding of the US regulatory process. While the AIR2 trial was the pivotal trial associated with the FDA's approval of the Alair System, multiple studies conducted at different times and with varied patient populations showed directionally consistent improvements and were assessed by the FDA as an indicator of a treatment effect. Moreover, bronchial thermoplasty was assessed via the PMA process, which is the most rigorous approval pathway for medical devices in the United States. Boston Scientific requests that the HCA remove the statement that FDA approval of the Alair Bronchial Thermoplasty System was based on a single, double-blind sham-controlled RCT wherever the statement appears in the report and clarify that multiple RCTs were considered in the FDA's assessment of the procedure's safety and effectiveness."	Thank you for your comments. In the FDA Summary of Safety and Effectiveness Data for the Alair Bronchial Thermoplasty System (p. 15), it is stated that "The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of bronchial thermoplasty with the Alair Bronchial Thermoplasty System for 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...**Data from this clinical study were the basis for the PMA approval decision**. A summary of the clinical study [AIR2 pivotal trial] is presented below." Furthermore, the FDA Summary of Safety and Effectiveness Data conclusions for safety and effectiveness are based on data collected during the AIR2 clinical trial. "Safety conclusions: The adverse events of the device are based on data collected in the AIR2 clinical study conducted to support PMA approval...Overall, the safety data demonstrate an acceptable safety profile for the Alair System." "Effectiveness Conclusions: The primary effectiveness analysis examined the difference between mean-integrated AQLQ scores between the treatment and sham arms of the pivotal study; this analysis did not meet its prespecified success criterion and is not the basis of approval. Other endpoints, however, provided compelling evidence that the Alair system offers clinical benefits." We acknowledge that other data from preclinical studies were summarized in the FDA Summary of Safety and Effectiveness Data document. Because the wording in the

Comment and Source	Response
	Draft Report coincides with the FDA document, we believe these statements to be accurate. However, we have modified these statements so that it is clear that AIR2 was the pivotal trial on which the FDA PMA was primarily based.
Comment: "In general, the author's assessment of the literature regarding bronchial thermoplasty was comprehensive, however there are a number of instances in which Boston Scientific found inaccuracies or misinterpretations of data. Each of those areas is described in more detail in the following paragraphs: In the Executive Summary, on page 1, the report states, "The prevalence of asthma has increased over the past 30 to 40 years and was at 8.2% in 2009; however for the U.S. population as a whole, the frequency of asthma attacks has reached a plateau in recent years and remains at approximately 4%." The report appears to be mixing two different concepts: the prevalence of asthma and the frequency of asthma attacks. A review of the source for these data cited in the report reveals that the prevalence of asthma attacks, not the frequency, has reached a plateau in recent years and remains at approximately 4%.i Boston Scientific requests that the report be amended to reflect the important difference between frequency and prevalence."	We have changed "frequency" to "prevalence" in the Clinical Background section.
Comment: "In its discussion of randomized controlled trials for bronchial thermoplasty on page 7, the report states that because the outcomes in the Asthma Intervention Research Trial 2 (AIR2 trial) "were evaluated using Bayesian methods rather than traditional statistical tools, the term 'meaningful improvement' must be used instead of the term 'statistically significant.'" This statement is incorrect and calls into question the assessors' interpretation of the study data. The AIR2 publication first mentions the word "meaningful" in the context of a clinically meaningful improvement in the Asthma Quality of Life Questionnaire (AQLQ) scores: "In the ITT population, a larger proportion of subjects in the BT group (79%) compared with the sham group (64%) had a clinically meaningful improvement in AQLQ score of 0.5 or greater (PPS, 99.6%)."	Thank you for the comment. There does not appear to be any real disagreement here. It is correct that the term "statistical significance" should not be used to discuss Bayesian results and the authors pointed this out to the reader who may not be familiar with the differences between inferential and Bayesian methods. We are happy to include the term "posterior probability of superiority" to further increase clarity in interpretation of results, and have since included that terminology on page 7 pf the report.

Comment and Source	Response
In this statement, “meaningful improvement” is used to assess the clinical significance of the outcome, not the statistical (Bayesian or otherwise) significance. That said, the authors of the report are correct in that the term “statistically significant” is in general not used with Bayesian analyses, which offer the probability of some normative statement (e.g. “whether BT improves the AQLQ of a treated subject as compared to a SHAM treated subject”). The output of this type of analysis is a probability distribution (“posterior probability of superiority” or “PPS”) that allows for the likelihood of accepting that statement. In the above case, “PPS, 99.6%” means that there is a 99.6% likelihood that BT patients have a clinically meaningful improvement in AQLQ (i.e. improvement in AQLQ greater than 0.5). Moreover, it should be noted that the principal investigators of the AIR2 trial as well as the FDA accepted a Bayesian approach to the study to allow for information from subject participants in the trial to inform the posterior probability distribution. Bayesian statistical methods are being used increasingly in clinical research because the Bayesian approach is ideally suited to adapting to information that accrues during a trial, potentially allowing for smaller, more informative trials and for patients to receive better treatment. This type of trial is often referred to as an “adaptive clinical trial.” Based on the information provided in these comments, Boston Scientific recommends that the discussion be amended to reflect the following: “because the outcomes in the Asthma Intervention Research Trial 2 (AIR2 trial) were evaluated using Bayesian methods rather than traditional statistical tools, the term ‘posterior probability of superiority’ must be used instead of the term ‘statistically significant’.”	
Comment: “On pages 7 and 37 of the draft assessment, the report misstates the findings regarding the posterior probability of superiority (PPS) for days lost from work, school, or other activities due to asthma. Boston Scientific respectfully requests that the PPS be corrected in both places to reflect “PPS>0.99; PPS=0.993” in order to factually report data published in peer-reviewed literature. ”	Thank you for your comment, although the statement in the Draft Report reads “days lost from work, school, or other activities due to asthma (1.3 versus 3.9 per year; PPS=0.99).” We have now reported the PPS out to the thousandths (PPS=0.993), instead of the hundredths (PPS=0.99), as requested. We have also changed emergency department

Comment and Source	Response
	visits to read "PPS=0.999."
Comment: "On page 7, the report also inaccurately conveys the difference in improvement in AQLQ that was experienced by subjects in the treatment group versus subjects in the control group, stating, "AQLQ scores (mean ± SD) were slightly greater in the bronchial thermoplasty group than the sham group (1.35 ± 1.10 versus 1.16 ± 1.23; PPS=0.96). However, this difference did not reach the planned PPS of 96.4%. Moreover, the degree of improvement in this measure (difference = 0.2) was much smaller than the improvement in the control group (+1.2), which can presumably be attributed to a placebo effect." This discussion reflects a misunderstanding regarding the definition of "meaningful improvement" in quality of life based on the AQLQ. According to the author of this validated instrument for assessing asthma quality of life, "The Asthma Quality of Life Questionnaire (AQLQ) was developed to assess areas of quality of life impairment that are important to adult asthmatic patients. The questionnaire was designed to be responsive to within-subject change (Juniper 1992). The questionnaire was further validated for a within-subject change in score of 0.5 as representing the minimal important difference (MID).The Minimal Important Difference is defined as the smallest change in treatment that a patient considers important and would justify a change in treatment (in the absence of undue side effects and excessive costs). In the AIR2 trial, the proportion of patients in the treatment arm with a clinically meaningfully difference in their AQLQ was significantly more likely (n.b. greater than 99% PPS) to be greater than the proportion observed among sham treatment. (79% percent of bronchial thermoplasty and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (PPS, 99.6%)). This improvement relative to sham suggests it is extremely likely that bronchial thermoplasty provides patients an increased likelihood of a meaningful clinical benefit in asthma patients' quality of life. According to Elizabeth Juniper, MSCP, MSc, the developer of the	Thank you for your comment. Further clarification has been provided to explain the results Changes include the following: "The primary outcome measure of the Castro et al. (2010) study was improvement from baseline in AQLQ scores. Scores (mean ± SD) were greater in the bronchial thermoplasty group than the sham group (1.35 ± 1.10 versus 1.16 ± 1.23; PPS=0.96), but this difference did not reach the PPS planned of 96.4% thereby narrowly failing to meet the study's primary outcome. " "The AQLQ is designed to measure the within-subject change in quality of life over time, and the results demonstrated meaningful improvements (i.e. within-subject change of ≥0.5) in 78.9% of patients in the bronchial thermoplasty group and in 64.3% of subjects in the sham group with a PPS of 0.996. The likelihood of improvement was therefore found to be greater for subjects having undergone bronchial thermoplasty. There was a higher than expected improvement in the sham group which can presumably be attributed to a large placebo effect."

Comment and Source	Response
AQLQ instrument, in a memo discussing the interpretation of AQLQ in the AIR2 trial [Appendix A], "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 benefiting. Thus, in the medical context, the interpretation should be that there is a 96% likelihood that BT provides a population-wide benefit to AQLQ above and beyond any benefit experienced as a mere "placebo effect." Based on the correct definition of clinically meaningful benefit as determined by the AQLQ, Boston Scientific requests that the HCA amend the discussion of the improvement in AQLQ to reflect that there is a 99.6% likelihood that bronchial thermoplasty provides patients a clinically meaningful improvement in their quality of life when compared to sham procedure.	
Comment: "The report also states, on page 8, that "Outcomes at 3 to 5 years follow-up in the thermoplasty group were reported graphically and statistical analyses were not reported." This statement is inaccurate. Follow up out to 5 years was done under a non-inferiority study design with each subsequent year compared to the Year 1 findings with regards to the proportion of subjects experiencing one or more severe exacerbations. In fact, statistical analysis of the data was provided in the publication and summarized as follows: "Compared to the 12 months prior to BT treatment, the average reduction over 5 years in the rate of severe exacerbations was 48%. The upper 95% confidence limit for the difference in percentages for Years 2, 3, 4, and 5 compared to Year 1 (Subsequent Year – Year 1) was 0.5, 11.3, 14.0, and -1.6, respectively. All were less than the pre-defined non-inferiority margin of 20%." Boston Scientific respectfully requests that the author remove the statement that "outcomes at 3 to 5 years follow-up in the thermoplasty group were reported graphically and statistical analyses were not reported," wherever it appears in the technology assessment."	Thank you for your comment. We have removed this statement.
Comment: "In several places in the technology assessment, the report hypothesizes that there is an apparent loss of benefits from bronchial thermoplasty	Thank you for your comment. However, we disagree with Boston Scientific's objection. The evidence clearly shows that in the study

Comment and Source	Response
during longer follow-up, possibly due to the analysis by Zafari et al that assumed a declining effect for bronchial thermoplasty after the fifth year. For example, on page 6 describing the Cox et al. 2007 study, the report states that, "the apparent loss of benefits of thermoplasty during longer follow-up may indicate loss of effectiveness over time and may be an artifact of selective dropping out of control group patients who had the most poorly controlled asthma." Boston Scientific objects to the suggestion that there is a loss of benefits associated with bronchial thermoplasty over time. To date, none of the available literature reports a statistically significant loss of benefit. Moreover, the suggestion that an unproven reduction in benefit over time "may" be due to "selective dropping out of control group patients" is also not documented in any available literature. Thus, the report's statements are based on conjecture and should not be included in an evidence-based technology assessment. Therefore we request that these editorial statements, which are found throughout the report (i.e., pages 6, 20, 24, 39, 44, and 54) and are not based on peer-reviewed published evidence be stricken from the report wherever they are found."	by Cox et al. (2007), at 1-year follow-up, compared with the control group, thermoplasty was associated with statistically significant improvements in mean change in the following measures: mild exacerbations without LABA; mild exacerbations with LABA; AQLQ; ACQ; symptom-free days; symptom scores; rescue bronchodilator use; morning peak expiratory flow. In contrast, at 1-year follow-up, no significant differences were seen between the thermoplasty group and the control group on the following measures: severe exacerbations; airway responsiveness; FEV_1. At 3 years follow-up, although airway responsiveness was significantly improved in the bronchial thermoplasty group compared with the control group, there were no significant differences between the bronchial thermoplasty group and the control group in other respiratory parameters, oral glucocorticoid use, worsening of asthma, emergency department visits, or hospitalizations. The lack of significant differences at 3 years, as opposed to the differences observed at 1-year follow-up, is a loss of benefits. Drawing conclusions from the evidence and interpreting the data is not editorial but rather an important step in the HTA process.
Comment: "On page 13 of the report, the report states, "The reviewed studies did not provide definitions for clinically meaningful changes for any outcome measures other than AQLQ." While factually accurate, the authors of the AIR2 trial believed the clinical meaningfulness of reductions in the outcomes measures in AIR2 other than AQLQ (e.g., reductions in exacerbations, ER visits, hospitalizations, physician office visits, etc.) were self-evident and thus did not require further definition. Boston Scientific therefore requests that the HCA remove this statement from the report, as it is unfairly negative. "	Thank you for your comment. Because this statement is factually accurate, we are retaining it in the Final Report.

Comment and Source	Response
Comment: "On pages 19 and 50 of the assessment, the HCA states that the cost of bronchial thermoplasty is $50,470. This statement is incorrect. In actuality, $50,470 represents the average total cost of treatment over a five year period when some patients are treated with bronchial thermoplasty and some are treated with standard care. Notably, the average total cost of standard care alone over five years is $49,510. Thus, over the five-year period, bronchial thermoplasty increases the total cost of treatment by $960 (considering both device costs and savings associated with reductions in exacerbations), however the procedure is associated with superior quality of life, and the procedure is shown to be cost-saving after approximately 7 years. The cost of bronchial thermoplasty in the Cangelosi et al manuscript cited in the report is $14,100, which is inclusive of both hospital and physician reimbursement for the procedure based on Medicare payment rates in 2015. Boston Scientific requests that the HCA both correct its characterization of the cost of bronchial thermoplasty to reflect $14,100 and characterize the amount of $50,470 as the total cost of treatment including both bronchial thermoplasty and standard of care over a five year period. "	Thank you for your comment. We have modified the statement to clarify that the average cost was over a 5-year period. We also added a sentence to clarify that the difference between the cost for bronchial thermoplasty ($50,470) and standard care ($49,510) is $960.
Comment: "On page 29, the report cites the cost of an inpatient stay with bronchial thermoplasty as ranging from $20,000 to $272,000. While cost ranges are interesting, Boston Scientific requests that the HCA consider mean costs and payments for both inpatient and outpatient stays related to bronchial thermoplasty as a more informative measure of the potential impact of the procedure for Washington State. Moreover, Boston Scientific requests that the HCA also consider the site of service mix for bronchial thermoplasty in Washington to accurately estimate the true economic impact of the procedure. Nationally, the majority of bronchial thermoplasty procedures (~89%) are performed on an outpatient basis, therefore it is very misleading to only report the higher costs associated with inpatient care. An analysis of claims for bronchial thermoplasty in MedPAR 2014 and OPPS 2014 (Medicare claims	Thank you for your comment.

Comment and Source	Response
databases containing inpatient and outpatient claims data) indicates that of a total of 787 claims for bronchial thermoplasty, 89% (697 claims) were for outpatient services. Moreover, the 2014 weighted average mean cost payment for the outpatient claims was approximately $2,098, and the weighted average mean cost payment for the inpatient claims was approximately $13,520."	
Comment: "On page 37, the author also incorrectly reports or interprets several data elements in the AIR2 trial, and we respectfully request that these inaccuracies be corrected. Specifically: The report inaccurately states, "Moreover, the degree of improvement in this measure (difference = 0.2) was much smaller than the improvement in the control group (+1.2), which can presumably be attributed to a placebo effect." This statement is comparing a difference (i.e. improvement in AQLQ among the control group pre-post sham procedure = 1.16) to a difference-in-difference between two groups (improvement in AQLQ among BT subjects = 1.35, thus ~0.2 additional improvement in AQLQ; PPS=96% - i.e a 96% likelihood of bronchial thermoplasty providing a population-wide benefit to quality of life as measured by the AQLQ) is an inappropriate comparison. Note too that this difference-in-difference (i.e. 0.2) has already subtracted the observed 'placebo effect' and thus the language raising the point of a comparison to a measure perhaps characteristic of the 'placebo effect' should be deleted. This difference in benefit of AQLQ is demonstrative of the *population-wide* clinical efficacy of the Bronchial Thermoplasty procedure. We additionally draw attention to a significantly greater percentage of *individual* bronchial thermoplasty subjects compared to sham who showed clinically meaningful improvement in their quality of life, as measured by the AQLQ (79% percent of bronchial thermoplasty and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (PPS, 99.6%)). Moreover, we draw attention to the quote from Elizabeth Juniper, MSCP, MSc, the developer of the AQLQ instrument, in a memo discussing the	Thank you for your comment. We have amended the report to reflect the fact that the sham group experienced a higher than anticipated mean improvement in AQLQ (0.5 anticipated versus 1.16 observed) likely due, as noted by the authors, to higher than expected placebo effect for patients undergoing the sham procedure. Please note that the Draft Report does state that "Significantly more patients in the bronchial thermoplasty group showed a clinically meaningful improvement of 0.5 or greater in AQLQ scores compared with the sham group (78.9% versus 64.3%; PPS=0.996)."

Comment and Source	Response
interpretation of AQLQ in the AIR2 trial [Appendix A], (n.b. emphasis added) "Thus, in the medical context, the interpretation should be that there is a 96% likelihood that BT provides a population-wide benefit to AQLQ above and beyond any benefit experienced as a mere "placebo effect." Boston Scientific respectfully requests that the report be amended in this interpretation to note the likelihood of Bronchial Thermoplasty to generate a population-wide benefit to AQLQ (PPS=96%), using patient selection aligned with the inclusion and exclusion criteria of the AIR2 trial, as well as the likelihood – using these same patient selection criteria – of an individual clinically-meaningful benefit in AQLQ (79% for BT vs. 64% for Sham; PPS=99.6%)."	
Comment: "The report states that "An additional year of uncontrolled follow-up for 166 thermoplasty group patients (87%) evaluated with traditional statistical tools showed no statistically significant differences within this group…" A more accurate approach to discussing the results would be to state that the data showed no statistically significant increase or decrease, as this would lead to the correct interpretation of this statistical indifference as meaning that the treatment effect of BT observed at 1 year would continue out to at least 2 years and is therefore durable and long-lasting. "	We have changed "differences" to "increases or decreases."
Comment: "In two areas (Pages 9 and 39) of the assessment, the report cites patient withdrawals from the AIR2 trial as a study limitation, however the author does not provide the context that the 12% of patients withdrawing from the study before undergoing bronchial thermoplasty represents two patients who were assessed as not being candidates for the procedure. Boston Scientific requests that the HCA either remove these statements or add the context that the 12% of patients withdrawing from the study prior to having bronchial thermoplasty was actually two patients who were not candidates for the procedure. "	We have added context stating the reasons for withdrawal from the study prior to the first bronchial thermoplasty procedure.

Comment and Source	Response
Comment: "On page 45, the report states that "The rate of hospitalization appeared to be higher in studies that enrolled patients with more severe asthma." The report only provides two data points, both of which may be considered outside current labeling: (1) a study (Cox et al 2006) of subjects with stable mild to moderate asthma (n.b. per FDA labeling, *"Bronchial Thermoplasty System 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."*) and (2) a study of subjects with severe asthma with obstructed airflow (FEV1<50%) (Doeing et al., 2013) (n.b. per FDA labeling *"WARNINGS AND PRECAUTIONS Caution should be taken in patients with the following conditions due to a potential increased risk of adverse events that may be associated with the procedure…Post-bronchodilator FEV1 < 65% predicted."*) It is not clear whether the authors' statement is based on a statistical analysis of the relationship between severity of asthma and the rate of hospitalizations – or, if such an analysis was conducted, whether their hypothesis was statistically significant. Moreover, the data used for the evaluation of this relationship is drawn from bronchial thermoplasty usage outside current FDA labeling. Given the lack of statistical evidence of a relationship between severity of asthma and the rate of peri-procedural hospitalizations and data for this relationship exclusively drawn from usage outside FDA labeling, Boston Scientific requests that this statement be removed from the assessment wherever it appears or, at the very least, state that the hospitalizations in these studies occurred in patients outside of the technology's current FDA labeling."	Although bronchial thermoplasty has only been approved by the FDA for severe asthma, 1 of the 3 randomized controlled trials (RCTs) and 1 of 4 nonrandomized studies assessed in the current report included patients with moderate or severe asthma. As noted in the methods section, study inclusion was not limited to studies assessing use of bronchial thermoplasty in severe asthma. The rate of hospitalization in thermoplasty patients among the nonrandomized studies ranged from 0% to 62.5%. The rate of hospitalization appeared to be higher in studies that enrolled patients with more severe asthma. This observation was based on an observed pattern of hospitalizations and severity of asthma among the reviewed studies. To offer a more complete overview of this pattern, we have added in the following sentences: "The percentage of patients hospitalized ranged from 0% to 5.5% in studies that included patients with mild and/or moderate asthma. The percentage of patients hospitalized ranged from 5% to 62.5% in studies that included patients with only severe asthma."
Comment: "In its discussion of results from the Research In Severe Asthma (RISA) trial (Pavord et al, 2013), the HCA report provides some, but not all, critical data points, potentially biasing the assessment. Specifically, there is no discussion of patient satisfaction with the procedure and willingness to undergo the procedure again or to recommend the procedure to family members. In the publication of the RISA data, Pavord et	No changes made. Patient satisfaction was not included, as it was not one of the outcome measures of interest outlined in the PICO statement.

Comment and Source	Response
al report that, *"Eleven of the 12 patients who completed the 5-year follow-up provided responses to the questions regarding satisfaction with the procedure, with an overwhelming satisfaction with the procedure 5 years after treatment. In response to the question, "Would you undergo the bronchial thermoplasty procedure if you had to do it all over again?" 10 responses were "definitely yes" and one response was "probably yes." When asked, "Would you recommend this treatment to a friend or family member?" 9 responses were "definitely yes" and 2 responses were "probably yes."* Boston Scientific requests that the results of patient satisfaction with the procedure be included in the discussion of the RISA five-year results to present a comprehensive view of the outcomes of that study."	
Comment: "In the body of the assessment, an overall answer to the question of whether bronchial thermoplasty is cost-effective is not provided, however in the Executive Summary the report states that the overall body of evidence regarding cost-effectiveness is moderate in quality. Boston Scientific requests that the body of the report be amended to be consistent with the Executive Summary and to reflect the finding in multiple analyses that the procedure is cost-effective. "	No changes have been made because we believe that the body of the report is in line with the information provided in the Executive Summary. The introductory paragraph for the Cost-Effectiveness section states "The literature search identified 3 cost-effectiveness assessments for bronchial thermoplasty for asthma...In these studies, although bronchial thermoplasty increased costs in the short term, it was found to increase quality-adjusted life-years (QALYs) in the longer term."
Comment: "In its discussion of the complications associated with bronchial thermoplasty, on page 54, the report states that "**all** of the reviewed studies reported an increased need for hospitalization during the treatment period." In actuality, only one RCT found that there was a statistically significant difference in the need for hospitalization during the treatment period between the control and treatment groups. Boston Scientific respectfully requests that the HCA correct this statement to reflect that "**one** of the reviewed studies reported a statistically significant increase in the need for hospitalization during the treatment period." "	Thank you for your comment. We have modified this sentence.
Comment: "In its discussion of systematic reviews of bronchial thermoplasty, the report does not appropriately recognize the statistically significant finding of a decrease in the incidence of respiratory	No changes have been made because the report already states the statistically significant decrease in the incidence of respiratory adverse events from years 1 to 5

Comment and Source	Response
adverse events from years 1 to 5 (P<0.00001). This finding is extremely significant, and Boston Scientific requests that it be noted as such in the report."	as follows: "Zhou et al. (2015) conducted a meta-analysis on the long-term safety and effectiveness data from the 3 RCTs analyzed in this report…There was a statistically significant decrease in the incidence of respiratory adverse events from years 1 to 5 (relative risk [RR], 3.4; 95% CI, 3.0 to 3.9; *P*<0.00001)."
Comment: "On page 6 of the technology assessment, the report states that, "All of the RCTs were supported by the device manufacturer and performed in part by investigators who had financial relationships with the device manufacturer." While this statement is correct, Boston Scientific objects to its inclusion in this technology assessment as irrelevant and inflammatory, and we request that the HCA remove the statement from the final report. Industry-sponsored research is a cornerstone of medical research today and is ubiquitous for all novel drugs, diagnostics and medical devices. The cost of conducting clinical research on technologies not yet approved by the FDA would be prohibitive if not largely borne by the manufacturers of those technologies, and it would be extremely difficult to find investigators to conduct research if they were not compensated for their time and resources. Moreover, clinical trial designs control for the potential for bias through multicenter protocols, randomization and other accepted clinical research methods."	Thank you for your comment. We have added additional text to the report to make it clear that although the studies were industry-sponsored, this does not automatically introduce bias, and did not affect assessment of the quality of the evidence. "All of the RCTs were supported by the device manufacturer and performed, in part, by investigators who had financial relationships with the device manufacturer (Cox et al., 2007; Pavord et al., 2007; Castro et al., 2010). Industry-supported funding of clinical trials does not introduce automatic bias into the results of the study, and was not considered a limitation when evaluating the quality of the evidence; however, this information may be of interest to the reader."
Comment: "The report on bronchial thermoplasty rates the quality of evidence based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. While GRADE is widely used methodology for assessing the quality of evidence, a recent publication has described limitations of the methodology. According to Gartlehner et al, *"GRADE uses information about risk of bias, imprecision, inconsistency, indirectness, and reporting bias to categorize the degree of uncertainty concerning the correctness of findings into four grades of quality of evidence (QOE)…Decision makers who rely on the GRADE approach assume that estimates of effect that are graded as high QOE are 'close to the true effect' and, therefore, will remain*	Thank you for your comments. Hayes is aligned with GRADE as well as other internationally recognized quality assessment tools including those of the Agency for Healthcare Research and Quality (AHRQ) and the Cochrane Collaboration. As outlined in Appendix II of the Draft Report, Hayes uses internal quality assessment checklists for rating both individual studies and overall bodies of evidence. Individual studies are appraised by taking into account study design, execution, and analysis using the Hayes checklist. Each individual study is rated as very poor, poor, fair, or good. The aim of individual study appraisal is to assess the risk of bias and to determine if the study findings are valid.

Comment and Source	Response
stable as new evidence emerges. By contrast, decision makers can interpret effect estimates that are graded as low QOE as quite likely to change as new evidence accrues. In a recent international survey, [Gartlehner et al] determined that producers and users of systematic reviews associated each grade of QOE with a distinct likelihood that estimates of effect will remain stable as new evidence emerges." Based on these findings, it is important that the quality of evidence be appropriately characterized, as its characterization as high, moderate or low can have a lasting impact on the acceptance and adoption of new technologies and procedures. Gartlehner et al also state, *"To be considered useful in practice, any tool that conveys certainties and uncertainties of estimates of effect should have a high ability to discriminate between estimates that will remain stable in the future and those that will substantially change; it should also be able to associate respective likelihoods of stability with an expected outcome. Our research indicates that the EPC approach to GRADE only partly fulfilled these qualities of predictive validity."* The authors concluded that the way systematic reviewers operationalize GRADE appears to be too strict: *"More than half of estimates graded as insufficient (very low) (defined as ''we have no confidence in the estimate of effect for this outcome'') remained stable; this indicates that the approach too often leads to low or insufficient (very low) grades of QOE. Possible reasons could be: (a) systematic reviewers use GRADE too mechanistically, (b) recommended thresholds for downgrading in guidance documents are too strict, or (c) a tool with four levels of QOE is not granular enough to categorize uncertainty."* While at this point, Boston Scientific would not propose use of a completely different method of assessing data, we do ask that the authors reconsider their classification of the quality of bronchial thermoplasty evidence and its characterization of its concern regarding the safety and efficacy of the procedure. The rationale for our request follows: a. Despite the report's assertion that the quality of evidence for bronchial thermoplasty is poor, in the Evidence Tables in Appendix IV, all of the randomized	The overall body of evidence for each outcome is subsequently assessed taking into account applicability of the outcome measures to the PICO statement (populations, interventions, comparators, health outcomes of interest); quantity of data available (number of studies and sample sizes); precision of the data (the degree of certainty around the effect estimate); consistency of results across studies; and any evidence of publication bias. Bodies of evidence are graded as very low, low, moderate, or high. A high-quality body of evidence indicates that there is reliable consistent evidence reflecting the true treatment effect, and the findings are unlikely to change with future studies. A moderate-quality body of evidence indicates that there is reasonable confidence that the results represent the true direction of effect; however, it is possible that the effect estimate might change with future studies. A low-quality body of evidence indicates that there is little confidence in the direction of the effect due to poor-quality studies, inconsistent results, or paucity of studies; and future studies are likely to change the effect estimates and possibly the direction of the effect. A very-low-quality body of evidence indicates that there is no confidence in any result found due to the paucity of data; we cannot make a statement on the findings. Based on the above criteria, the overall quality of the body of evidence for the effectiveness and safety of bronchial thermoplasty for treating asthma was considered to be of low quality reflecting the balance of benefits and harms. This assessment is based on the best available evidence at the present time.

Comment and Source	Response
controlled studies were characterized as being of "fair" or "good" quality. Boston Scientific therefore respectfully requests that the report's overall conclusion regarding the quality of evidence for bronchial thermoplasty be amended to "moderate" or "fair" to be consistent with the findings in the Evidence Tables."	
Comment: "b. Based on the volume of studies of bronchial thermoplasty and the consistency of findings of both safety and durable effectiveness across these studies, Boston Scientific believes that the body of evidence should be characterized as "Moderate" rather than "Poor." Gartlehner et al found that only evidence graded as having Moderate quality was found to have satisfactory predictive validity. We believe that the consistency of outcomes across bronchial thermoplasty trials is strong evidence of the stability of predicted results, and therefore the evidence quality should be rated "Moderate.""	No changes have been made. Please see the previous response.
Comment: "c. It is not appropriate to rate non-randomized, non-controlled studies using the same standards applied to evidence from randomized controlled studies. These studies should either not be rated, or they should be rated in the context of other non-randomized, non-controlled studies. Boston Scientific therefore requests that the HCA amend the ratings in Appendix IVb to pertain to non-randomized, non-controlled studies."	No changes have been made. Hayes methodology is in alignment with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, which was developed by the GRADE Working Group, an international collaborative body and is also aligned with other internationally recognized bodies.
Comment: "d. In its discussion of the quality of the evidence, the author states that "The evidence for the safety of bronchial thermoplasty for treating asthma was considered to be of low quality because of the small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long term safety of bronchial thermoplasty." Boston Scientific disagrees with this characterization and requests that the HCA reclassify the quality of safety evidence as "Moderate." The author appears to be applying clinical research standards appropriate for pharmacologic therapies to a device-based treatment. In reality, the sample size and quantity of RCTs for bronchial thermoplasty represents the most significant body of evidence among available bronchoscopic therapies. The FDA found the evidence to be sufficient to approve the technology through its most rigorous review process (the Pre-Market Approval, or	No changes have been made. We disagree that the grading of evidence is inaccurate. The overall body of evidence concerning bronchial thermoplasty for treatment of asthma was small in size and low in quality. The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3 very-poor-quality case series. The evidence for the effectiveness of bronchial thermoplasty for treating asthma was considered to be of low quality because of some positive but inconsistent results regarding short-term benefits of bronchial thermoplasty, varied patient selection criteria across studies, small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long-term efficacy of bronchial

Comment and Source	Response
PMA process), and both clinical guidelines and other technology assessments (i.e., CTAF) have found the evidence to be sufficient to recommend bronchial thermoplasty as a treatment option for patients with severe, poorly controlled asthma."	thermoplasty. Future well-designed studies may help to increase the quality of the body of evidence and to better answer the Key Questions posed in this report: RCTs and long-term cohort studies of sufficient size, design, and length to further investigate the safety and efficacy of bronchial thermoplasty in patients with severe asthma (e.g., controlled long-term safety and effectiveness data); studies designed to systematically investigate differential effectiveness and safety according to patient characteristics (e.g., severity of asthma, baseline respiratory function and medication needs, and previous treatment history); additional studies investigating the impact of bronchial thermoplasty on quality of life and functional status.
Comment: "e. In several instances in the report, the author expresses a "high" level of concern regarding safety and efficacy of bronchial thermoplasty. Yet in its discussion of the evidence itself, the report acknowledges that the complications associated with bronchial thermoplasty were mild or moderate in severity and that outcomes were maintained out to five years. Therefore, the high level of concern expressed by the author, particularly in light of the limitations of the GRADE approach in predicting stability of outcomes, is inconsistent with the evidence. The report should provide *a priori* a basis for the concerns stated. Only in this context can ongoing and future research provide information to address these concerns by directly addressing the gaps or perceived inadequacies of the evidence, which forms the basis for these concerns. Additionally, Boston Scientific would argue that the posterior concern(s) (i.e. after evaluating the evidence base) associated with bronchial thermoplasty must be evaluated in the context of those treatment options provided in absence of bronchial thermoplasty. Many of these treatment options are associated with high concerns regarding safety (e.g. oral corticosteroids), high concerns regarding efficacy (oral corticosteroids	Thank you for your comments. We agree that additional studies of high quality that are designed to directly compare bronchial thermoplasty with other active treatments would be highly informative and may strengthen the body of evidence. However, our rigorous assessment of the body of evidence determined that the current body of evidence evaluating thermoplasty for treatment of asthma was small in size and low in quality. The body of evidence comprised 1 good-quality RCT, 2 fair-quality RCTs, 1 very-poor-quality retrospective cohort study, and 3 very-poor-quality case series. Additional well-designed studies would greatly enhance the confidence of the direction and consistency of the treatment effect.

Comment and Source	Response
and a non-100% response rate for many monoclonal antibody treatment options) and high concerns of cost (omalizumab and mepolizumab). Even in the absence of these treatment options, the authors' concerns relating to bronchial thermoplasty should be evaluated against the concerns associated with the unavailability of adequate treatment alternatives, as the patient population considered for bronchial thermoplasty includes those who have severe, uncontrolled asthma, which by definition is inadequately treated. Finally, follow-up of bronchial thermoplasty treated patients out to at least 5 years has not provided cause for high concern for safety. Boston Scientific therefore requests that the HCA characterize the level of concern regarding safety and effectiveness to be "moderate," in keeping with both the way the report describes the risks of the procedure and its durable outcomes, and also the risks and inadequate benefits associated with other treatment alternatives for patients with severe, uncontrolled asthma. "	
Comment: "Boston Scientific appreciates the author's efforts to be comprehensive in its discussion of guidelines discussing bronchial thermoplasty and insurance coverage policies for the procedure. However, there were several important guidelines, statements of support from professional specialty societies or recognized asthma authorities, and positive coverage policies that were inadvertently not captured in the author's review. Boston Scientific requests that the report be amended as follows to more accurately reflect the current state of guidelines, statements of support and insurance coverage for bronchial thermoplasty: a. Both the discussion of guidelines in the body of the report as well as the list of guidelines provided in Appendix V, "Summary of Practice Guidelines," should be amended to include: i. The INTERASMA manifesto on bronchial thermoplasty (http://www.interasma.org/images/manifesto3.pdf);	Thank you for your comments. We have reviewed the brief statements by INTERASMA and ACAAI. Because these are brief statements that do not provide citations, methodology used by the committee, and other important details, we do not consider these to be practice guidelines. The University of Wisconsin (UW) Medical Foundation clinical practice guideline is a regional endorsement of recommendations of the 2015 GINA guideline, which is included in our assessment of guidelines. At the direction of Washington State HCA, the coverage policies for the following organizations were reviewed: Aetna, CMS, Oregon Health Evidence Review Commission (HERC), GroupHealth, and Regence Blue Cross/Blue Shield.

Comment and Source	Response
ii. The statement on bronchial thermoplasty by the American College of Allergy, Asthma, and Immunology (http://college.acaai.org/publications/advocacy-insider/statement-bronchial-thermoplasty); and iii. The Diagnosis and Management of Asthma – Pediatric/Adult – Inpatient/Ambulatory Clinical Practice Guideline, developed by a task force of representatives from the University of Wisconsin (UW) Medical Foundation, UW Hospital and Clinics, UW Health Department of Family Medicine and Internal Medicine, Unity Health Insurance, Physicians Plus Insurance Corporation, and Group Health Cooperative (2015)(Attached as Appendix B). b. Although the author is correct that some commercial insurers have published non-coverage policies for bronchial thermoplasty, there are several large insurers that do cover the procedure (please refer to Appendix C). These positive coverage policies should be represented discussed in the technology assessment to assure factual accuracy and non-biased consideration.	
Comment: "References to the Cost of Novocure Device on page 50 of the assessment are unrelated to the bronchial thermoplasty procedure and should be removed from the report."	Thank you for your comment. We have corrected this typographical error. The section heading now reads "Cost of Bronchial Thermoplasty Procedure."
Comment: "To summarize our comments, Boston Scientific appreciates the thorough approach to the assessment of bronchial thermoplasty and respectfully requests that the HCA address the various inaccuracies and inconsistencies that are described in the body of this comment letter. Thank you in advance for your consideration of our response to the Washington State Health Care Authority's Draft Evidence Report on bronchial thermoplasty. We look forward to the April 15, 2016 publication of the final report and to the public coverage discussion by the Health Technology Clinical Committee on May 20, 2016. Please do not hesitate to contact me should you have any questions or need clarification."	Thank you for your comment.

Comment and Source	Response
March 18, 2015 e-mail from Navdeep S. Rai, M.D., FACP, FCCP (Pulmonary/Critical Care Physician, Tacoma, WA)	
Comment: "Having read your draft report, I feel compelled to write about my prospective on bronchial thermoplasty. This is not something I have ever done before. I am a board certified pulmonary/critical care physician practicing in Tacoma, WA since 2001. I have performed BT on approximately 15 patients. Every one of my patients has benefitted from the procedure. Some have had a few days for worsening asthma symptoms after the procedure. This to be expected after the airway is stimulated, much in the same way a patient would experience pain and swelling from a surgical procedure. One was hospitalized for 2 days following the treatment. My patients have had greatly improved quality of life. The number of exacerbations have been reduced. I do not have financial data, but with the reduced exacerbations come decreased ER visits and hospitalizations, which I can not help but think if financially beneficial as well. In reading your summary statements, you raise concerns that are disproportionate with the published data and clinical experience. Your draft, to my reading, seems lukewarm to this technology. BT is now part of the recommended treatments of several guidelines, including one most often used by US physicians, the Global Initiative on Asthma. It is endorsed by multiple organizations, including the American College of Chest Physicians, British Thoracic Society, and the American College of Allergy, Asthma, and Immunology. The patients who need this procedure have exhausted all treatment options through step 6 for the treatment of severe persistent asthma. BT can serve to improve the quality of life and reduce the financial and social burden of this disease for such patients. I would urge you to support the implementation of the procedure in Washington."	Thank you for your comment.

Comment and Source	Response
March 17, 2015 e-mail from Seth Hartung, M.D., Ph.D. (Pulmonary and Critical Care Medicine, Western Washington Medical Group and Providence Everett Hospital, Everett, WA)	
Comment: "I am writing this short statement in support of bronchial thermoplasty as a tested procedure for the treatment of severe refractory asthma, particularly for its potential value in treating patients who have failed all other therapies. As you know, to date it has been found to be safe and effective in reducing prednisone use, potentially effective in reducing hospitalization utilization and potentially effective in improving quality of life in these patients with severe airways disease. Please consider this utmost request that bronchial thermoplasty remain a viable option for patients that have failed all other approved treatments for asthma."	Thank you for your comment.

Corporate Headquarters
100 Boston Scientific Way
Marlborough, MA 01752

March 18, 2016

SUBMITTED ELECTRONICALLY

Josh Morse, MPH
Program Director
Washington State Healthcare Authority
Health Technology Assessment Program
P.O. Box 42712
Olympia, WA 98504-2712

Re: Comments on Washington State Health Care Authority (HCA) Draft Evidence Report on Bronchial Thermoplasty

Dear Mr. Morse:

Boston Scientific Corporation appreciates the opportunity to provide comments to the Draft Evidence Report on Bronchial Thermoplasty published by the Washington State Health Care Authority (HCA).

Bronchial thermoplasty is an innovative procedure 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 beta2-agonists. Treatment with bronchial thermoplasty has been shown to significantly reduce healthcare utilization, presenting an opportunity to improve patient outcomes and quality of life while reducing overall health care costs. Bronchial thermoplasty has been shown to be a safe, effective, and long-lasting treatment option for a well-defined population of adults.

Boston Scientific applauds the thorough assessment of the peer-reviewed literature regarding the safety, effectiveness and durability of the bronchial thermoplasty procedure within the Draft Evidence Report. We appreciate the HCA's consideration of previous comments submitted on November 3, 2015 in response to the draft Key Questions posed as part of this assessment.

The comments contained in this letter are intended to address several areas in which Boston Scientific believes the interpretation of the literature to be inaccurate or incomplete. Specifically, our comments will address elements in the following categories:

1. Inaccuracies in statements regarding the evidence upon which FDA approval of the Alair™ Bronchial Thermoplasty System was based;
2. Interpretation and representation of clinical trial data;

3. Use of the GRADE methodology to assess the quality of evidence for bronchial thermoplasty;
4. Discussion of evidence to address the "high" level of concern expressed by the requestor of the assessment ;
5. Current status of guidelines and insurance coverage for bronchial thermoplasty; and
6. Typographical errors.

Discussion

1. Studies Considered in the FDA Review Process

The Draft Evidence Report inaccurately states in at least four places (pages 6, 23, 36 and 53) that FDA approval of the Alair™ Bronchial Thermoplasty System was based on a single, double-blind sham-controlled RCT (AIR2). Such statements reflect a fundamental lack of understanding of the US regulatory process. While the AIR2 trial was the pivotal trial associated with the FDA's approval of the Alair System, multiple studies conducted at different times and with varied patient populations showed directionally consistent improvements and were assessed by the FDA as an indicator of a treatment effect. Moreover, bronchial thermoplasty was assessed via the PMA process, which is the most rigorous approval pathway for medical devices in the United States.

Boston Scientific requests that the HCA remove the statement that FDA approval of the Alair Bronchial Thermoplasty System was based on a single, double-blind sham-controlled RCT wherever the statement appears in the report and clarify that multiple RCTs were considered in the FDA's assessment of the procedure's safety and effectiveness.

2. Interpretation and Representation of Clinical Trial Data

In general, the author's assessment of the literature regarding bronchial thermoplasty was comprehensive, however there are a number of instances in which Boston Scientific found inaccuracies or misinterpretations of data. Each of those areas is described in more detail in the following paragraphs:

a. In the Executive Summary, on page 1, the report states, "The prevalence of asthma has increased over the past 30 to 40 years and was at 8.2% in 2009; however for the U.S. population as a whole, the frequency of asthma attacks has reached a plateau in recent years and remains at approximately 4%." The report appears to be mixing two different concepts: the prevalence of asthma and the frequency of asthma attacks.

   A review of the source for these data cited in the report reveals that the prevalence of asthma attacks, not the frequency, has reached a plateau in recent years and remains at approximately 4%.[i]

   Boston Scientific requests that the report be amended to reflect the important

difference between frequency and prevalence.

b. In its discussion of randomized controlled trials for bronchial thermoplasty on page 7, the report states that because the outcomes in the Asthma Intervention Research Trial 2 (AIR2 trial) "were evaluated using Bayesian methods rather than traditional statistical tools, the term 'meaningful improvement' must be used instead of the term 'statistically significant.'" This statement is incorrect and calls into question the assessors' interpretation of the study data.

   The AIR2 publication first mentions the word "meaningful" in the context of a clinically meaningful improvement in the Asthma Quality of Life Questionnaire (AQLQ) scores: "In the ITT population, a larger proportion of subjects in the BT group (79%) compared with the sham group (64%) had a clinically meaningful improvement in AQLQ score of 0.5 or greater (PPS, 99.6%)."[ii]

   In this statement, "meaningful improvement" is used to assess the clinical significance of the outcome, not the statistical (Bayesian or otherwise) significance. That said, the authors of the report are correct in that the term "statistically significant" is in general not used with Bayesian analyses, which offer the probability of some normative statement (e.g. "whether BT improves the AQLQ of a treated subject as compared to a SHAM treated subject"). The output of this type of analysis is a probability distribution ("posterior probability of superiority" or "PPS") that allows for the likelihood of accepting that statement. In the above case, "PPS, 99.6%" means that there is a 99.6% likelihood that BT patients have a clinically meaningful improvement in AQLQ (i.e. improvement in AQLQ greater than 0.5).

   Moreover, it should be noted that the principal investigators of the AIR2 trial as well as the FDA accepted a Bayesian approach to the study to allow for information from subject participants in the trial to inform the posterior probability distribution. Bayesian statistical methods are being used increasingly in clinical research because the Bayesian approach is ideally suited to adapting to information that accrues during a trial, potentially allowing for smaller, more informative trials and for patients to receive better treatment.[iii] This type of trial is often referred to as an "adaptive clinical trial."

   Based on the information provided in these comments, Boston Scientific recommends that the discussion be amended to reflect the following: "because the outcomes in the Asthma Intervention Research Trial 2 (AIR2 trial) were evaluated using Bayesian methods rather than traditional statistical tools, the term 'posterior probability of superiority' must be used instead of the term 'statistically significant'."

c. On pages 7 and 37 of the draft assessment, the report misstates the findings regarding the posterior probability of superiority (PPS) for days lost from

work, school, or other activities due to asthma.

Boston Scientific respectfully requests that the PPS be corrected in both places to reflect "PPS>0.99; PPS=0.993" in order to factually report data published in peer-reviewed literature.

d. On page 7, the report also inaccurately conveys the difference in improvement in AQLQ that was experienced by subjects in the treatment group versus subjects in the control group, stating, "AQLQ scores (mean ± SD) were slightly greater in the bronchial thermoplasty group than the sham group (1.35 ± 1.10 versus 1.16 ± 1.23; PPS=0.96). However, this difference did not reach the planned PPS of 96.4%. Moreover, the degree of improvement in this measure (difference = 0.2) was much smaller than the improvement in the control group (+1.2), which can presumably be attributed to a placebo effect."

   This discussion reflects a misunderstanding regarding the definition of "meaningful improvement" in quality of life based on the AQLQ. According to the author of this validated instrument for assessing asthma quality of life,

   "The Asthma Quality of Life Questionnaire (AQLQ) was developed to assess areas of quality of life impairment that are important to adult asthmatic patients. The questionnaire was designed to be responsive to within-subject change (Juniper 1992). The questionnaire was further validated for a within-subject change in score of 0.5 as representing the minimal important difference (MID).[iv] *The Minimal Important Difference is defined as the smallest change in treatment that a patient considers important and would justify a change in treatment (in the absence of undue side effects and excessive costs)."*[v]

   In the AIR2 trial, the proportion of patients in the treatment arm with a clinically meaningfully difference in their AQLQ was significantly more likely (n.b. greater than 99% PPS) to be greater than the proportion observed among sham treatment. (79% percent of bronchial thermoplasty and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (PPS, 99.6%)).

   This improvement relative to sham suggests it is extremely likely that bronchial thermoplasty provides patients an increased likelihood of a meaningful clinical benefit in asthma patients' quality of life.

   According to Elizabeth Juniper, MSCP, MSc, the developer of the AQLQ instrument, in a memo discussing the interpretation of AQLQ in the AIR2 trial [Appendix A],

   "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 benefiting

from the treatment) as compared to optimal standard of care."[vi] *Thus, in the medical context, the interpretation should be that there is a 96% likelihood that BT provides a population-wide benefit to AQLQ above and beyond any benefit experienced as a mere "placebo effect."*

Based on the correct definition of clinically meaningful benefit as determined by the AQLQ, Boston Scientific requests that the HCA amend the discussion of the improvement in AQLQ to reflect that there is a 99.6% likelihood that bronchial thermoplasty provides patients a clinically meaningful improvement in their quality of life when compared to sham procedure.

e. The report also states, on page 8, that "Outcomes at 3 to 5 years follow-up in the thermoplasty group were reported graphically and statistical analyses were not reported." This statement is inaccurate. Follow up out to 5 years was done under a non-inferiority study design with each subsequent year compared to the Year 1 findings with regards to the proportion of subjects experiencing one or more severe exacerbations. In fact, statistical analysis of the data was provided in the publication and summarized as follows:

"Compared to the 12 months prior to BT treatment, the average reduction over 5 years in the rate of severe exacerbations was 48%. The upper 95% confidence limit for the difference in percentages for Years 2, 3, 4, and 5 compared to Year 1 (Subsequent Year – Year 1) was 0.5, 11.3, 14.0, and -1.6, respectively. All were less than the pre-defined non-inferiority margin of 20%."[vii]

Boston Scientific respectfully requests that the author remove the statement that "outcomes at 3 to 5 years follow-up in the thermoplasty group were reported graphically and statistical analyses were not reported," wherever it appears in the technology assessment.

f. In several places in the technology assessment, the report hypothesizes that there is an apparent loss of benefits from bronchial thermoplasty during longer follow-up, possibly due to the analysis by Zafari et al that assumed a declining effect for bronchial thermoplasty after the fifth year. For example, on page 6 describing the Cox et al. 2007 study, the report states that, "the apparent loss of benefits of thermoplasty during longer follow-up may indicate loss of effectiveness over time and may be an artifact of selective dropping out of control group patients who had the most poorly controlled asthma."

Boston Scientific objects to the suggestion that there is a loss of benefits associated with bronchial thermoplasty over time. To date, none of the available literature reports a statistically significant loss of benefit. Moreover, the suggestion that an unproven reduction in benefit over time "may" be due to "selective dropping out of control group patients" is also not documented in any available literature. Thus, the report's statements are based on conjecture

and should not be included in an evidence-based technology assessment.

Therefore we request that these editorial statements, which are found throughout the report (i.e., pages 6, 20, 24, 39, 44, and 54) and are not based on peer-reviewed published evidence be stricken from the report wherever they are found.

g. On page 13 of the report, the report states, "The reviewed studies did not provide definitions for clinically meaningful changes for any outcome measures other than AQLQ." While factually accurate, the authors of the AIR2 trial believed the clinical meaningfulness of reductions in the outcomes measures in AIR2 other than AQLQ (e.g., reductions in exacerbations, ER visits, hospitalizations, physician office visits, etc.) were self-evident and thus did not require further definition.

   Boston Scientific therefore requests that the HCA remove this statement from the report, as it is unfairly negative.

h. On pages 19 and 50 of the assessment, the HCA states that the cost of bronchial thermoplasty is $50,470. This statement is incorrect. In actuality, $50,470 represents the average total cost of treatment over a five year period when some patients are treated with bronchial thermoplasty and some are treated with standard care. Notably, the average total cost of standard care alone over five years is $49,510. Thus, over the five-year period, bronchial thermoplasty increases the total cost of treatment by $960 (considering both device costs and savings associated with reductions in exacerbations), however the procedure is associated with superior quality of life, and the procedure is shown to be cost-saving after approximately 7 years.[viii]

   The cost of bronchial thermoplasty in the Cangelosi et al manuscript cited in the report is $14,100, which is inclusive of both hospital and physician reimbursement for the procedure based on Medicare payment rates in 2015.

   Boston Scientific requests that the HCA both correct its characterization of the cost of bronchial thermoplasty to reflect $14,100 and characterize the amount of $50,470 as the total cost of treatment including both bronchial thermoplasty and standard of care over a five year period.

i. On page 29, the report cites the cost of an inpatient stay with bronchial thermoplasty as ranging from $20,000 to $272,000. While cost ranges are interesting, Boston Scientific requests that the HCA consider mean costs and payments for both inpatient and outpatient stays related to bronchial thermoplasty as a more informative measure of the potential impact of the procedure for Washington State.

   Moreover, Boston Scientific requests that the HCA also consider the site of

service mix for bronchial thermoplasty in Washington to accurately estimate the true economic impact of the procedure. Nationally, the majority of bronchial thermoplasty procedures (~89%) are performed on an outpatient basis, therefore it is very misleading to only report the higher costs associated with inpatient care.

An analysis of claims for bronchial thermoplasty in MedPAR 2014 and OPPS 2014 (Medicare claims databases containing inpatient and outpatient claims data) indicates that of a total of 787 claims for bronchial thermoplasty, 89% (697 claims) were for outpatient services. Moreover, the 2014 weighted average mean cost payment for the outpatient claims was approximately $2,098, and the weighted average mean cost payment for the inpatient claims was approximately $13,520.[ix]

j. On page 37, the author also incorrectly reports or interprets several data elements in the AIR2 trial, and we respectfully request that these inaccuracies be corrected. Specifically:

   i. The report inaccurately states, "Moreover, the degree of improvement in this measure (difference = 0.2) was much smaller than the improvement in the control group (+1.2), which can presumably be attributed to a placebo effect." This statement is comparing a difference (i.e. improvement in AQLQ among the control group pre-post sham procedure = 1.16) to a difference-in-difference between two groups (improvement in AQLQ among BT subjects = 1.35, thus ~0.2 additional improvement in AQLQ; PPS=96% - i.e a 96% likelihood of bronchial thermoplasty providing a population-wide benefit to quality of life as measured by the AQLQ) is an inappropriate comparison. Note too that this difference-in-difference (i.e. 0.2) has already subtracted the observed 'placebo effect' and thus the language raising the point of a comparison to a measure perhaps characteristic of the 'placebo effect' should be deleted.

      This difference in benefit of AQLQ is demonstrative of the *population-wide* clinical efficacy of the Bronchial Thermoplasty procedure. We additionally draw attention to a significantly greater percentage of *individual* bronchial thermoplasty subjects compared to sham who showed clinically meaningful improvement in their quality of life, as measured by the AQLQ (79% percent of bronchial thermoplasty and 64% of sham subjects achieved changes in AQLQ of 0.5 or greater (PPS, 99.6%)).

      Moreover, we draw attention to the quote from Elizabeth Juniper, MSCP, MSc, the developer of the AQLQ instrument, in a memo discussing the interpretation of AQLQ in the AIR2 trial [Appendix A], (n.b. emphasis added)

"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 benefiting from the treatment) as compared to optimal standard of care."[x] ***Thus, in the medical context, the interpretation should be that there is a 96% likelihood that BT provides a population-wide benefit to AQLQ above and beyond any benefit experienced as a mere "placebo effect."***

Boston Scientific respectfully requests that the report be amended in this interpretation to note the likelihood of Bronchial Thermoplasty to generate a population-wide benefit to AQLQ (PPS=96%), using patient selection aligned with the inclusion and exclusion criteria of the AIR2 trial, as well as the likelihood – using these same patient selection criteria – of an individual clinically-meaningful benefit in AQLQ (79% for BT vs. 64% for Sham; PPS=99.6%).

ii. The report states that "An additional year of uncontrolled follow-up for 166 thermoplasty group patients (87%) evaluated with traditional statistical tools showed no statistically significant differences within this group…"

A more accurate approach to discussing the results would be to state that the data showed no statistically significant increase or decrease, as this would lead to the correct interpretation of this statistical indifference as meaning that the treatment effect of BT observed at 1 year would continue out to at least 2 years and is therefore durable and long-lasting.

k. In two areas (Pages 9 and 39) of the assessment, the report cites patient withdrawals from the AIR2 trial as a study limitation, however the author does not provide the context that the 12% of patients withdrawing from the study before undergoing bronchial thermoplasty represents two patients who were assessed as not being candidates for the procedure.

Boston Scientific requests that the HCA either remove these statements or add the context that the 12% of patients withdrawing from the study prior to having bronchial thermoplasty was actually two patients who were not candidates for the procedure.

l. On page 45, the report states that "The rate of hospitalization appeared to be higher in studies that enrolled patients with more severe asthma." The report only provides two data points, both of which may be considered outside current labeling: (1) a study (Cox et al 2006) of subjects with stable mild to moderate asthma (n.b. per FDA labeling, *"Bronchial Thermoplasty System 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.") and (2) a study of subjects with severe asthma with obstructed airflow (FEV_1<50%) (Doeing et al., 2013) (n.b. per FDA labeling *"WARNINGS AND PRECAUTIONS Caution should be taken in patients with the following conditions due to a potential increased risk of adverse events that may be associated with the procedure…Post-bronchodilator FEV1 < 65% predicted."*)

It is not clear whether the authors' statement is based on a statistical analysis of the relationship between severity of asthma and the rate of hospitalizations – or, if such an analysis was conducted, whether their hypothesis was statistically significant. Moreover, the data used for the evaluation of this relationship is drawn from bronchial thermoplasty usage outside current FDA labeling.

Given the lack of statistical evidence of a relationship between severity of asthma and the rate of peri-procedural hospitalizations and data for this relationship exclusively drawn from usage outside FDA labeling, Boston Scientific requests that this statement be removed from the assessment wherever it appears or, at the very least, state that the hospitalizations in these studies occurred in patients outside of the technology's current FDA labeling.

m. In its discussion of results from the Research In Severe Asthma (RISA) trial (Pavord et al, 2013), the HCA report provides some, but not all, critical data points, potentially biasing the assessment. Specifically, there is no discussion of patient satisfaction with the procedure and willingness to undergo the procedure again or to recommend the procedure to family members. In the publication of the RISA data, Pavord et al report that,

"Eleven of the 12 patients who completed the 5-year follow-up provided responses to the questions regarding satisfaction with the procedure, with an overwhelming satisfaction with the procedure 5 years after treatment. In response to the question, "Would you undergo the bronchial thermoplasty procedure if you had to do it all over again?" 10 responses were "definitely yes" and one response was "probably yes." When asked, "Would you recommend this treatment to a friend or family member?" 9 responses were "definitely yes" and 2 responses were "probably yes."[xi]

Boston Scientific requests that the results of patient satisfaction with the procedure be included in the discussion of the RISA five-year results to present a comprehensive view of the outcomes of that study.

n. In the body of the assessment, an overall answer to the question of whether bronchial thermoplasty is cost-effective is not provided, however in the Executive Summary the report states that the overall body of evidence

regarding cost-effectiveness is moderate in quality.

Boston Scientific requests that the body of the report be amended to be consistent with the Executive Summary and to reflect the finding in multiple analyses that the procedure is cost-effective.

o. In its discussion of the complications associated with bronchial thermoplasty, on page 54, the report states that "**all** of the reviewed studies reported an increased need for hospitalization during the treatment period." In actuality, only one RCT found that there was a statistically significant difference in the need for hospitalization during the treatment period between the control and treatment groups.

Boston Scientific respectfully requests that the HCA correct this statement to reflect that "**one** of the reviewed studies reported a statistically significant increase in the need for hospitalization during the treatment period."

p. In its discussion of systematic reviews of bronchial thermoplasty, the report does not appropriately recognize the statistically significant finding of a decrease in the incidence of respiratory adverse events from years 1 to 5 ($P<0.00001$).

This finding is extremely significant, and Boston Scientific requests that it be noted as such in the report.

q. On page 6 of the technology assessment, the report states that, "All of the RCTs were supported by the device manufacturer and performed in part by investigators who had financial relationships with the device manufacturer." While this statement is correct, Boston Scientific objects to its inclusion in this technology assessment as irrelevant and inflammatory, and we request that the HCA remove the statement from the final report.

Industry-sponsored research is a cornerstone of medical research today and is ubiquitous for all novel drugs, diagnostics and medical devices. The cost of conducting clinical research on technologies not yet approved by the FDA would be prohibitive if not largely borne by the manufacturers of those technologies, and it would be extremely difficult to find investigators to conduct research if they were not compensated for their time and resources. Moreover, clinical trial designs control for the potential for bias through multicenter protocols, randomization and other accepted clinical research methods.

3. **Use of the GRADE Methodology to Assess the Quality of Bronchial Thermoplasty Evidence**

The report on bronchial thermoplasty rates the quality of evidence based on the

GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. While GRADE is widely used methodology for assessing the quality of evidence, a recent publication has described limitations of the methodology.

According to Gartlehner et al,

"GRADE uses information about risk of bias, imprecision, inconsistency, indirectness, and reporting bias to categorize the degree of uncertainty concerning the correctness of findings into four grades of quality of evidence (QOE)…Decision makers who rely on the GRADE approach assume that estimates of effect that are graded as high QOE are 'close to the true effect' and, therefore, will remain stable as new evidence emerges. By contrast, decision makers can interpret effect estimates that are graded as low QOE as quite likely to change as new evidence accrues. In a recent international survey, [Gartlehner et al] determined that producers and users of systematic reviews associated each grade of QOE with a distinct likelihood that estimates of effect will remain stable as new evidence emerges."[xii]

Based on these findings, it is important that the quality of evidence be appropriately characterized, as its characterization as high, moderate or low can have a lasting impact on the acceptance and adoption of new technologies and procedures. Gartlehner et al also state,

"To be considered useful in practice, any tool that conveys certainties and uncertainties of estimates of effect should have a high ability to discriminate between estimates that will remain stable in the future and those that will substantially change; it should also be able to associate respective likelihoods of stability with an expected outcome. Our research indicates that the EPC approach to GRADE only partly fulfilled these qualities of predictive validity."[xiii]

The authors concluded that the way systematic reviewers operationalize GRADE appears to be too strict:

"More than half of estimates graded as insufficient (very low) (defined as ''we have no confidence in the estimate of effect for this outcome'') remained stable; this indicates that the approach too often leads to low or insufficient (very low) grades of QOE. Possible reasons could be: (a) systematic reviewers use GRADE too mechanistically, (b) recommended thresholds for downgrading in guidance documents are too strict, or (c) a tool with four levels of QOE is not granular enough to categorize uncertainty."[xiv]

While at this point, Boston Scientific would not propose use of a completely different method of assessing data, we do ask that the authors reconsider their classification of the quality of bronchial thermoplasty evidence and its characterization of its concern regarding the safety and efficacy of the procedure. The rationale for our request follows:

a. Despite the report's assertion that the quality of evidence for bronchial thermoplasty is poor, in the Evidence Tables in Appendix IV, all of the randomized controlled studies were characterized as being of "fair" or "good" quality. Boston Scientific therefore respectfully requests that the report's overall conclusion regarding the quality of evidence for bronchial thermoplasty be amended to "moderate" or "fair" to be consistent with the findings in the Evidence Tables.

b. Based on the volume of studies of bronchial thermoplasty and the consistency of findings of both safety and durable effectiveness across these studies, Boston Scientific believes that the body of evidence should be characterized as "Moderate" rather than "Poor." Gartlehner et al found that only evidence graded as having Moderate quality was found to have satisfactory predictive validity.[xv] We believe that the consistency of outcomes across bronchial thermoplasty trials is strong evidence of the stability of predicted results, and therefore the evidence quality should be rated "Moderate."

c. It is not appropriate to rate non-randomized, non-controlled studies using the same standards applied to evidence from randomized controlled studies. These studies should either not be rated, or they should be rated in the context of other non-randomized, non-controlled studies. Boston Scientific therefore requests that the HCA amend the ratings in Appendix IVb to pertain to non-randomized, non-controlled studies.

d. In its discussion of the quality of the evidence, the author states that "The evidence for the safety of bronchial thermoplasty for treating asthma was considered to be of low quality because of the small quantity of RCTs available, small sample sizes in most of the reviewed studies, and insufficient evidence concerning the long term safety of bronchial thermoplasty."

   Boston Scientific disagrees with this characterization and requests that the HCA reclassify the quality of safety evidence as "Moderate." The author appears to be applying clinical research standards appropriate for pharmacologic therapies to a device-based treatment. In reality, the sample size and quantity of RCTs for bronchial thermoplasty represents the most significant body of evidence among available bronchoscopic therapies. The FDA found the evidence to be sufficient to approve the technology through its most rigorous review process (the Pre-Market Approval, or PMA process), and both clinical guidelines and other technology assessments (i.e., CTAF) have found the evidence to be sufficient to recommend bronchial thermoplasty as a treatment option for patients with severe, poorly controlled asthma.[xvi]

e. In several instances in the report, the author expresses a "high" level of concern regarding safety and efficacy of bronchial thermoplasty. Yet in its discussion of the evidence itself, the report acknowledges that the complications associated with bronchial thermoplasty were mild or moderate

in severity and that outcomes were maintained out to five years. Therefore, the high level of concern expressed by the author, particularly in light of the limitations of the GRADE approach in predicting stability of outcomes, is inconsistent with the evidence.

The report should provide *a priori* a basis for the concerns stated. Only in this context can ongoing and future research provide information to address these concerns by directly addressing the gaps or perceived inadequacies of the evidence, which forms the basis for these concerns.

Additionally, Boston Scientific would argue that the posterior concern(s) (i.e. after evaluating the evidence base) associated with bronchial thermoplasty must be evaluated in the context of those treatment options provided in absence of bronchial thermoplasty. Many of these treatment options are associated with high concerns regarding safety (e.g. oral corticosteroids), high concerns regarding efficacy (oral corticosteroids and a non-100% response rate for many monoclonal antibody treatment options) and high concerns of cost (omalizumab and mepolizumab). Even in the absence of these treatment options, the authors' concerns relating to bronchial thermoplasty should be evaluated against the concerns associated with the unavailability of adequate treatment alternatives, as the patient population considered for bronchial thermoplasty includes those who have severe, uncontrolled asthma, which by definition is inadequately treated.

Finally, follow-up of bronchial thermoplasty treated patients out to at least 5 years has not provided cause for high concern for safety.

Boston Scientific therefore requests that the HCA characterize the level of concern regarding safety and effectiveness to be "moderate," in keeping with both the way the report describes the risks of the procedure and its durable outcomes, and also the risks and inadequate benefits associated with other treatment alternatives for patients with severe, uncontrolled asthma.

4. **Current Status of Guidelines, Statements of Support and Insurance Coverage Policies**

Boston Scientific appreciates the author's efforts to be comprehensive in its discussion of guidelines discussing bronchial thermoplasty and insurance coverage policies for the procedure. However, there were several important guidelines, statements of support from professional specialty societies or recognized asthma authorities, and positive coverage policies that were inadvertently not captured in the author's review.

Boston Scientific requests that the report be amended as follows to more accurately reflect the current state of guidelines, statements of support and insurance coverage

for bronchial thermoplasty:

a. Both the discussion of guidelines in the body of the report as well as the list of guidelines provided in Appendix V, "Summary of Practice Guidelines," should be amended to include:

   i. The INTERASMA manifesto on bronchial thermoplasty (http://www.interasma.org/images/manifesto3.pdf);

   ii. The statement on bronchial thermoplasty by the American College of Allergy, Asthma, and Immunology (http://college.acaai.org/publications/advocacy-insider/statement-bronchial-thermoplasty); and

   iii. The Diagnosis and Management of Asthma –Pediatric/Adult – Inpatient/Ambulatory Clinical Practice Guideline, developed by a task force of representatives from the University of Wisconsin (UW) Medical Foundation, UW Hospital and Clinics, UW Health Department of Family Medicine and Internal Medicine, Unity Health Insurance, Physicians Plus Insurance Corporation, and Group Health Cooperative (2015)(Attached as Appendix B).

b. Although the author is correct that some commercial insurers have published non-coverage policies for bronchial thermoplasty, there are several large insurers that do cover the procedure (please refer to Appendix C). These positive coverage policies should be represented discussed in the technology assessment to assure factual accuracy and non-biased consideration.

5. **Typographical Error: Reference to Novocure Device**

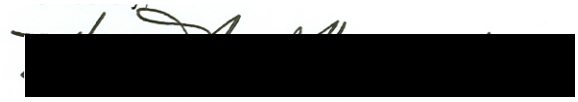
   References to the Cost of Novocure Device on page 50 of the assessment are unrelated to the bronchial thermoplasty procedure and should be removed from the report.

Summary and Closing

To summarize our comments, Boston Scientific appreciates the thorough approach to the assessment of bronchial thermoplasty and respectfully requests that the HCA address the various inaccuracies and inconsistencies that are described in the body of this comment letter.

Thank you in advance for your consideration of our response to the Washington State Health Care Authority's Draft Evidence Report on bronchial thermoplasty. We look forward to the April 15, 2016 publication of the final report and to the public coverage discussion by the Health Technology Clinical Committee on May 20, 2016. Please do not hesitate to contact me should you have any questions or need clarification.

Sincerely,



Maria B. Stewart
Director, Health Economics & Reimbursement
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Appendix A: Internal Communication from Juniper EF. Interpretation of the AQLQ Score Change and its Application in the AIR2 Trial. December 18, 2008.

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December 18, 2008

Interpretation of the AQLQ Score Change and its Application in the AIR2 Trial

The Asthma Quality of Life Questionnaire (AQLQ) was developed to assess areas of quality of life impairment that are important to adult asthmatic patients. The questionnaire was designed to be responsive to within-subject change (Juniper 1992). The questionnaire was further validated for a within-subject change in score of 0.5 as representing the minimal important difference (MID) (Juniper 1994). This score was very similar for both improvement and deterioration. The Minimal Important Difference is defined as the smallest change in treatment that a patient considers important and would justify a change in treatment (in the absence of undue side effects and excessive costs).

The method for determining whether between-treatment differences in AQLQ scores can be considered clinically important have been published by Guyatt et all (1998). The method uses the proportion of patients who improve and deteriorate by the MID (+0.5 and –0.5) in the two treatment groups. Thus any abnormality in distribution may be taken into account.

Based on my review of the AQLQ data from the AIR2 Trial, I consider that an analysis that includes both subjects who improved by ≥0.5 and subjects who deteriorated by ≤ -0.5 is appropriate to fully utilize the power of the AQLQ and identify the true benefit of the Alair treatment. The following analysis provides this perspective.

Figure 1 illustrates the % of subjects in both groups who improved, i.e. achieved an AQLQ score change of ≥ 0.5; Figure 2 illustrates the % of subjects in both groups who deteriorated, i.e. had an AQLQ score change of ≤ -0.5. The Intent to Treat (ITT) population includes all patients that received at least one bronchoscopy, and the Per Protocol (PP) population includes all patients with complete Alair treatments and complete follow-up, at 6, 9, and 12 months.

First, let us consider responders in the AIR2 Trial using the per protocol data (PP)

81% of patients showed a clinically important improvement when treated with the Alair System whereas only 63% of the sham group benefited. In contrast, 7% of the sham group had a clinically important deterioration compared to only 3% in the Alair System treated patients.

Therefore, the net percentage of patients who had a benefit (% improving - % deteriorating) in the Alair group was 78% and the net benefit in the sham group was reduced to 56%. Taking this one step further, the difference in true benefit between Alair and sham was 22% (78% - 56%). This means that 22% of patients would benefit in a clinically meaningful way from Alair compared with if they had received the sham treatment.

Table 1 shows the difference in the proportion of patients that benefitted from the Alair procedure.

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.

Figure 1: Improvements in Integrated AQLQ Score

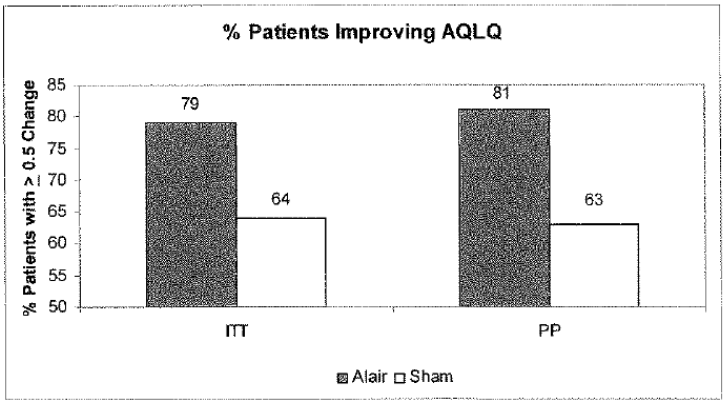

Figure 2: Declines in Integrated AQLQ Score

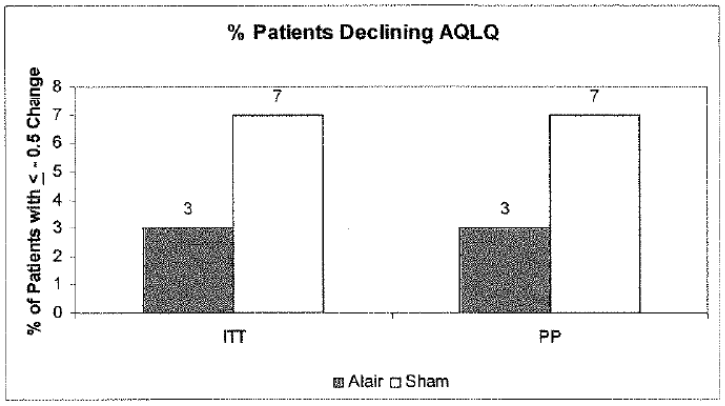

Table 1: Net Proportion of Patients That Benefit from Alair over Sham

AQLQ Score	Group	% ≥ 0.5 (Increase)	% Increase over Sham[1]	% ≤ -0.5 (Deterioration)	% With Net Increase[2]	Proportion that benefitted[3]	% Increase over Sham[4]
Intent-to-Treat Population	Alair	79	15	3	76	19	33%
	Sham	64		7	57		
Per Protocol Population	Alair	81	18	3	78	22	39%
	Sham	63		7	56		

[1] The difference between Alair and Sham in the % of patients with ≥ 0.5 improvement
[2] The difference in % of patients with ≥ 0.5 improvement and ≤ 0.5 deterioration
[3] The difference between Alair and Sham in the % of patients with a net improvement.
[4] Proportion that benefitted divided by % of Sham patients with net improvement.

References:

Juniper E, Guyatt GH, Epstein RS, et al. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992; 47:76–83

Juniper EF, Guyatt GH, Willan A, et al. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994; 47:81–87

Guyatt GH, Juniper EF, Walter SD, et al. Interpreting treatment effects in randomised trials. BMJ 1998; 316:690–693

Elizabeth F. Juniper MCSP MSc
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Appendix B: Unity Health Insurance Guideline for the Diagnosis and Management of Asthma

Guideline for the Diagnosis and Management of Asthma in Adult and Pediatric Patients

The Clinical Practice Guideline for the Diagnosis and Management of asthma in Adult and Pediatric Patients was reviewed and approved by Unity's Clinical Quality Improvement Committee (CQIC) on September 25, 2015. The guideline was previously approved by CQIC on November 15, 2013, September 16, 2011, November 20, 2009; November 16, 2007; November 18, 2005; November 19, 2004; November 14, 2002; January 8, 2001; and February 3, 1999. The UW Medical Foundation, UW Hospital and Clinics, UW Health Department of Family Medicine and Internal Medicine, Unity Health Insurance, Physicians Plus Insurance Corporation, and Group Health Cooperative participated in the development and revision of this guideline. The task force was a multidisciplinary work group comprised of physicians, asthma specialists, a pharmacist, nurses, and quality improvement staff.

Diagnosis and Management of Asthma – Pediatric/Adult – Inpatient/Ambulatory Clinical Practice Guideline

Table of Contents

Note: Active Table of Contents -- Click to follow link

Release Date: July 2015

Expiration Date: July 2017

Executive Summary

Guideline Overview

We agreed to endorse the 2015 Global Initiative for Asthma (GINA) *Global Strategy for Asthma Management and Prevention Guideline* (accessed 5/15/15).[1]

Key Practice Recommendations & Companion Documents

We supports the following key recommendations summarized from GINA[1], in addition to those recommendations found within the 2015 GINA quick-reference pocket guides available online (accessed on 5/15/15):

- GINA Pocket Guide for Asthma Management and Prevention (Age 6 or older)
- GINA Pocket Guide for Asthma Management and Prevention (Age 5 or younger)

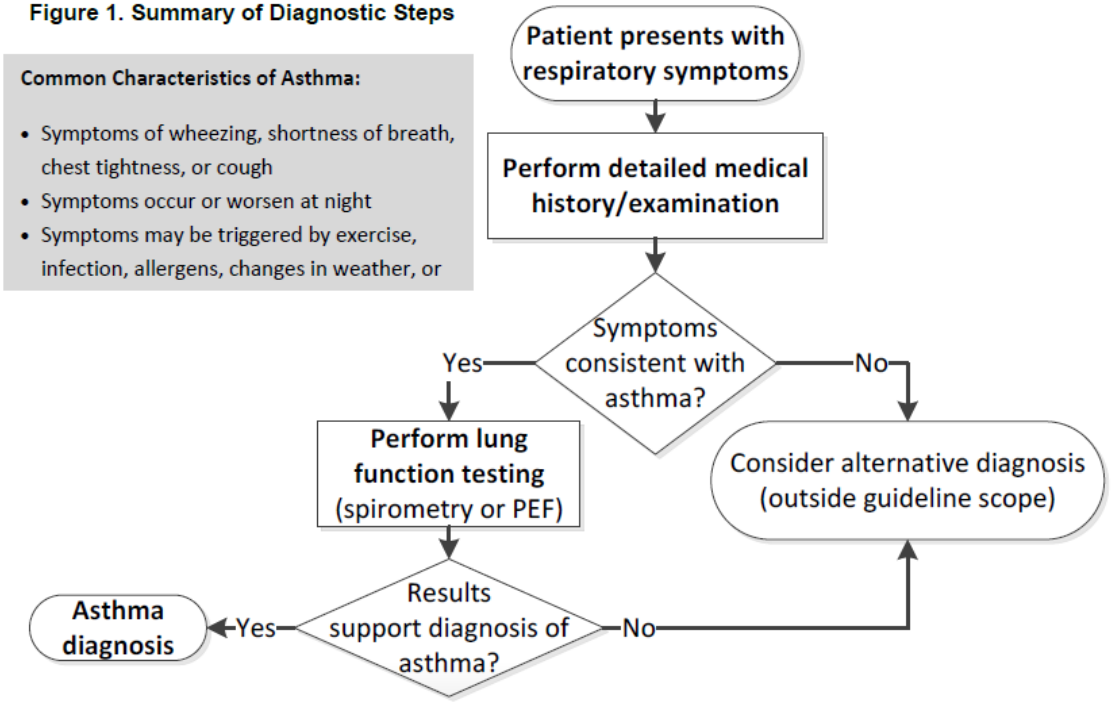
WHAT IS ASTHMA?

Asthma is a chronic inflammatory disorder of the airways which causes symptoms of wheezing, shortness of breath, tightness in the chest, and cough that may vary in frequency and over time.

ESTABLISHING A DIAGNOSIS

It is recommended to complete a medical history to establish respiratory symptoms, as well as lung function testing using spirometry or peak expiratory flow (PEF) (see **Figure 1**). A diagnosis of asthma may be made after consideration of a patient's history and whether the patient exhibits variable expiratory airflow limitations (i.e., difficulty exhaling due to bronchoconstriction, airway wall thickening, and increased mucus).

Figure 1. Summary of Diagnostic Steps

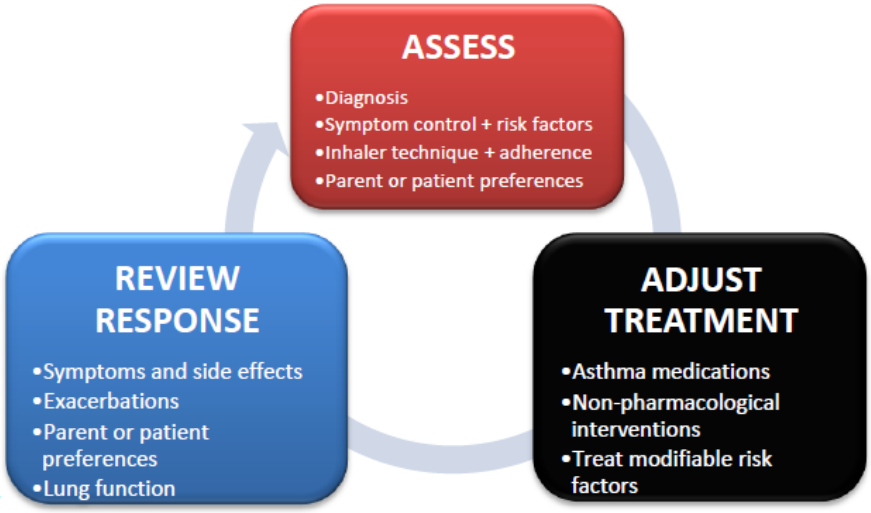


PROVIDING TREATMENT AND ASSESSMENT

The goals of asthma treatment include:

- Prevention of chronic asthma symptoms and asthma exacerbations;
- Maintenance of normal activity levels;
- Patient satisfaction with asthma care and quality of life (i.e., having normal or near normal lung function, experiencing no or minimal side effects).

Asthma treatment should follow a repeating pattern of assessment of control, adjustment of treatment, and review of response to the treatment.



Assessment

An age-appropriate questionnaire should be used to help determine asthma control and efficacy of the treatment plan. It is recommended to assess asthma control at least annually.

- Asthma Control Test (ACT) for patients age 12 years or older.
- Childhood Asthma Control Test (cACT) for patients age 6-11 years.
- Test for Respiratory and Asthma Control in Kids (TRACK) for patients age 5 years or younger.

Treatment

The age-differentiated Stepwise Approach to Control should be used to guide the prescription of asthma medication (controllers and rescue). A full listing of medications available in the United States is summarized in the Asthma Rescue and Controller Medication Table, and dosing options for inhaled corticosteroids are available in the Asthma Medication Dosing Table.

All patients should have a written asthma action plan, which should include:

- A list of medications and a description of how to use them
- Environmental triggers

Patients age 18 years or older with uncontrolled severe-persistent asthma, despite use of recommended therapeutic regimens and referral to an asthma specialist (Step 5) may be candidates for a non-pharmacological intervention of Bronchial Thermoplasty.

Review Response
It is recommended that patients be seen every 1-3 months after initiating treatment and every 3-12 months thereafter.

Patients should be seen by the provider managing their asthma within 1 week following an exacerbation to re-evaluate the patient compliance and treatment plan efficacy.

MANAGING ASTHMA EXACERBATIONS
Asthma exacerbations are acute or subacute episodes of progressively worsening asthma symptoms (i.e., shortness of breath, coughing, wheezing, chest tightness).

Treatment algorithms should be followed to guide exacerbation management within the outpatient, emergency department, and inpatient settings:

- Asthma Exacerbation- Primary Care Algorithm

- Asthma Exacerbation- Emergency Department (Pediatric) Algorithm
- Asthma Exacerbation- Inpatient (Pediatric) Algorithm

- Asthma Exacerbation- Emergency Department (Adult) Algorithm
- Asthma Exacerbation- Inpatient (Adult) Algorithm

Companion Documents

1. GINA Pocket Guide for Asthma Management and Prevention (Age 6 or older)
2. GINA Pocket Guide for Asthma Management and Prevention (Age 5 or younger)
3. GINA Appendices to the Global Strategy for Asthma Management and Prevention

Patient Resources

1. Health Information: Asthma
2. Health Information: Asthma Action Plan
3. Health Information: Asthma Action Plan: Green Zone
4. Health Information: Asthma Action Plan: Yellow Zone
5. Health Information: Asthma Action Plan: Red Zone
6. Health Information: Asthma and GERD
7. Health Information: Asthma and Vocal Cord Problems
8. Health Information: Asthma and Wheezing
9. Health Information: Asthma Attack
10. Health Information: Asthma Diary
11. Health Information: Asthma During Pregnancy
12. Health Information: Asthma in Children
13. Health Information: Asthma in Children: Helping a Child Use A Metered-Dose Inhaler and Mask Spacer
14. Health Information: Asthma in Children: Knowing How Bad an Attack Is

Scope

Disease/Condition(s): Asthma

Clinical Specialty: Pulmonary, Allergy, Family Medicine, Internal Medicine, Pediatrics, Hospitalists, Respiratory Therapy, Emergency Medicine

Intended Users: Physicians, Advanced Practice Providers, Respiratory Therapists, Registered Nurses, Pharmacists, Asthma Educators

CPG objective(s): To provide evidence-based recommendations for the management of asthma across age groups and clinical settings.

Target Population: Any pediatric (0-11 years), adolescent (12-17 years), or adult (18 years or older) patient diagnosed with asthma.

Methodology

The GINA guideline[1] was produced using the standard methodology of the GINA Science Committee outlined on page vi of the full guideline (http://www.ginasthma.org).

Rating Scheme for the Strength of the Evidence/Recommendations:

Sources of evidence		Definition
A	Randomized controlled trials (RCTs) and meta-analyses. Rich body of data.	Evidence is from endpoints of well designed RCTs or meta-analyses that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of patients.
B	Randomized controlled trials (RCTs) and meta-analyses. Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs or meta-analysis of such RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were under-taken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials. Observational studies.	Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.
D	Panel consensus judgement.	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above listed criteria.

Introduction

Asthma is a chronic inflammatory disorder of the airways. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The goals of asthma therapy are to prevent chronic asthma symptoms and asthma exacerbations, maintain normal activity levels, have normal or near normal lung function, experience no or minimal side effects and have patient satisfaction with asthma care.

Recommendations

We endorse the recommendations outlined within the 2015 GINA Guideline[1] located online at http://www.ginasthma.org/documents/4 (accessed on 5/15/15).

The full guideline document references appendices, located here: http://www.ginasthma.org/local/uploads/files/GINA_Appendix_2015.pdf (accessed on 5/18/15).

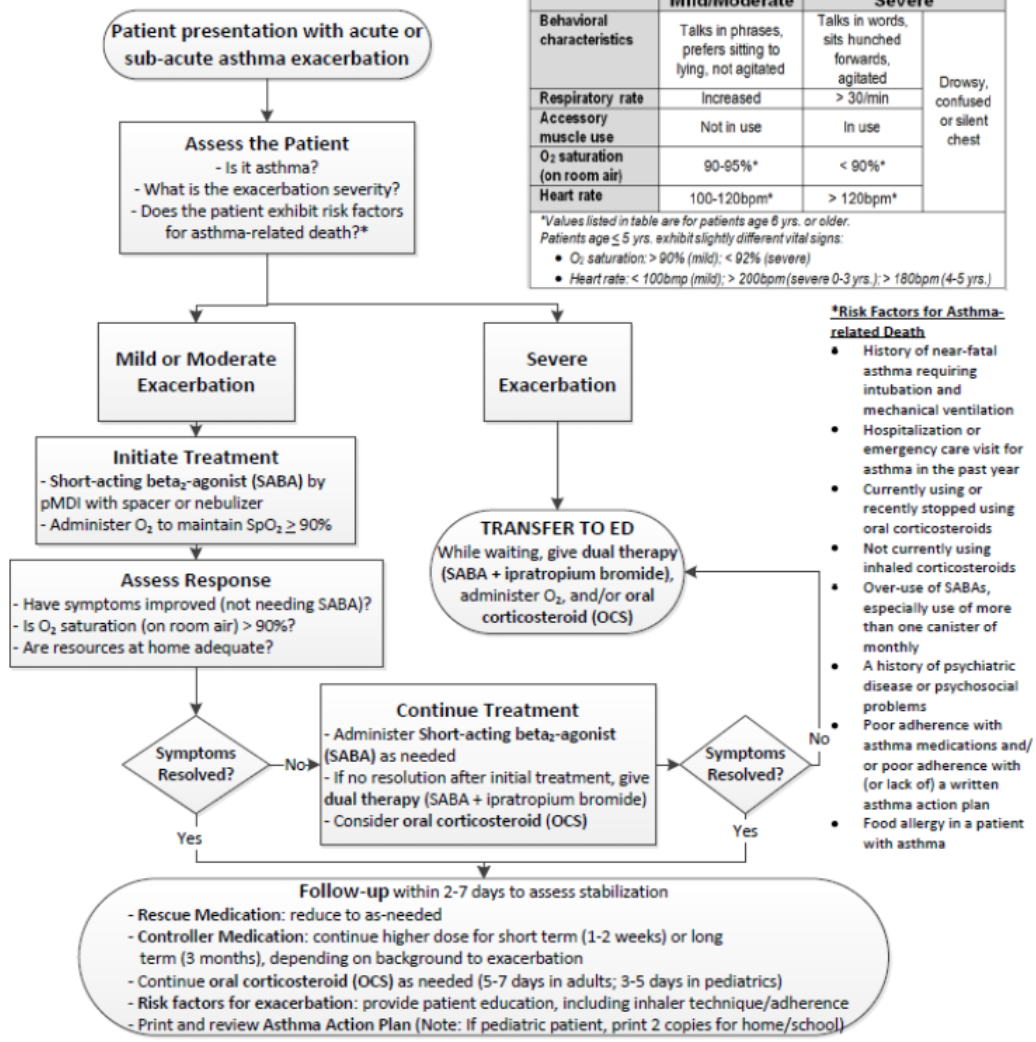
Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2015. Available from www.ginasthma.org
2. Gorelick MH, Stevens MW, Schultz TR, Scribano PV. Performance of a Novel Clinical Score, the Pediatric Asthma Severity Score (PASS), in the Evaluation of Acute Asthma. *Academic Emergency Medicine*. 2004;11(1):10-18.

Management of Asthma Exacerbation in Primary Care (Age 2 years or older)



Determine Exacerbation Severity	Mild/Moderate	Severe	
Behavioral characteristics	Talks in phrases, prefers sitting to lying, not agitated	Talks in words, sits hunched forwards, agitated	Drowsy, confused or silent chest
Respiratory rate	Increased	> 30/min	
Accessory muscle use	Not in use	In use	
O_2 saturation (on room air)	90-95%*	< 90%*	
Heart rate	100-120bpm*	> 120bpm*	

*Values listed in table are for patients age 6 yrs. or older.
Patients age ≤ 5 yrs. exhibit slightly different vital signs:
- O_2 saturation: > 90% (mild); < 92% (severe)
- Heart rate: < 100bmp (mild); > 200bpm (severe 0-3 yrs.); > 180bpm (4-5 yrs.)

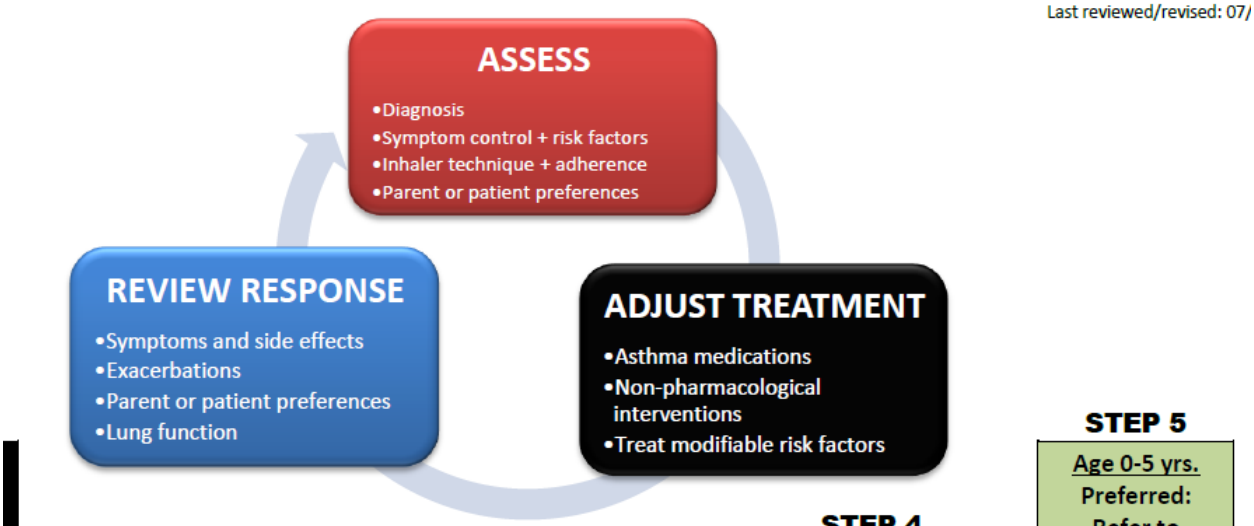
***Risk Factors for Asthma-related Death**

- History of near-fatal asthma requiring intubation and mechanical ventilation
- Hospitalization or emergency care visit for asthma in the past year
- Currently using or recently stopped using oral corticosteroids
- Not currently using inhaled corticosteroids
- Over-use of SABAs, especially use of more than one canister of monthly
- A history of psychiatric disease or psychosocial problems
- Poor adherence with asthma medications and/or poor adherence with (or lack of) a written asthma action plan
- Food allergy in a patient with asthma

Medications		Dose & Frequency	Route
Short-acting Beta2-agonist (SABA)	albuterol	(age < 12 yrs.) 2.5 mg Q20min x3 (age ≥ 12 yrs.) 5 mg Q20min x3	Nebulizer
		4-8 puffs Q20min x3	pMDI + spacer
Ipratropium	Ipratropium bromide	(age < 5 yrs.) 250 mcg Q20min x3 (age ≥ 5 yrs.) 500 mcg Q20min x3	Nebulizer
Oral Corticosteroid (OCS)	methylprednisolone (age < 12 yrs.)	1-2 mg/kg in 2 divided doses; max 60 mg per day	Oral
	prednisone (age ≥ 12 yrs.)	1 mg/kg/day PO in 1-2 divided doses; max 50 mg/day	Oral
Corticosteroid Alternative	*dexamethasone (age ≤ 18 yrs. only)*	*0.6 mg/kg per dose 36-48 hrs. apart; max 16 mg/dose*	*Oral*

Stepwise Approach to Asthma Symptom Control

Last reviewed/revised: 07/



STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
All Ages *Alternative: Low dose ICS*	Age 0-5 yrs. **Preferred: Low dose ICS** *Alternatives: LTRA or intermittent ICS*	Age 0-5 yrs. **Preferred: Double low dose ICS** *Alternative: Add LTRA*	Age 0-5 yrs. **Preferred: Refer to asthma specialist** *Alternatives: Add LTRA or increase ICS frequency or add intermittent ICS*	Age 0-5 yrs. **Preferred: Refer to asthma specialist**
	Age 6-11 yrs. **Preferred: Low dose ICS** *Alternatives: LTRA*	Age 6-11 yrs. **Preferred: Medium dose ICS or Low dose ICS + LABA** *Alternative: Low dose ICS + LTRA*	Age 6-11 yrs. **Preferred: Refer to asthma specialist** *Alternatives: Medium dose ICS + LABA or High dose ICS + LABA*	Age 6-11 yrs. **Preferred: Refer to asthma specialist** *Alternative: Omalizumab*
	Age ≥ 12 yrs. **Preferred: Low dose ICS** *Alternatives: LTRA or theophyline*	Age ≥ 12 yrs. **Preferred: Low dose ICS + LABA** *Alternatives: Medium dose ICS or Low dose ICS + LTRA + theophyline*	Age ≥ 12 yrs. **Preferred: Medium dose ICS + LABA** *Alternatives: High dose ICS + LABA and/or LTRA + theophylline or add tiotropium**	Age ≥ 12 yrs. **Preferred: Refer to asthma specialist** *Alternatives: Add tiotropium* or omalizumab or bronchial thermoplasty**

**For adult patients only. Not indicated or recommended for patients younger than 18 years.*

All Ages

Preferred: PRN Short-acting Beta$_2$-agonist (SABA)

Consider stepping up if uncontrolled symptoms, exacerbations or risks. Always evaluate diagnosis, inhaler technique, and adherence before making therapy changes.

Consider stepping down if symptoms controlled for 3 months and low risk for exacerbations.

Ceasing ICS is not advised

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Table 1. Asthma Medications Chart

NOTE: The following table objectively outlines selected asthma medications available in the United States, and does not provide recommendations for or against their use. The listing does not indicate inclusion on the formulary. Prescribing providers should refer to specific formulary listings for status of various agents.

	Medication	Inhaler	Nebulization Solution	Oral (Injectable products where noted)	Purpose	Considerations
RESCUE Medications	***Short-acting beta agonists***					
	Albuterol Sulfate - ProAir® MDI - Proventil® MDI - Ventolin® MDI - Accuneb® nebulization - VoSpire® ERT	108 mcg/act	0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5 mg/mL	Tablet: 2 mg, 4 mg Oral Syrup: 2 mg/5 mL ERT: 4 mg, 8 mg	Bronchodilation through smooth muscle relaxation	Although available, oral albuterol is not recommended.
	Levalbuterol - Xopenex® MDI - Xopenex® nebulization	45 mcg/act	0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/3 mL 1.25 mg/0.5 mL			
	Terbutaline - tablet - injection			Tablet: 2.5 mg, 5 mg Injection: 1 mg/mL		
	Short-acting anticholinergics					
	Ipratropium Bromide - Atrovent® MDI - Atrovent ® nebulization	17 mcg/act	0.5 mg/2.5 mL		Bronchodilation through inhibition of muscarinic receptors to reduce intrinsic vagal tone of the airway	May be an alternative to short-acting beta agonists in patients who cannot tolerate short-acting beta agonists
	Combination short-acting beta agonist and short-acting anticholinergic					
	Albuterol Sulfate/Ipratropium Bromide - Combivent Respimat® MDI - Duoneb® nebulization	100/20 mcg/act	2.5/0.5 mg/3 mL		See individual agents	
	Systemic corticosteroids					
	Prednisone - tablet - Rayos® delayed-release tablet - solution - Intensol® concentrated solution			Tablet: 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg Delayed-release tablet: 1 mg, 2 mg, 5 mg Solution: 5 mg/5 mL 5 mg/1 mL		
	Methylprednisolone - Medrol® tablet - Solu-Medrol® injection			Tablet: 2 mg, 4 mg, 8 mg, 16 mg, 32 mg Pak: 4 mg tablets x 21 Injection: 40 mg, 125 mg, 500 mg, 1000 mg		
	Dexamethasone - Tablet - Solution - Intensol® concentrated solution - Elixir			Tablet: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, 6 mg Solution: 0.5 mg/5 mL 1 mg/mL Elixir: 0.5 mg/5 mL Injection: 4 mg/mL, 10 mg/mL		

MDI: metered dose inhaler
DPI: dry powder inhaler
ERT: extended-release tablet

inh: inhalation
act: actuation

	Medication	Inhaler	Nebulization Solution	Oral (Injectable products where noted)	Purpose	Considerations
CONTROLLER Medications	***Long-acting beta agonists***					
	Formoterol Fumarate - Foradil Aerolizer® DPI - Perforomist® nebulization	12 mcg/inh	20 mcg/2 mL		Bronchodilation	Should be used in combination with an inhaled corticosteroid
	Salmeterol Xinafoate - Serevent Diskus ® DPI	50 mcg/inh				
	Inhaled corticosteroids					
	Beclomethasone Dipropionate - Qvar® MDI	40 mcg/act 80 mcg/act			Reduce airway hyperrespon-siveness, inhibit inflammatory cell migration and activation, and block late phase reaction to allergen	MDIs may be used with a spacer
	Budesonide - Pulmicort Flexhaler® DPI - Pulmicort® nebulization	90 mcg/inh 180 mcg/inh	0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL			
	Ciclesonide - Alvesco® MDI	80 mcg/act 160 mcg/act				
	Flunisolide - Aerospan® MDI	80 mcg/act				
	Fluticasone Furoate - Arnuity Ellipta® MDI	100 mcg/act 200 mcg/act				
	Fluticasone Propionate - Flovent Diskus® DPI - Flovent® MDI	DPI: 50 mcg/inh 100 mcg/inh 250 mcg/inh MDI: 44 mcg/act 110 mcg/act 220 mcg/act				
	Mometasone Furoate - Asmanex® DPI - Asmanex® MDI	DPI: 110 mcg/inh 220 mcg/inh MDI: 100 mcg/act 200 mcg/act				
	Combination long-acting beta agonists and corticosteroid					
	Budesonide/Formoterol Fumarate - Symbicort® MDI	80/4.5 mcg/act 160/4.5 mcg/act			See individual agents	
	Mometasone Furoate /Formoterol Fumarate - Dulera® MDI	100/5 mcg/act 200/5 mcg/act				
	Fluticasone Propionate/ Salmeterol Xinafoate - Advair Diskus® DPI - Advair® MDI	DPI: 100/50 mcg/inh 250/50 mcg/inh 500/20 mcg/inh MDI: 45/21 mcg/act 115/21 mcg/act 230/21 mcg/act				
	Long-acting anticholinergics					
	Tiotropium - Spiriva® Handihaler DPI - Spiriva® Respimat MDI	DPI: 18 mcg/inh MDI: 2.5 mcg/act			Bronchodilation through inhibition of muscarinic receptors to reduce intrinsic	

					vagal tone of the airway	
	Mast cell stabilizers					
	Cromolyn -nebulization		20 mg/2 mL		Stabilize mast cells	
	Methylxanthines					
	Aminophylline - injection			Injection: 25 mg/mL	Bronchodilation through smooth muscle relaxation and the suppression of airway response to stimuli	
	Theophylline Theochron® 12-hour ERT - 24-hour ERT - Theo-24® 24-hour ER capsule - oral solution - Elixophyllin® elixir - injection			12-hour ERT: 100 mg, 200 mg, 300 mg, 450 mg 24-hour ERT: 400 mg, 600 mg 24-hour ER capsule: 100 mg, 200 mg, 300 mg, 400 mg Solution and Elixir: 80 mg/15 mL Injection: 0.8 mg/mL, 1.6 mg/mL		
CONTROLLER Medications	***Leukotriene Modifiers***					
	Montelukast - Singulair®			Tablet: 10 mg Chewable tablet: 4 mg, 5 mg Packet: 4 mg	Interfere with the pathway of leukotriene mediators, which are released from mast cells, eosinophils, and basophils.	
	Zafirlukast - Accolate®			Tablet: 10 mg, 20 mg		
	Zileuton - Zyflo® - Zyflo ER®			Tablet: 600 mg 12-hour ERT: 600 mg		
	Immunomodulators					
	Omalizumab - Xolair®			Injection: 150 mg vial	Prevents binding of IgE to the high-affinity receptors on basophils and mast cells	

MDI: metered dose inhaler
DPI: dry powder inhaler
ERT: extended-release tablet
inh: inhalation
act: actuation

Asthma Medications- Low, Medium and High Doses of Inhaled Corticosteroids

This table provides an estimate of comparative daily doses for inhaled corticosteroids administered to children and adults with asthma. It may be used in conjunction with the Stepwise Approach to Asthma Symptom Control found within the Asthma Guideline.

Medication	Daily Dose (mcg)								
	Low			Medium			High		
	Child (≤ 5 yrs.)	Child (6-11 yrs.)	Adult (≥ 12 yrs.)	Child (≤ 5 yrs.)	Child (6-11 yrs.)	Adult (≥ 12 yrs.)	Child (≤ 5 yrs.)	Child (6-11 yrs.)	Adult (≥ 12 yrs.)
Beclomethasone HFA	100	50-100	80-240	NA	>100-200	>240-480	NA	>200	>480
Budesonide DPI	200	100-200	180-540	NA	>200-400	>540-1080	NA	>400	>1080
Budesonide (nebule)	250-500	250-500	NA	>500-1000	>500-1000	NA	>1000	>1000	NA
Ciclesonide HFA	160	80	80-160	NA	>80-160	160-320	NA	>160	>320
Flunisolide HFA	NA	160	320	NA	320	>320-640	NA	>640	>640
Fluticasone HFA	100	100-200	44-264	>100-352	>200-500	>264-440	>352	>500	>440
Fluticasone DPI	NA	100-200	100-300	NA	>200-400	>300-500	NA	>400	>500
Momentasone DPI	NA	110	110-220	NA	≥220-<440	220-440	NA	≥440	>440

Last reviewed/revised: 07/2015

References:

1. Global Intiative for Asthma. Global Strategy for Asthma Management and Prevention, 2015. Available from www.ginasthma.org
2. Program NAEAP. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007; 120(5 Suppl):S94-138.

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Bronchial Thermoplasty Summary for Primary Care Providers

Overview: Bronchial Thermoplasty (BT) is an innovative procedure for the treatment of severe persistent asthma. This procedure is performed in an outpatient setting under moderate sedation, and is accomplished in three separate bronchoscopic sessions scheduled approximately 3 weeks apart. In the first procedure, airways under direct vision and reachable by the bronchoscope in the right lower lobe are treated. During the second procedure, targeted airways in the left lower lobe are treated, and in the third and final procedure, targeted airways in both upper lobes are treated.[1-2]

Target Population: A potential treatment option for highly-selected patients aged 18 years and older with uncontrolled asthma, despite use of recommended therapeutic regimens and referral to an asthma specialist (Step 5).[3] *(GINA Evidence B)*

Outcomes: Bronchial thermoplasty has been studied in four clinical studies in patients with asthma; three of which were randomized controlled clinical trials and the results for which have been published in peer-reviewed journals. Most notably, published data from the Asthma Intervention Research 2 (AIR2) clinical trial demonstrates that bronchial thermoplasty continues to show benefits in adult patients with severe uncontrolled asthma out to at least five years.[4] Bronchial thermoplasty was shown to provide long term asthma control, demonstrated by a sustained reduction in the rate of severe exacerbations (asthma attacks) and emergency room (ER) visits over a five year period after treatment.[5]

Risk assessment: The most common side effect found in the clinical studies was an expected transient increase in the frequency and worsening of respiratory-related symptoms, including asthma (multiple symptoms), respiratory tract infections, wheezing, dyspnea, and chest pain.
Long-term follow-up out to 5 years has been completed in 4 studies: the safety profile for the BT treated patients has demonstrated consistency over time based on the percent of subjects reporting respiratory adverse events, the number of respiratory adverse events per subject, and the number of hospitalizations and emergency room visits due to respiratory symptoms per subject.

Pre-Approval Needs: While non-coverage policies exist, there is a need to request pre-approval to the insurer by submitting documentation that supports a severe asthma diagnosis. This documentation is inclusive of differentiating other respiratory-related disorders (i.e., COPD, bronchiectasis, vocal cord dysfunction, obstructive sleep apnea), management of comorbidities (i.e., allergic rhinitis, sinusitis, GERD), and observations of compliance and/or attempts to manage their asthma with current standard medications (i.e., minimum of ICS+LABA) over at least a 3 month period yet still demonstrating evidence of exacerbations, activity limitation and/or risk of future exacerbations. As coverage policies get implemented, a shorter, more specific pre-authorization form may be required.

Last reviewed/revised: 07/2015

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1. Cox G, Miller JD, McWilliams A, Fitzgerald JM, Lam S. Bronchial thermoplasty for asthma. Am J Respir Crit Care Med. 2006;173(9):965-969.
2. ECRI. Bronchial Thermoplasty for Treating Adult Patients with Severe Persistent Asthma. 2013.
3.Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2015. Available from: www.ginasthma.org
4. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med. 2010;181(2):116-124.
5. Wechsler ME, Laviolette M, Rubin AS, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol. 2013;132(6):1295-1302.e1293.

Appendix C: Commercial Payers Covering BT as of March 18, 2016

Health Plan	State/Region	Approximate Number of Covered Lives	Policy Link
Avera Health Plans	IA, NE, SD	70,000	
AvMed	FL	300,000	
CareFirst BlueCross BlueShield	MD, VA, DC	3,400,000	Medical Policy (No. 7.01.102)
Health Care Service Corporation (HCSC) Operating through BlueCross BlueShield plans in Illinois, Montana, New Mexico, Oklahoma and Texas	IL, MT, NM, OK, TX	14,500,000	Medical Policy (SUR706.014)
HealthChoice	OK	217,000	
HealthPartners	MN	700,000	Medical Policy (No. 53678)

Independence Health Group: including Independence Blue Cross, AmeriHealth, AmeriHealth Administrators, and AmeriHealth Caritas	AL, CA, DC, DE, FL, GA, IL, IN, KY, LA, MD, MI, MN, MO, NC, NE, NJ, NY, NV, OK, PA, RI, SC, TN, TX, WV, VA	10,000,000	Medical Policy
Ohio State University Health Plan	OH	58,000	
Optima Health	VA	444,000	
PreferredOne	MN	350,000	Medical Criteria (No. MC/K002)
Priority Health	MI	600,000	Medical Policy (No. 91577-R0)
SelectHealth	ID, UT	634,000	
Tufts Health Plan	MA, RI	1,033,640	Medical Policy
Unity Health	WI	90,000	Asthma CPG
University of Cincinnati Health	OH	10,000	
TOTAL		**32,406,640**	

References Cited in Boston Scientific's Comments

[i] Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005-2009. Natl Health Stat Report. 2011;(32):1-14. PMID: 21355352.

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[iii] Donald Berry. Bayesian Clinical Trials. Nature Reviews Drug Discovery. 2006(5)27-36.

[iv] Juniper EF et al. Determining a minimal important change in a disease-specific quality of life instrument. J Clin Epidemiol 1994; 47: 81-87.

[v] Internal Communication from Juniper EF. Interpretation of the AQLQ Score Change and its Application in the AIR2 Trial. December 18, 2008.

[vi] Ibid.

[vii] Wechsler ME, e. al., Bronchial Thermoplasty: Long-Term Safety and Effectiveness in Patients with Severe Persistent Asthma. J Allergy Clin Immunol. 2013 Dec;132(6):1295-1302.

[viii] M. Cangelosi, J. Ortendahl, L. Meckley and e. al., "Cost-effectiveness of bronchial thermoplasty in commercially-insured patients with poorly controlled, severe, persistent asthma," Expert Review of Pharmacoeconomics and Outcomes Research, pp. 357-364, 2015.

[ix] Boston Scientific Corporation analysis of OPPS: 2014 All (Multiples and Singles , added multiples as multiples already have higher costs and we are including that in calculation) and Medpar : 2014.

[x] Ibid.

[xi] Pavord ID, e. al., Safety of Bronchial Thermoplasty in Patients with Severe Refractory Asthma. Ann Allergy Asthma Immunol. 2013 Nov;111(5):402-7.

[xii] Gartlehner e. al., The predictive validity of quality of evidence grades for the stability of effect estimates was low: a meta-epidemiological study. Journal of Clinical Epidemiology 70 (2016) 52-60.

[xiii] Ibid.

[xiv] Ibid.

[xv] Ibid.

[xvi] Bronchial thermoplasty for the treatment of severe asthma. California Technology Assessment Forum website: http://ctaf.org/reports/bronchial-thermoplasty-treatment-severe-asthma.

[redacted]

From: Navdeep Rai [redacted]
Sent: Friday, March 18, 2016 9:00 AM
To: HCA ST Health Tech Assessment Prog
Subject: Bronchial Thermoplasty

Follow Up Flag: Follow up
Flag Status: Completed

Dear Members of the committee,

Having read your draft report, I feel compelled to write about my prospective on bronchial thermoplasty. This is not something I have ever done before.

I am a board certified pulmonary/critical care physician practicing in Tacoma, WA since 2001. I have performed BT on approximately 15 patients.

Every one of my patients has benefitted from the procedure. Some have had a few days for worsening asthma symptoms after the procedure. This to be expected after the airway is stimulated, much in the same way a patient would experience pain and swelling from a surgical procedure. One was hospitalized for 2 days following the treatment. My patients have had greatly improved quality of life. The number of exacerbations have been reduced. I do not have financial data, but with the reduced exacerbations come decreased ER visits and hospitalizations, which I can not help but think if financially beneficial as well.

In reading your summary statements, you raise concerns that are disproportionate with the published data and clinical experience. Your draft, to my reading, seems lukewarm to this technology. BT is now part of the recommended treatments of several guidelines, including one most often used by US physicians, the Global Initiative on Asthma. It is endorsed by multiple organizations, including the American College of Chest Physicians, British Thoracic Society, and the American College of Allergy, Asthma, and Immunology.

The patients who need this procedure have exhausted all treatment options through step 6 for the treatment of severe persistent asthma. BT can serve to improve the quality of life and reduce the financial and social burden of this disease for such patients.

I would urge you to support the implementation of the procedure in Washington. Should have questions, please feel free to contact me at the email above, or at phone [redacted].

[redacted]

Before printing, think about ENVIRONMENTAL responsibility

[redacted]

From: Hartung, Seth <seth.hartung@wwmedgroup.com>
Sent: Thursday, March 17, 2016 5:41 PM
To: HCA ST Health Tech Assessment Prog
Subject: Bronchial thermoplasty, please consider the value it has for patients with no other option

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Sir or md.,

I am writing this short statement in support of bronchial thermoplasty as a tested procedure for the treatment of severe refractory asthma, particularly for its potential value in treating patients who have failed all other therapies. As you know, to date it has been found to be safe and effective in reducing prednisone use, potentially effective in reducing hospitalization utilization and potentially effective in improving quality of life in these patients with severe airways disease. Please consider this utmost request that bronchial thermoplasty remain a viable option for patients that have failed all other approved treatments for asthma.

Do not hesitate to contact me with any questions on my statement. Thank you for your time,

Seth Hartung

Seth Hartung, M.D. PhD Pulmonary and critical care medicine

Western Washington medical group and

P{rovidence Everett Hospital, Everett, Washington