There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

National Institute for Health and Care Excellence

IP675/2 Bronchial thermoplasty for severe asthma

IPAC date: 12 July 2018

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
First consultation				
1	Consultee 1 University Hospitals Birmingham "Heartlands Hospital"	**1.1**	I would like to share our experience with bronchial thermoplasty and argue for its clinical utility as an important tool in the management of severe asthma. We have started the treatment in 2012 and so far conduction about 60 treatment sessions (treating 18 patients fully) we kept record on patients outcomes and participated to NICE audit and national registry. Our response rate was approximately 70% in which patients experience significant improvement that led to reduced exacerbations and hospitalisation and improved overall quality of life. We had 2 patients who were on longterm omalizumab managed to stop due to BT benefit. Patients requirement for oral steroids was significantly reduced by >50%. We had several reports for life changing experience from BT treated patients. The treatment was generally well tolerated and we experience no serious side effects related to the treatment. We followed strict treatment protocol in patient selection, stabilisation before procedure and follow up post procedure. We feel this is crucial for successful treatment outcome. We appreciate the lack of clarity on which patient group would be most suitable for this treatment but we use the criteria of severe asthma patient,	Thank you for your comment. According to the Global Initiative for Asthma 2018 report, cited in section 2.3 of the guidance, severe asthma is asthma that requires Step 4 or 5 treatment, e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment. Section 2.3 of the guidance states that 'In the UK, treatment for asthma follows NICE guideline 80 and guidelines from the Global Initiative for Asthma', which is consistent with the NICE Technology Appraisal on Benralizumab for treating severe eosinophilic asthma (currently in development).

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			with prominent bronchodilator response to beta 2 agonists and continuing poor control despite treatment at step 4 to 5 of BTS/SIGN guidelines. We effectively treated about 1.8% of our patient base with BT compared to a forecast of 34% eligible patients within our population (our published audit) and therefore the treatment can be offered to more patients. the reason for this slow uptake is mainly due to logistics and clinical capacity to administer the treatment. The treatment has the advantage of one off treatment delivery therefore liked by certain patients who don't wish to receive fortnightly or monthly injections for life. This would also have financial savings to the NHS. On behalf of our centre, I would like to see this treatment is supported and provided to more patient and would also support the need for further research to establish more clearly which patients are more likely to respond to this treatment. Yours faithfully. [redacted]	
2	Consultee 2 Company Boston Scientific	**1.1 – 1.5**	"We are pleased that NICE is reviewing the interventional procedure guidance on Bronchial Thermoplasty for severe asthma. However, we are disappointed to see that the current guidance shows some concern on the limited evidence on long-term safety and efficacy. We would like NICE to further consider that Bronchial Thermoplasty (BT) is an established, clinically proven, minimally invasive 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 beta-agonists, in particular that this treatment has been shown to significantly reduce future healthcare utilization, presenting an opportunity to improve patient outcomes and asthma-related quality of life, while	Thank you for your comment. Reference 1 (Chupp et al., 2017) is included in table 2 of the overview (study 7). Reference 2 (Bonta et al., 2018) was identified in the updated literature search and has been added to the appendix of the overview.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			also reducing subsequent health care utilization and associated costs. Several studies have shown long term safety and efficacy out to 5 years post procedure [1; 2; 3], for instance, recently published â€œreal worldâ€• data from the PAS2 study demonstrated long term safety and durability of treatment effect [1]. In addition, Bonta PI et al (2018) confirm that â€˜randomized, controlled clinical trials have shown BT to be safe and effective in reducing severe exacerbations, improving quality of life, and decreasing emergency department visits. Five-year follow-up studies have provided evidence of the functional stability of BT-treated patients with persistence of a clinical benefitâ€™. For all three RCTs, 5-year long-term follow-up data are available (221 patients) [4], and the real-world PAS2 registry (190 patients and currently 3-year follow-up) confirms the results seen in the previous RCTs regarding an acceptable long-term safety profile and the reduction in severe exacerbations, emergency department visits and hospitalisations [2]. Therefore, considering the body of evidence available on safety of BT, we would ask NICE to reconsider providing standard arrangements for this procedure. [1] Chupp G. et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. Eur Respir J. 2017 Aug 31;50(2).Mechanism of Action. [2] Bonta PI et al. Bronchial Thermoplasty in Severe Asthma: Best Practice Recommendations from an Expert Panel. Respiration 2018; 95:289-300 DOI: 10.1159/000488291. [3] Blaiss MS et al. Guiding principles for use of newer biologics and bronchial thermoplasty for patients with severe asthma. Ann Allergy Asthma Immunol. 2017 Dec;119(6):533-540. doi: 10.1016/j.anai.2017.09.058. Epub 2017 Nov 2.	Reference 3 (Blaiss et al., 2017) was identified in the updated literature search and has been added to the appendix of the overview. Reference 4 (Wechsler ME et al., 2013) is included in table 2 of the overview (study 3).

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			[4] Wechsler ME et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol. 2013 Dec;132(6):1295-302. doi: 10.1016/j.jaci.2013.08.009. Epub 2013 Aug 30. "	
3	Consultee 2 Company Boston Scientific	**1.1**	"Having carefully read the â€œOverviewâ€• document and in particular the section about the evidence review of the literature, we would like NICE to consider the following as good evidence of long-term durability of efficacy: â€¢ There was a statistically significant reduction in the rate of severe exacerbations from baseline in PAS 2 (74% [141/190] to 40% [67/168], p<0.0001) and in AIR 2 (52% [98/190] to 33% [55/165], p<0.0001) at 3-year follow-up7. (page 7 of 57) â€¢ In the systematic review (SR) of 6 studies, the frequency of hospital admissions for respiratory events was not statistically significantly different between 1-year and 5-year follow-up (RR 1.47, 95% CI 0.69 to 3.12, p=0.32; I2=36%) in patients who had BT2. (page 9 of 57) â€¢ In the case series of 14 patients, the rate of hospitalisations per patient per year reduced from 0.71 at baseline to 0.23 at 5-year follow-up, corresponding to a 68% reduction (p value not reported)6. (page 9 of 57) â€¢ In the SR of 6 studies, the frequency of visits to the emergency department (ED) because of respiratory events was not statistically significantly different between 1-year and 5-year follow-up (RR 1.06, 95% CI 0.77 to 1.46, p=0.71; I2=0%) in patients who had BT2. (page 10 of 57) â€¢ In the case series of 162 patients who had BT, the percentage of patients needing visits to the ED because of respiratory symptoms reduced by 78% from baseline to 5-year follow-up (p value not reported)3,4. (page 10 of 57) â€¢ In the RCT of 69 patients, the rate of visits to ED was not statistically significantly different for patients who had BT compared	Thank you for your comment. This comment was discussed by the committee, along with other comments received during consultation, and the main recommendation was subsequently changed.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			with standard medical care (SMC at 1-year to 3-year follow-up5. (page 10 of 57) â€¢ In the NRCS of 380 patients there was a statistically significant reduction in the rate of ED visits compared with baseline in PAS 2 (27% [52/190] to 11% [18/168], p =0.0003) and in AIR 2 (29% [55/190] to 8% [13/165], p<0.0001) at 3-year follow-up7(page 10 of 57). Within the evidence review of the literature (Overview document), we would like NICE to consider the following areas as good evidence of long-term safety: â€¢ In a systematic review of studies, pre-bronchodilator FEV1 percentage predicted was not statistically significantly different between 1-year and 5-year follow-up in patients who had BT (weighted mean difference [WMD] 0.75, 95% CI 3.36 to 1.85, p=0.57; I2=0%). There was also no statistically significant difference in post-bronchodilator FEV1 percentage predicted between 1-year and 5-year follow-up (WMD 0.62, 95% CI 3.32 to 2.08, p=0.65; I2=0%)2. (page 7 of 57) â€¢ In the case series of 162 patients the rate of hospital admissions for respiratory symptoms was 2% (0 to 3.96) at 5-year follow-up compared with 4% (1.4 to 7.1) in the 12 months before BT, p value not reported3,4. (page 9 of 57) â€¢ In the RCT of 69 patients the proportion of patients having respiratory adverse events was higher in the BT group (84% [38/45]) compared with SMC (75% [18/24]) at 1-year follow-up, but similar at 3-year follow-up (56% [24/43] BT group, 57% [12/21] SMC group)5. (page 11 of 57) â€¢ The case series of 162 patients reported no incidence of pneumothorax, intubation or mechanical ventilation, cardiac arrhythmias, or death as a result of BT treatment over the 5 years of follow-up3-6,9 (page 11 of 57). In addition, there were no findings on High-resolution computed tomography (HRCT) suggestive of long term safety risk five years post BT (Wechsler	

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			ME et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol. 2013 Dec;132(6):1295-302. doi: 10.1016/j.jaci.2013.08.009. Epub 2013 Aug 30). In sum, evidence to date ....(please see the continuation of this comment in the next comment)"	
4	Consultee 2 Company Boston Scientific	**1.1**	...continuation from previous comment In sum, evidence to date has shown a readily-manageable safety consideration in the immediate post-procedure period of approximately 8 weeks. To date, long-term follow up of BT patients out to 5 years has not demonstrated any delayed safety consideration that may inform risk-benefit equipoise considerations. We would kindly request that if long-term considerations by the committee are concerns beyond 5 years, that this clarity of language be provided so that the â€˜limitedâ€™ nature of evidence beyond 5-years is made clear. If concerns of long-term evidence are generally less than a 5-year time horizon, then the above points quoted from the evidence overview give a relatively robust body of evidence demonstrating long-term safety and efficacy and we ask that the committee removes the word â€˜limitedâ€™ from the committeeâ€™s assessment, particularly in this specific cohort of patients where other avenues for controlling their asthma are not effective (see next point).	Thank you for your comment. This comment was discussed by the committee, along with other comments received during consultation, and the main recommendation was subsequently changed.
5	Consultee 2 Company Boston Scientific	**3.5**	â€œThere is uncertainty about which patients may benefit from the procedure.â€•	Thank you for your comment.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			Despite some unanswered question on who benefits the most from bronchial thermoplasty, we believe there is enough evidence on who should be considered for this procedure. For instance, Blaiss MS et al. (2017) state as follows : â€œFor nonallergic, non-eosinophilic (non-TH2) severe asthma, bronchial thermoplasty can be a first option for patients with persistent symptoms and who have variable airflow obstruction as demonstrated by bronchodilator reversibility after failure of triple therapy with high-dose ICS plus LABA and tiotropium but before regular OCS use or a targeted biologic. Bronchial thermoplasty also can be considered an alternative therapy for patients with allergic or eosinophilic asthma who have had an inadequate response to initial biologic therapyâ€• [1]. [1] Blaiss MS et al. Guiding principles for use of newer biologics and bronchial thermoplasty for patients with severe asthma. Ann Allergy Asthma Immunol. 2017 Dec;119(6):533-540. doi: 10.1016/j.anai.2017.09.058. Epub 2017 Nov 2.	Blaiss et al., 2017 was identified in the updated literature search and it has been added to the appendix of the overview.
6	Consultee 2 Company Boston Scientific	**3.7**	â€œThis procedure may not suitable for people with bronchiectasisâ€• . We would kindly ask NICE to amend this sentence in order to reflect the limited evidence on this topic. Therefore, we would ask NICE to change the sentence as follows: â€œAn anecdotal adverse event on bronchiectasis and very limited evidence on this adverse event may suggest that this	Thank you for your comment. Section 3.7 of the guidance has been changed.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			procedure may not be suitable for people with bronchiectasis.â€•	
7	Consultee 2 Company Boston Scientific	**2.3**	Unfortunately, NICE guideline 80 does not cover managing severe asthma or acute asthma attacks, therefore it does not fully reflect the management of asthma in the UK.	Thank you for your comment. Section 2.3 of the guidance states that 'In the UK, treatment for asthma follows NICE guideline 80 and guidelines from the Global Initiative for Asthma', which is consistent with the NICE Technology Appraisal on Benralizumab for treating severe eosinophilic asthma (currently in development). The Global Initiative for Asthma guidelines are more up to date than the asthma guideline from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN).
8	Consultee 2 Company Boston Scientific	**General**	We would ask NICE to consider additional studies for the review of this guidance: â€¢ Chernyavsky IL, Russell RJ, Saunders RM, et al. In vitro, in silico and in vivo study challenges the impact of bronchial thermoplasty on acute airway smooth muscle mass loss. Eur Respir J 2018; 51: 1701680 https://doi.org/10.1183/13993003.01680-2017]. â€¢ Donovan GM et al. Unravelling a Clinical Paradox - Why Does Bronchial Thermoplasty Work in Asthma? Am J Respir Cell Mol Biol. 2018 Apr 18. doi: 10.1165/rcmb.2018-0011OC.	Thank you for your comment. Chernyavsky IL et al., 2018 was identified in the updated literature search and has been added to the appendix of the overview; it includes a small case series of 14 patients. Donovan GM et al., 2018 was identified in the updated literature search but it does not meet the inclusion criteria for the overview because it is a laboratory study.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

9	Consultee 2 Company Boston Scientific	**3.6**	Currently, Bronchial Thermoplasty is not commercialized or regulatory approved for use in children or young-adults (i.e. less than 18 years old). Inclusion of language pursuant to children or young adults is not relevant to the current guidance and should not influence guidance in adults greater than 18 years old. Additionally, it should be noted in the background of asthma that the majority of severe asthmatics have hypertrophic or excessive levels of ASM (measured as a percentage of airway biopsy histology slide), when compared to non-severe asthmatics or healthy controls (Aubier et al. Airway smooth muscle enlargement is associated with protease-activated receptor 2/ligand overexpression in patients with difficult-to-control severe asthma. J Allergy Clin Immunol. 2016 Sep;138(3):729-739.e11. doi: 10.1016/j.jaci.2015.12.1332. Epub 2016 Apr 20.).	Thank you for your comment. Section 3.6 of the guidance is a committee comment, noting that the device used in this procedure does not have a CE mark for use in people younger than 18 years.
10	Consultee 3 British Thoracic Society	**General**	We welcome NICE's review of bronchial thermoplasty and the acceptance that it has a role in the treatment algorithm in the UK and recognise the limited uptake to date within the UK. The literature review is limited and does not include several mechanistic studies from the French group led by Michel Aubier, US studies and studies from the Netherlands from Peter Bonta. All of these studies lead to new knowledge on the mechanism of action and demonstrate, that this is not solely through depletion of Airway smooth muscle. Additional safety evidence is published from NICE through its	Thank you for your comment. To conduct rapid assessments of novel procedures, the interventional procedures programme limits the studies presented in detail in the overview evidence tables to those most likely to be relevant and informative. Studies that do not contain clinical information on efficacy and safety outcomes (for example, narrative review articles, animal studies or studies reporting only on physiological outcomes) are not included in the overview, and are therefore not considered by the Committee.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			Registry and several international series are now available, confirming or supporting the data available within the trials and systematic review. We acknowledge the comments that in future bronchial thermoplasty may be complementary to monoclonal antibody therapy, but will remain utilised, for the foreseeable future, in patients with severe disease who are only partially responsive the pharmacotherapy.	The committee considered data from the UK BTS Difficult Asthma Registry (study 8 in the overview).
11	Consultee 3 British Thoracic Society	**1.4 and 1.5**	There are 2 concerns within the guidance that we believe is not representative of the current practice and evidence:- 1. That treated patients should be part of a clinical trial or registry. The formal UK and International bronchial registries have now completed data capture and are now closed to recruitment, meaning that formal registries or trials are not available within the UK. Phraseology that puts the management of BT on a par with monoclonal antibody therapy, is much more rational, ie BT should only be considered for use within the UK severe asthma network, and be provided in specialist centres approved for such treatments, where complete MDT review and assessment is considered for every patient. 2. The insistence on more long term data is probably unnecessary, though we are aware that attempts to provide this data are underway. However the principle appears discriminatory against device orientated therapies compared to pharmacotherapy. With the latter, there are very limited data-sets which look to establish benefit at more than 12	Thank you for your comment. Section 1.4 of the guidance states that clinicians should enter details of all patients who have the procedure on to the UK Severe Asthma Registry. The guidance will include this link to the registry: http://rs2.e-dendrite.com/csp/asthma/frontpages/index.html This comment was discussed by the committee, along with other comments received during consultation, and the main recommendation was subsequently changed.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			months and whilst antiIgE therapy has provided real world data out to 2 years, BT already has established persistence of benefit out to 5 years and yet, the NICE review continues to include statements regarding need for longer term evidence. Overall BTS welcomes the new guidance, provided the above points are addressed.	
IPAC date: 11 October 2018				
Second consultation				
1	Consultee 1 School of Medicine	**General**	You ask: Are there any issues that require special attention in light of NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others? My Comment: How are you making the consultation available to: • People with asthma who cannot read • People with asthma who do not speak or read English as their first language • People with asthma who do not have access to the internet	Thank you for your comment. The Public Involvement Programme informs all relevant patient groups and professional bodies of the consultations and encourage them to respond and disseminate to the individual patients. People who cannot read, for example through sight loss (or other reasons), often tend to have technology that will read out text and all the format that we use on our website should comply with government standards to comply with this. If we are producing a piece of guidance where we know that it affects a significant subpopulation whose first language is not English, it might be reasonable for us to translate either

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

				the consultation or the guidance into their first language If people do not have access to the internet they can request a paper copy of the consultation document.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

2	Consultee 2 NHS England	**General**	Please see below comments from NHS England Specialised Commissioning in relation to the Bronchial thermoplasty consultation. • This interventional procedures draft builds on the advice given in 2012. The additional evidence comes from systematic reviews and the BTS register. The numbers of patients worldwide who have undergone thermoplasty is small (<500). There have only been 131 in the UK over five years. • The draft recommendations appear reasonable with the caveat of the small numbers. • The NICE press release in the Guardian https://www.theguardian.com/society/2018/aug/31/new-treatment-for-severe-asthma-cases-gets-go-ahead-for-use-in-nhs was misleading. The treatment is not suitable for children and is not novel. The option for BT was in the very first specification for severe asthma published in 2013. • Many severe asthma centres have abandoned BT since the arrival of the new biologic options. Take up is therefore not likely to mushroom. • In the draft, current treatment (section 2.4) as described, is out of step from the NICE asthma guideline (it sounds like BTS/SIGN) • Thermoplasty only seems to improve exacerbation frequency and does not improve lung function or reduce corticosteroid use. (i.e. modest benefit) • There is no health economic comment or advice	Thank you for your comments. Section 2.4 of the guidance has been deleted. Cost-effectiveness is not within the remit of the Interventional Procedures Programme.
3	Consultee 3 British Thoracic Society	**1**	We welcome NICE's review of bronchial thermoplasty and the acceptance that it has a role in the treatment algorithm for severe asthma in the UK and recognise the limited uptake to date within the UK.	Thank you for your comment.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			We support the recommendation that the procedure should only be done by multi-disciplinary teams in specialist centres and that clinicians should enter details of patients who have had the procedure in the UK severe asthma registry.	
4	Consultee 3 British Thoracic Society	**2.3 and 2.4**	We note that these 2 paragraphs are not congruent. 2.4 does not summarise NICE guideline 80. It more accurately reflects the BTS/SIGN asthma guideline 2016 (although the use of the word step is not used in the latest BTS/SIGN guideline).	Thank you for your comment. Section 2.4 of the guidance has been deleted.
5	Consultee 4 Royal College of Physicians	**General**	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the British Thoracic Society (BTS).	Thank you for your comment.
6	Consultee 5 Company Boston Scientific	**General**	We are pleased to see the committeeâ€™s consideration and inclusion of the current evidence on Bronchial Thermoplasty (BT) in the second draft document. We believe the updated consultation document appropriately reflects current evidence on short and long-term efficacy and safety of BT.	Thank you for your comment.
7	Consultee 5 Company Boston Scientific	**1.4**	We agree on the importance of continuing â€œreporting details of patient selection and long-terms safety and efficacy outcomesâ€□. Currently 5-year long-term data are available on BT. Data from 3 randomized controlled studies have shown long term safety and efficacy out to 5 years post procedure [1; 2; 3]. In addition, recently published â€œreal worldâ€□ data from the PAS2 study also demonstrated long term safety and durability of treatment effect [1]. In addition to this, Boston Scientific is supporting research to continue building further long term clinical evidence on BT out to 10 years [4]. 1] Chupp G. et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. Eur Respir J. 2017 Aug 31;50(2).	Thank you for your comment. Chupp G et al. (2017) is included in table 2 of the overview (study 7) Bonta P et al. (2018) is included in the appendix of the overview. Blaiss M et al. (2017) is included in the appendix of the overview. The cited trial currently has the status of ‘recruiting’ on the clinicaltrials.gov website.

There were 2 consultation periods for this guidance, 1 ran from 24 May 2018 to 21 June 2018 and the other ran from 31 August 2018 to 28 September 2018.

			[2] Bonta PI et al. Bronchial Thermoplasty in Severe Asthma: Best Practice Recommendations from an Expert Panel. Respiration 2018; 95:289-300 DOI: 10.1159/000488291. [3] Blaiss MS et al. Guiding principles for use of newer biologics and bronchial thermoplasty for patients with severe asthma. Ann Allergy Asthma Immunol. 2017 Dec;119(6):533-540. doi: 10.1016/j.anai.2017.09.058. Epub 2017 Nov 2 [4] Bronchial Thermoplasty 10+ Year Study (ClinicalTrials.gov Identifier: NCT03243292)	

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."